Papers and Originals

Genetic Control of Phenylbutazone Metabolism in Man

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Summary: The purposes of the present investigation were to assess the genetic contribution to the variability between individuals in the rate at which they metabolize phenylbutazone and to characterize the type of inheritance that controls the metabolism of the drug. The 155 persons investigated included 43 unrelated random individual subjects and the members of 28 two-generation family units. None of these subjects had taken drugs in the six months preceding the experiments. Each subject ingested an oral dose of phenylbutazone and the plasma half-life of the drug was determined. These non-pretreated plasma phenylbutazone half-lives suggest the existence of polygenic control, but the value of the data is marred by the frequency distribution being very skewed.

The 142 persons given a second test, included 41 unrelated random subjects and 24 two-generation family units. A three-day course of oral phenobarbitone was followed by an oral dose of phenylbutazone and the plasma half-life of the latter determined. The phenobarbitone was given with the aim of "inducing" drug-metabolizing enzymes in the liver, thus rendering the environment more uniform. When the post-phenobarbitone half-lives were adjusted to a standard height they were approximately normally distributed. There was a significant regression of mean offspring value on mid-parent value, indicating that about 65% of the observed phenotypic variance of post-phenobarbitone plasma phenylbutazone half-lives is due to the additive effects of genes.

Phenylbutazone metabolism in man is thus shown to be under polygenic control, and genetically controlled in a similar manner and to a similar degree to body height.

Improved understanding of phenylbutazone metabolism may lead to improved therapeutic efficacy and a lower incidence of adverse reactions.

Introduction

Phenylbutazone is a widely used anti-inflammatory and anti-arthritic medication. Its clinical value is marred by a small but definite incidence of adverse reactions, the most serious being those which affect the bone marrow. The pharmacological effects, toxic effects, and adverse reactions of drugs may be correlated with plasma concentrations. Knowledge of the factors that control plasma phenylbutazone concentrations may therefore be important in understanding clinical effects.

The metabolism of phenylbutazone in man was first investigated by Burns *et al.* (1953, 1955). The compound was shown to be hydroxylated at two molecular sites: in the para-position on the phenyl ring and on the aliphatic side chain (Burns *et al.*, 1955). Variability in the plasma phenylbutazone half-life was observed among the 16 subjects investigated by these authors (Burns *et al.*, 1953). The variability of plasma phenylbutazone half-lives in a population of healthy people was investigated by Levi *et al.* (1968) in 36 persons who had not received any drug pretreatment and in 19 persons who had received pretreatment with various drugs. The values had a skewed unimodal frequency distribution varying between 50 and 120 hours in the non-pretreated subjects and between 30 and 100 hours in the pretreated subjects.

Drug hydroxylations generally occur in liver endoplasmic reticulum, which after homogenization becomes the particulate "microsomes" (Fouts, 1961). Microsomal enzymes, especially those concerned with hydroxylation, are known to be influenced by chemical compounds administered to mammalia in vivo. Phenobarbitone is a typical example of such a compound, and it causes "induction" of increased liver microsomal hydroxylase activity, which results in the more rapid metabolism (both in vivo and in vitro) of other drugs, including phenylbutazone (Burns and Conney, 1965; Remmer and Merker, 1965; Mannering, 1968). The metabolism of phenylbutazone can therefore vary between persons because their environments are different, causing them to be induced to a varying degree.

The probable contribution of genetic factors to the variability of phenylbutazone metabolism between persons was indicated by Vesell and Page (1968) in a study of twins who had not been subjected to pretreatment with any other drugs. Plasma half-lives of phenylbutazone were much more similar in identical than in fraternal twins.

In view of all these findings it seemed possible that phenylbutazone metabolism (as measured by its plasma half-life) was under polygenic control in man. Many quantitative characters show a continuous unimodal frequency distribution in the population and are controlled by an unknown number of allelic genes which cannot be individually identified, at an unknown number of loci which cannot be individually identified (polygenic inheritance). The first genetic studies of such characters were made by Galton (1889), who found that height exhibits the phenomenon of "regression." By this was meant regression towards the population mean—for example, tall parents tend to beget offspring who have heights which are greater than the population mean, but which lie closer to that mean than does the mean height of their parents.

