the picture is more complicated. Although there is no significant difference between the New Jersey and South Florida juveniles ($\chi_c^2 = 0.18$; $.75 > P < .5$), the Potomac, Maryland, individuals responded differently ($\chi_c^2 = 14.9$; d.f. = 2; $P < .001$) and showed a greater preference for fish (80 percent compared to 34 and 39 percent).

Thamnophis sirtalis has the greatest geographical range of any North American snake (*4*). Fitch (*1*) while allowing the possibility of geographical variation in feeding habits, suggested that "throughout the widespread area of its occurrence the species seems to be remarkably stable in its (feeding) habits." My results indicate that this species does show geographic variation, and that this difference is innate. This phenomenon may be associated with habitat differences between the areas. Although *Natrix sipedon* is an aquatic snake always closely associated with fresh water, in *Thamnophis sirtalis* the association tends to decrease as one moves northward. In Florida there is a marked seasonal drying of the Everglade ponds, and a resultant concentration of fish in small water bodies. This coincides with the production of large numbers of offspring in both *Thamnophis* and *Natrix* and may be a significant factor controlling selection of preference for fish in these snakes.

At times any species faces adverse changes in its environment. Snakes must adjust quickly to any change in abundance of prey. Intraspecifically, they show geographic variation in food preference, and furthermore, in any local population snakes show innate polymorphism in food preference; a small percentage of the population will accept prey not accepted by most of the population (Table 1). This provides flexibility and a potentiality for invading new habitats and meeting long-term environmental and climatic changes.

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Genetic Control of Drug Levels in Man: Phenylbutazone

Abstract. *Phenylbutazone was administered to seven pairs of identical (monozygotic) twins and to seven pairs of fraternal (dizygotic) twins. Individual half-lives ranged from 1.2 to 7.3 days. Subjects with identical genotypes (monozygotic twins) exhibited very similar phenylbutazone half-lives; significantly greater differences in half-life occurred in dizygotic twins. The previously established large variations among individuals in phenylbutazone metabolism appear to be genetically, rather than environmentally, determined.*

Increasing evidence indicates intraspecies variations in the metabolism of many drugs. Humans exhibit particularly large differences in the half-lives of phenylbutazone (*1*) and dicumarol (*2*), but it remains to be established whether such differences are due primarily to environmental or genetic causes. Multiple environmental factors are known to alter the rates of drug metabolism in experimental animals (*3*): for example, phenylbutazone and other drugs enhance their own metabolism in dogs (*4*).

In man several polymorphisms involving drugs have been described. Those with the highest frequency concern glucose-6-phosphate dehydrogenase deficiency and isoniazid acetylation; neither involves the liver microsomal enzymes that oxidize phenylbutazone, dicumarol, and many other drugs.

Individual differences in phenylbutazone metabolism have therapeutic implications. Toxicity may develop primarily in subjects having long half-lives in plasma, whereas those having short half-lives may not attain sufficient or sufficiently sustained levels to benefit from the drug.

This study was designed to determine whether the wide variability in phenylbutazone metabolism was due primarily to genetic or environmental factors. We employed 14 pairs of volunteer twins from the Washington, D.C., area; seven were identical and seven were fraternal. All subjects were Caucasian, over 21 years of age, and in good health. None took drugs for at least 1 month before administration of phenylbutazone. Each volunteer was typed for approximately 30 blood groups to document the nature of the twinship; the results confirmed the twins' views of whether they were identical or fraternal.

At 0800 hours each subject received a single oral dose of phenylbutazone (about 6 mg/kg) (*5*); since only 100-mg tablets were available, dosages were adjusted to the closest 50 mg. Because the dose was not always exactly 6 mg/kg, the initial levels of plasma phenylbutazone (Fig. 1) varied. However, in this study absolute plasma levels were not critical because, within the levels attained, they did not affect the values for phenylbutazone half-lives. Twenty-four (in some cases, 48) hours after administration of phenylbutazone, blood was drawn in tubes containing oxalate, and the plasma was assayed for phenylbutazone by the method of Burns *et al.* (*1*); subsequent specimens were drawn at regular intervals. To determine whether administration of a single dose of phenylbutazone changed the rate of elimination of a subsequent dose, two sets of identical twins received a second similar dose of phenylbutazone 9 days later.

Figure 1 shows the decay of phenylbutazone in plasma of three sets of identical and three sets of fraternal

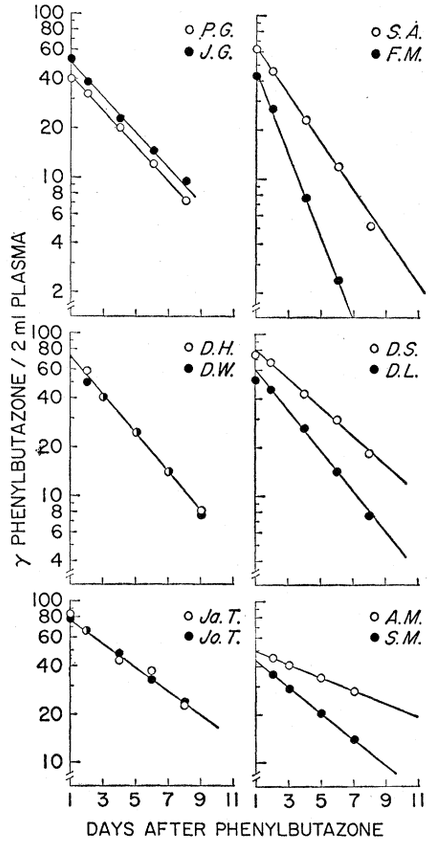

Fig. 1. Decline of phenylbutazone in the plasma of three sets of identical twins (left) and three sets of fraternal twins (right). The log of the phenylbutazone concentration in 2 ml of plasma is shown at intervals after a single oral dose (6 mg/kg).