Fisher (1921) produced a successful mathematical model of polygenic inheritance in terms of Mendel's laws. Falconer (1960) presented many of the ideas involved in a modern text. It can be considered that for a quantitative character

$$V_P = V_G + V_E$$

where V_P = phenotypic variance observed, V_G = genetic variance, and V_E = environmental variance.

Further

$$V_G = V_A + V_D + V_I$$

where V_A = variance due to the additive effects of the genes controlling the character, V_D = variance due to dominance effects, and V_I = variance due to interactions.

The regression coefficient of mean offspring values (y) on midparent values (x) gives an estimate of V_A/V_P, which is often termed the "heritability." It is difficult to make estimates of V_D and V_I in man, but when they can be measured in animals they are generally found to be small compared with V_A.

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The purposes of the present study were: (1) to measure the genetic contribution to intersubject variability in phenylbutazone plasma half-lives, and (2) to see if phenylbutazone plasma half-life is inherited as a character under polygenic control.

Subjects and Methods

All the 155 subjects studied were healthy volunteers. Forty-three unrelated random subjects were students, laboratory technicians, and other university staff. The 28 families investigated were those of physicians and personal friends of physicians. In 27 families both parents and all available offspring were studied. In the 28th family the mother was not available for study, but results from the father and his two offspring have been used for some computations. All subjects were carefully interrogated to ensure that no medications had been consumed in the preceding six months. Specific inquiries were made concerning all doctors' prescriptions, patent medicines, laxatives, vitamins, tonics, and contraceptive steroids. Sex, age, height, and weight were recorded for all subjects.

Phenylbutazone was administered orally to fasting subjects as sugar-coated 100-mg. tablets. The dosage scheme was used about 1·98 mg./kg. metabolically active mass (Drabkin, 1959). The subjects fasted for two hours after drug ingestion. Venous blood was taken into heparin at 24, 48, and 72 hours after drug ingestion. The plasma was separated within six hours of the blood being drawn and stored at 4°C. until analysis could be carried out, which took place within seven days. (It was ascertained that no decrease in plasma phenylbutazone concentration occurred during one week at 4°C.)

Phenobarbitone.—An interval of at least seven days was allowed to elapse between the initial dose of phenylbutazone and the beginning of phenobarbitone ingestion. About 1·2 mg. of phenobarbitone per kg. body weight was ingested nightly for three nights. On the morning of the fourth day—that is, about 12 hours after the last evening dose of phenobarbitone—an oral dose of phenylbutazone was ingested, the dosage schedule and conditions being the same as detailed above. Venous blood samples were drawn at 24, 48, and 72 hours after phenylbutazone ingestion and were processed as detailed above.

Plasma phenylbutazone concentrations were determined by the method of Burns *et al.* (1953), estimations being made in duplicate from each venous blood sample. Duplicate standards at 0, 10, 20, 30, and 40 μg. of phenylbutazone per ml. concentration were included in every determination procedure. The standards were prepared by dissolving phenylbutazone in 0·0025 N sodium hydroxide solution, and the pH was then brought to 7·0 by titrating with N hydrochloric acid. The phenylbutazone concentrations in the "unknowns" were computed from the absorbency values by using the "standard" line of regression of absorbency on concentration obtained on the same occasion.

Plasma phenylbutazone half-life was computed from the linear regression of $\log_{10}$ phenylbutazone concentrations against time, the three available values being used.

Steady State Plasma Concentrations.—Nineteen subjects had two procedures carried out. On one occasion the plasma phenylbutazone half-lives before and after phenobarbitone were determined as detailed above. On the other occasion the plasma phenylbutazone steady state concentration was determined as follows: 100 mg. of phenylbutazone was ingested daily for eight days; venous blood specimens were drawn at 9 a.m. on Days 7, 8, and 9 and plasma analysed as detailed above.

Independence of Measurements in Plasma.—The presence of phenobarbitone in the plasma does not interfere with the determination of plasma phenylbutazone.

Repeatability.—The complete procedure—that is, initial phenylbutazone half-life determination, phenobarbitone dosing, and second phenylbutazone half-life determination—was carried out on two occasions in 16 individuals. An interval of at least three months was allowed to elapse between the two occasions.

Statistical Techniques.—These were standard (Bailey, 1959), and those which involved the analysis of quantitative inheritance were according to Falconer (1960).

Results

Steady-state Plasma Concentration of Phenylbutazone

The steady-state plasma concentrations determined in 19 subjects showed a range of from 23·83 to 57·74 μg./ml.; the mean was 41·47 μg./ml. with a standard error of 2·08.

Plasma Phenylbutazone Half-life before Phenobarbitone

The distribution of this quantity was still somewhat skewed after $\log_{10}$ transformation (Fig. 1). In its $\log_{10}$ form it was significantly repeatable (Table I, line 1) but was not significantly correlated with steady-state plasma concentration (Table I, line 2).

Some of the variability in half-lives seemed to be due to the characteristics of the individuals, such as sex, age, height, and weight. The doses of drug had been allotted on the basis of body weight. There was a significant regression of half-life values on height, disregarding sex and age (Table I, line 3). Adjustment to a standard height seemed likely also for differences in sex, age, and measurements of metabolic

TABLE I.—*Plasma Phenylbutazone Half-life Before Phenobarbitone. Some Regressions Computed*

Line No.	x	y	n	b	a	r	t	P
1 ..	First estimate of $\log_{10}$ plasma PBZ half-life	Second estimate	16	0·5161	0·9373	0·6165*		
2 ..	Steady-state plasma PBZ concentration (μg./ml.)	$\log_{10}$ plasma PBZ half-life	19	0·0048	1·7932	0·4072	1·8384	>0·05
3 ..	Height (in.)	,, ,, ,,	155	0·0065	1·5116	0·2126	2·6918	<0·01
4 ..	Age (years)	$\log_{10}$ plasma PBZ half-life adjusted to a standard height of 66 in.	155	−0·0011	1·9770	0·1216	1·5159	>0·10
5 ..	Weight (lb.)	,, ,, ,,	155	−0·0003	1·9920	0·0768	0·9527	>0·10
6 ..	$\log_{10}$ plasma PBZ concentration at zero time	,, ,, ,,	155	0·2604	2·3639	0·1968	2·4827	<0·05
7 ..	Husband value for plasma PBZ half-life adjusted to a standard height of 66 in. (167·6 cm.)	Wife value for plasma PBZ half-life adjusted to a standard height of 66 in.	27	0·6940	0·5854	0·4999	2·8862	<0·01
8 ..	,, ,, ,,	,, ,, ,,	26	0·3888	1·1549	0·2995	1·5377	>0·10
9 ..	Mid-parent value for plasma PBZ half-life adjusted to a standard height of 66 in.	Mean offspring value for plasma PBZ half-life adjusted to a standard height of 66 in.	27	0·8257	0·3616	0·7414	5·5235	<0·001
10 ..	,, ,, ,,	,, ,, ,,	26	0·5032	0·9661	0·5272	3·0392	<0·01

PBZ = Phenylbutazone. n = Number of pairs of observations. b = Regression coefficient (slope). a = Intercept—that is, value of y when x = o (in units of y). r = Interclass Correlation coefficient. t = To test significance of r and b. P = Probability. *The approximate 95% confidence limits are 0·145 and 0·965; intra-class correlation 0·79.

activity such as surface area; and so the half-lives were adjusted to a standard height of 66 in. (167·6 cm.) with the calculated regression coefficient.

After this adjustment the half-life values still had a skewed distribution but no significant regression on age (Table I, line 4) or weight (Table I, line 5). There was a significant regression on $\log_{10}$ plasma phenylbutazone concentration at zero time (Table I, line 6). The height-adjusted half-life value for 87 males was 1·9355 ± S.E. 0·0152 and for 68 females 1·9514 ± S.E. 0·0194 (t = 0·65, degrees of freedom 153, P>0·10). The mean for 43 random subjects was 2·0051 ± S.E. 0·0235; significantly higher than the mean for all 55 parents studied, which was 1·9086 ± S.E. 0·0187 (t = 3·25, degrees of freedom 96, P<0·01); this difference remains unexplained.

In the family data there was a significant correlation between husband and wife (Table I, line 7) when the parents of Family D, who had exceptionally high values, were included but none when the parents of this family were excluded (Table I, line 8). A significant correlation between unrelated spouses suggests an environmental influence. The mean for all 55 parents was compared with the mean for all 57 offspring (1·9278 ± S.E. 0·0192). Because there is a correlation a special value of t needs to be derived. This has been computed as 1·51 with about 25 degrees of freedom; indicating no significant difference between parents and offspring.