twins. Table 1 gives the half-lives, determined from such curves, for each subject. The lines were fitted by eye. One subject (A.M.) markedly differed from all others in having a phenylbutazone half-life of 7.3 days. With this subject included and excluded, the contribution of heredity to the trait under study was calculated from the formula (*6*):

$$\frac{\text{variance within pairs of fraternal twins} - \text{variance within pairs of identical twins}}{\text{variance within pairs of fraternal twins}}$$

This formula permits a range of values from zero, suggesting negligible contribution by heredity, to 1, indicating strong hereditary influence. Variance within pairs was calculated from the formula (*6*):

$$[\Sigma \text{ (difference between twins)}^2]/2n$$

The results both with A.M. included

$$(1.59 - 0.02)/1.59 = 0.99$$

and excluded

$$(0.15 - 0.02)/0.15 = 0.87$$

indicated that hereditary factors controlled the wide variation in the rate of decay of phenylbutazone in plasma. The difference between identical and fraternal twins in intrapair variance was significant (see Table 1). The intrapair correlation coefficient of 1.0 for identical twins and of 0.45 for fraternal twins, excluding A.M. and S.M., gave further strength to the hypothesis. Since fraternal twins have in common approximately half of their total number of genes, a value of 0.5 would be expected in fraternal twins for a trait under genetic control, whereas in identical twins a value of 1.0 would be expected for a genetically determined trait.

In four of the seven sets of identical twins studied, the sibs lived in different households, so that their similarity in half-lives cannot be attributed to such environmental factors. The half-lives of serum phenylbutazone in two sets of identical twins who received second doses 9 days after the first were unchanged by the second; this and earlier observations (*1*) suggest that the rate of decay of phenylbutazone in plasma is a stable trait.

There appeared to be no sex difference in the rate of disappearance of phenylbutazone from plasma: mean values for the half-lives in the 12 males and 16 females (with standard errors) were 3.1 ± 0.2 days and 2.9 ± 0.3 days, respectively (Table 1). However, with A.M. excluded, the value for females became 2.6 ± 0.1 days. The mean half-life (with standard error) in the 28 subjects was 3.0 ± 0.3 days, in exact agreement with the literature (*7*).

Most half-lives were between 2.6 and 4.0 days, but one subject had a very short half-life of 1.2 days, and another had an extremely long one of 7.3 days (Table 1, Fig. 1). Because plasma half-lives exceeding about 4.0 days have been associated with liver disease in individuals not receiving drugs (*8*), the subject showing 7.3 days was studied intensively. Her history and physical examination revealed a normal 21-year-old girl lacking any suggestion of liver disease. Laboratory studies, including hemogram, urinalysis, serum proteins, protein-bound iodine, bilirubin, lactate dehydrogenase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase, all showed normal results. Her excretion of sulfobromophthalein was 4 percent in 45 minutes. At the time of administration of phenylbutazone her liver apparently functioned normally.

Table 1. Half-lives of phenylbutazone in plasma of twins. The difference between monozygotic and dizygotic twins in intrapair variance is significant at the 0.01 level with A.M. excluded (F, 7.5; N_1, 6; N_2, 7) or at the 0.001 level with A.M. included (F, 79.5; $N_1 = N_2 = 7$).

Twin	Age, sex	Half-life (days)
	Identical twins	
J.G.	22, M	2.8
P.G.	22, M	2.8
D.H.	26, F	2.6
D.W.	26, F	2.6
D.T.	43, F	2.8
U.W.	43, F	2.9
Ja.T.	44, M	4.0
Jo.T.	44, M	4.0
Ge.L.	45, M	3.9
Gu.L.	45, M	4.1
He.M.	48, M	1.9
Ho.M.	48, M	2.1
C.J.	56, F	3.2
F.J.	56, F	2.9
	Fraternal twins	
A.M.	21, F	7.3
S.M.	21, M	3.6
L.D.	21, F	2.9
L.W.	21, F	3.0
Ja.H.	24, F	2.6
Je.H.	24, F	2.3
E.K.	31, F	1.9
R.K.	31, M	2.1
S.A.	33, F	2.1
F.M.	33, F	1.2
D.L.	36, F	2.3
D.S.	36, F	3.3
F.D.	48, M	2.8
P.D.	48, M	3.5

Variability in the rate of phenylbutazone decline in human plasma appears from these studies to be a genetically determined trait. Its mode of inheritance is unclear from these data but may be elucidated in the future by pedigree analysis.

Genetic control of the variability in levels of phenylbutazone in plasma may involve the liver microsomal enzyme that hydroxylates phenylbutazone; alternatively, since phenylbutazone is 98-percent bound to plasma proteins (*1*), it may involve the binding sites or rate of catabolism of albumin. Heterogeneity of albumin has been described, but available evidence suggests that the albumins of most individuals are similar (*9*). However, preliminary studies of twins receiving antipyrine, a drug bound only 10 percent by plasma proteins (*10*), suggest that individual variations are due to differences in drug metabolism rather than in binding.

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