The regression of mean offspring values for the height-adjusted $\log_{10}$ phenylbutazone plasma half-lives on mid-parent values was significant (Table I, line 9; Fig. 2). A disproportionately large contribution to the calculation is made by Family D, in which parental and offspring values are high. When this family is excluded there remains, however, a regression (Table I, line 10) with a lower significance and smaller regression coefficient.

The conclusion with the pre-phenobarbitone data is suggestive, therefore, of polygenic control of phenylbutazone metabolism, but is unsatisfactory because (1) of poor repeatability, (2) half-lives do not correlate with steady-state values, (3) distribution of half-lives is skewed, (4) correlation between husbands and wives is suggested, and (5) there is uneven distribution of half-lives is skewed, (4) correlation between tergram (Fig. 2).

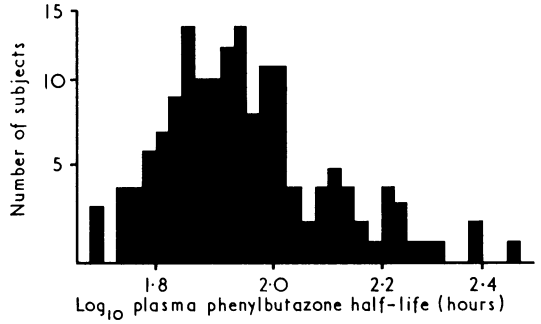

FIG. 1.—Frequency distribution of plasma phenylbutazone half-lives in the $\log_{10}$ transformation. These results were obtained without pretreatment with phenobarbitone.

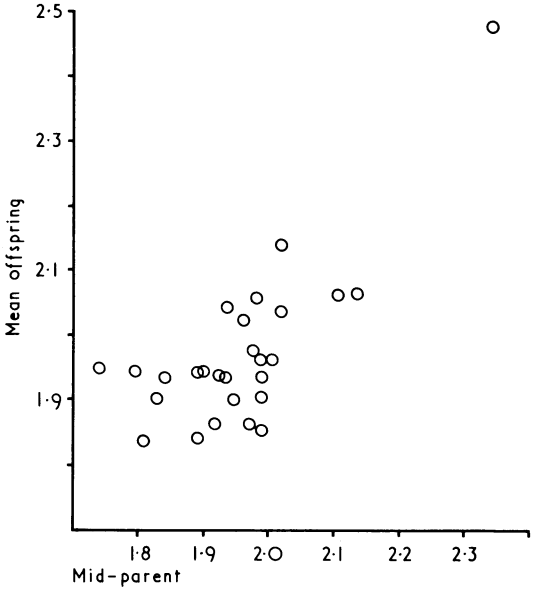

FIG. 2.—Regression of mean offspring plasma phenylbutazone half-lives on mid-parent values. These results have been adjusted to a standard height and were obtained without pretreatment with phenobarbitone.

Phenobarbitone and Phenylbutazone Metabolism

The effect of phenobarbitone on phenylbutazone metabolism was expressed by the differences between pre-phenobarbitone and post-phenobarbitone plasma half-lives. This difference was correlated with the pre-phenobarbitone half-life (Fig. 3). The same relationship was shown another way in the correlation between the pre- and post-phenobarbitone half-lives (r = 0·64, degrees of freedom 140, P<0·001). Persons who had a long pre-phenobarbitone half-life showed the

TABLE II.—*Regressions Calculated Using Plasma Phenylbutazone Half-lives After Phenobarbitone*

Line No.	x	y	n	b	a	r	t	P
1 ..	First estimate of $\log_{10}$ PBZ $T_{\frac{1}{2}}$	Second estimate	16	0·6919	0·5555	0·7825*		
2 ..	Steady-state plasma concentration of phenylbutazone (μg./ml.)	Log_{10} PBZ $T_{\frac{1}{2}}$	19	0·0080	1·5952	0·5802	2·9373	<0·01
3 ..	Mid-parent value (with no adjustment) of $\log_{10}$ PBZ $T_{\frac{1}{2}}$	Mean offspring value (with no adjustment) of $\log_{10}$ PBZ $T_{\frac{1}{2}}$	24	0·6636	0·6105	0·4701	2·4984	<0·05
4 ..	Husband value (with no adjustment) of $\log_{10}$ PBZ $T_{\frac{1}{2}}$	Wife value (with no adjustment) of $\log_{10}$ PBZ $T_{\frac{1}{2}}$	24	0·0632	1·7742	0·0751	0·3532	>0·10
5 ..	Height (in.)	Log_{10} PBZ $T_{\frac{1}{2}}$	142	0·0094	1·2873	0·3266	4·0880	<0·001
6 ..	Weight (lb.)	Log_{10} plasma PBZ $T_{\frac{1}{2}}$ adjusted to a height of 66 in.	142	−0·0001	1·9191	−0·0231	0·2738	>0·10
7 ..	Age (years)	,, ,, ,,	142	−0·0001	1·9097	−0·0153	0·1809	>0·10
8 ..	Log_{10} plasma PBZ concentration at zero time	,, ,, ,,	142	−0·1687	2·1836	−0·1542	1·8468	>0·05
9 ..	Husband value of $\log_{10}$ plasma PBZ $T_{\frac{1}{2}}$ adjusted to a height of 66 in.	Wife value of $\log_{10}$ plasma PBZ $T_{\frac{1}{2}}$ adjusted to a height of 66 in.	24	0·1110	1·7075	0·1271	0·6011	>0·10
10 ..	Mid-parent value of $\log_{10}$ plasma PBZ $T_{\frac{1}{2}}$ adjusted to a height of 66 in.	Mean offspring value of $\log_{10}$ plasma PBZ $T_{\frac{1}{2}}$ adjusted to a height of 66 in.	24	0·6529	0·6351	0·5588	3·1605	<0·01

$T_{\frac{1}{2}}$ = Half-life. PBZ = Phenylbutazone. Other abbreviations as in Table I. *The approximate 95% confidence limits are: 0·445 and 0·925.; intraclass correlation 0·89.

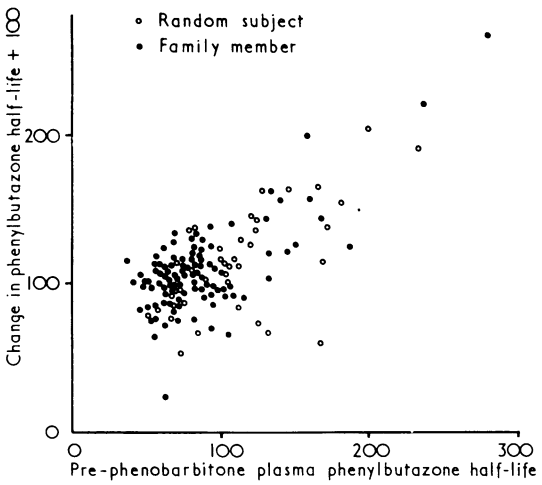

FIG. 3.—Relationship between the change in the plasma phenylbutazone half-life produced by phenobarbitone (y) and the pre-phenobarbitone value (x).

greatest shortening of half-life under the influence of phenobarbitone, and vice versa (Fig. 3).

The mean value of $\log_{10}$ plasma phenylbutazone half-lives was significantly reduced by phenobarbitone (pre-phenobarbitone mean 1·9475 ± S.E. 0·0132, post-phenobarbitone mean 1·9080 ± S.E. 0·0120; t = 2·28, degrees of freedom 282, $P<0·05$), and the variance was reduced but not significantly so (F = 1·21; $P>0·05$).

Plasma Phenylbutazone Half-life after Phenobarbitone

This value was about normally distributed in the $\log_{10}$ transformation and was found to be repeatable (Table II, line 1) and to correlate with steady-state phenylbutazone concentration (Table II, line 2).

No significant correlation was found between husband value and wife value (Table II, line 4), but there was a significant regression of mean offspring value on mid-parent value (Table II, line 3).

Some of the variability in the half-lives seemed to be due to variations in body build. There was a significant regression of half-life on height (Fig. 4; Table II, line 5). The half-lives were therefore adjusted to a standard height of 66 in. (167·6 cm.) using the calculated regression coefficient. After this adjustment was made the value was again about normally distributed (Fig. 5) and there was no significant regression of half-life on weight (Table II, line 6), age (Table II, line 7), or $\log_{10}$ plasma phenylbutazone concentration at zero time (Table II, line 8).

The half-life values adjusted for height showed no significant sex difference. The mean for 80 males was 1·8997 ± S.E. 0·0158 and for 62 females 1·9137 ± S.E. 0·0163 (t=0·6087). Within the group of parents there were no sex differences; nor were there any sex differences within the group of random subjects (Table III).

TABLE III.—*$\log_{10}$ Post-phenobarbitone Plasma Phenylbutazone Half-lives Adjusted to a Standard Height of 66 in. (167·6 cm.)*

	Male Parents	Female Parents	Male Random Subjects	Female Random Subjects
No.	25	24	23	18
Mean (m)	1·8812	1·9153	1·9535	1·9705
Variance	0·0194	0·0140	0·0213	0·0152
Standard deviation	0·1393	0·1182	0·1458	0·1231
Standard error of the mean (m)	0·0279	0·0241	0·0304	0·0290

One-way analysis of variance: $F=2·01$; degrees of freedom 3 and 86; $P>0·05$

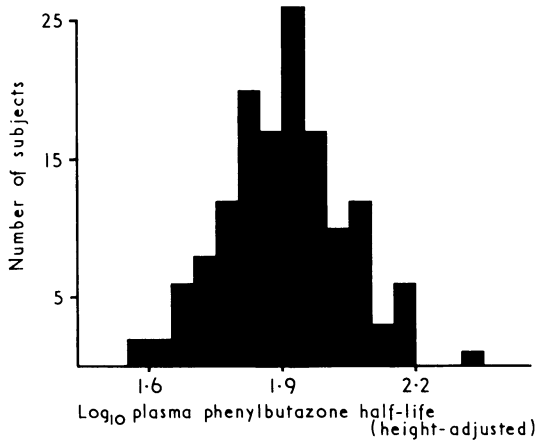

FIG. 5.—Frequency distribution of $\log_{10}$ post-phenobarbitone plasma phenylbutazone half-lives adjusted to a standard height.

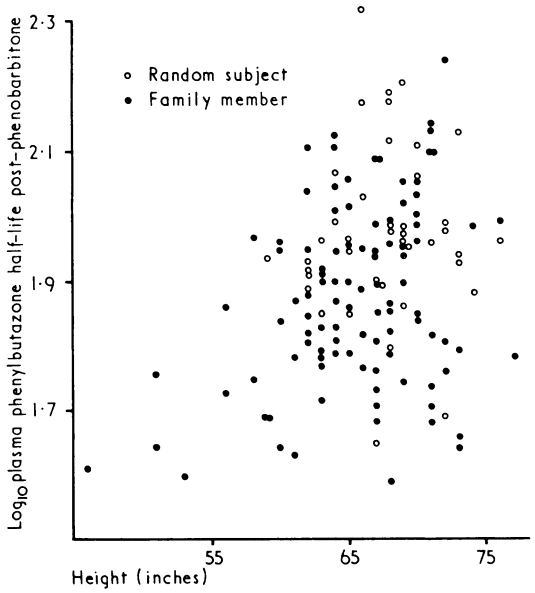

FIG. 4.—Relationship between $\log_{10}$ post-phenobarbitone plasma phenylbutazone half-lives and height.

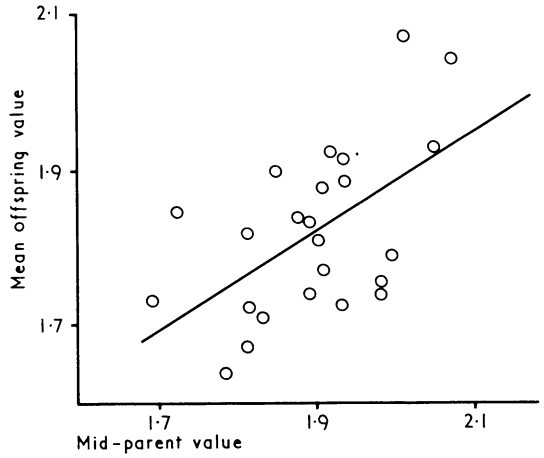

FIG. 6.—Regression of mean offspring $\log_{10}$ post-phenobarbitone plasma phenylbutazone half-lives on mid-parent values. These results have been adjusted to a standard height.

When parents were compared with random subjects the mean of 49 parents was 1·8979 ± S.E. 0·0184 and for 41 random subjects 1·9609 ± S.E. 0·0211. For this comparison of means $t=2·26$ and $P<0·05$. This difference remains unexplained. When parents were compared with offspring the mean of 49 parents was 1·8979 ± S.E. 0·0184 and of 52 offspring 1·8698 ± S.E. 0·0181. Since there is a correlation, a special value of t needs to be derived. This has been computed as 1·23 with about 25 degrees of freedom, indicating no significant difference between parents and offspring.

When the height-adjusted values of half-lives were used for computation there was still no correlation between husband values and wife values (Table II, line 9). The regression of mean offspring values on mid-parent values retained a very similar slope, but the scatter of points about the regression line was reduced as a result of the height adjustment (Table II, line 10; Fig. 6).

Thus the estimate $\frac{V_A}{V_P}$ —that is, the "heritability"—for phenylbutazone metabolism in man (as determined by means of single dose plasma half-life) is 0·65 ± standard error of 0·21 (approximately).

Discussion

Phenobarbitone and Plasma Phenylbutazone Half-life

Our results show that phenobarbitone influences plasma phenylbutazone half-life. The half-lives were shortened, particularly in persons who had excessively long half-lives before the phenobarbitone was administered. Hence the frequency distribution histogram of post-phenobarbitone half-lives does not possess the tail towards the high values shown by the pre-phenobarbitone distribution curve. An important consequence of this bringing the data to normal is to uncover the heritability. Probably if one takes individuals at random and examines their capacity to metabolize a drug which is biotransformed by microsomal enzymes such individuals will be in varying states of induction and repression, which has the effect of enlarging the environmental component of variance and so makes it more difficult to show genetic mechanisms.

Inducers such as phenobarbitone are known to enhance metabolism by microsomal enzymes. In some instances—for example, with antipyrine—this has been proved by finding an increased production of metabolite after phenobarbitone administration (Cucinell *et al.*, 1965). Nevertheless, phenobarbitone might affect other processes. Absorption of bishydroxycoumarin has been shown by Aggeler and O'Reilly (1969) to be impaired by heptabarbitone administration. Absorption, distribution, plasma-protein binding, tissue binding, biotransformation, and excretion of phenylbutazone could theoretically all be influenced by phenobarbitone administration. There is no evidence concerning most of these possibilities. Another explanation is provided by the studies of Cho *et al.* (1970) and Davies (1970), which suggest that phenylbutazone has an inhibitory effect on microsomal enzyme systems which can be annulled by phenobarbitone.

Validity of Single-dose Half-life

The validity of a single-dose half-life as a reliable index of an individual's metabolism of a drug has been based in the present work on two criteria: (1) repeatability and (2) correlation with steady-state plasma concentration.

Falconer (1960) expressed the repeatability of a measurement in a population as:

$$\frac{V_G + V_{Eg}}{V_P}$$

where V_{Eg} refers to environmental variance contributing to the between-individual component and arising from permanent or non-localized circumstances. "The repeatability, therefore, expresses the proportion of the variance of single measurements that is due to permanent or non-localized differences between individuals both genetic and environmental" (Falconer, 1960). Phenobarbitone increases the proportion of V_P which is due to $(V_G + V_{Eg})$. The post-phenobarbitone half-life is not as constant in an individual as, for example, his height, but it is constant enough to use as a tool to investigate the contribution made to the observed phenotypic variance V_P by genetic factors.

Under steady-state conditions the amount of absorbed drug should be equal to the amount eliminated. The plasma concentration is kept almost constant in equilibrium with the body tissues. The steady-state plasma concentration is generally regarded as a reliable pharmacokinetic expression of the capacity of an individual to metabolize a drug by enzymic biotransformation. The higher the plasma concentration level the less active the metabolism, and vice versa.

After single dose administration both absorption and elimination are occurring to varying extents simultaneously. In the present work plasma sampling was begun 24 hours after phenylbutazone ingestion. This allowed absorption and distribution to be completed so that metabolism and excretion would be responsible for the fall in plasma concentrations. Significant correlation with steady-state plasma concentration indicates that the post-phenobarbitone plasma phenylbutazone half-life can be regarded as a reliable index of the metabolism of the drug. The pre-phenobarbitone values do not correlate with the plasma concentration values and so cannot be viewed with the same confidence.

Assessment of Heritability in Twins

Vesell and Page (1968) assessed the influence of heredity on plasma phenylbutazone half-life after a single oral dose, by studying seven pairs of identical and seven pairs of fraternal twins. Their data have been subjected to computation according to the method of Falconer (1960), namely:

$$2(r_I - r_F) = \frac{V_A + 1\frac{1}{2} V_D}{V_P}$$

where r_I = intraclass correlation of identical twins and r_F = intraclass correlation of fraternal twins.

When the plasma phenylbutazone half-lives are in the $\log_{10}$ form the value of $\frac{V_A + 1\frac{1}{2} V_D}{V_P}$ is 0·88

The standard error of the difference between two correlation coefficients is large; and, furthermore, twin data in man do not enable V_A and V_D to be measured separately.

In using twin studies the assumption is that environmental influences within identical twinships are similar to those within fraternal twinships, and this assumption may in certain circumstances be untrue. Twin studies are valuable as a means of estimating the magnitude of V_G in relation to V_P, but do not indicate the nature of hereditary transmission. For example, the twin experiment of Bönicke and Lisboa (1957) does not show that isoniazid metabolism is a polymorphic character governed by alleles at a single locus. Similarly, the twin study of Vesell and Page (1968) does not show that plasma phenylbutazone half-life in man is a polygenic character.

Phenylbutazone Metabolism and Height

Analysis of height data in the families studied in the present work has shown, after suitable adjustment for age and sex, that:

$\frac{V_A}{V_P} = 0·62$ (Galton's data of 1889 give a figure of about 0·66)

The families studied in the present work yield $\frac{V_A}{V_P} = 0.65$ for post-phenobarbitone phenylbutazone half-life corrected for height. These results are clearly of much the same order. The same genes do not control the two characters, since the post-phenobarbitone phenylbutazone half-life data have been adjusted to a standard height.

Therapeutic Implications

Some drugs are known to show a correlation between plasma level and (1) therapeutic effect and (2) occurrence of toxic (or adverse) effects. Bruck *et al.* (1954) showed that various toxic effects were more common in patients receiving phenylbutazone whose blood levels exceeded 100 µg./ml. than in those with concentrations below this level. On the other hand, subjective improvement in rheumatoid arthritics was more frequent above blood phenylbutazone concentrations of 50 µg./ml. than below this level. The variability in phenylbutazone half-life is therefore relevant in regard to the consequences of phenylbutazone therapy. It is also relevant that for a pharmacological phenomenon in a population of patients, V_P may be increased by additions to V_E owing, for example, to disease, differing modes of administration, etc. On the other hand, V_G cannot be diminished. Thus possibly in the future attention to the variability between persons may result in the development of improved therapeutics.

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Autonomic Control of Insulin Secretion and the Treatment of Heart Failure

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Summary: To investigate the role of the autonomic nervous system in controlling insulin secretion 13 normal subjects and 5 patients with heart failure underwent insulin secretion tests. Alpha-adrenergic stimulation and beta-receptor blockade significantly depressed the secretion of insulin in response to intravenous tolbutamide in normal subjects, while both alpha-blockade and beta-stimulation significantly increased the insulin secretion response in both normal subjects and patients in heart failure. Parasympathetic stimulation and blockade had no significant effect on the insulin secretion response. These findings suggest that drugs that block the alpha-adrenergic receptors or stimulate the beta-adrenergic receptors by their ability to counteract the insulin suppression resulting from increased sympathetic nervous activity may play a vital metabolic part in the deranged metabolism of the failing heart in addition to their direct haemodynamic benefits.

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Introduction

The normal insulin secretion response to glucose and tolbutamide is suppressed in patients with severe power failure of the heart, whether this is due to cardiogenic shock after myocardial infarction (Allison *et al.*, 1969; Taylor *et al.*, 1969), severe congestive heart failure (Sharma *et al.*, 1970), or pumping failure after open-heart surgery (Majid *et al.*, 1970). Evidence has suggested that one of the major factors responsible for this suppression of insulin secretion was the greatly increased sympathetic stimulation found in such patients (Taylor *et al.*, 1969; Majid *et al.*, 1970; Sharma *et al.*, 1970). The present investigation was therefore directed to examining the effect of pharmacological stimulation and blockade of the sympathetic and parasympathetic receptors on insulin release from the pancreas of normal subjects and patients in severe heart failure.

Methods

Thirteen volunteer normal male subjects, with a mean age of 35 (range 20-54) years, and five patients, three men and two women, aged 46, 50, and 58, and 32 and 43 years, respectively, in severe heart failure were studied. The purpose of the study was explained in detail to all the subjects and their