Table 1. Experimentally determined values of the filtration coefficient, L_p, for the mosaic and the control membranes. The fraction of active membrane surface area occupied by cation exchanger, γ_e, is indicated. Values in parentheses are means of values listed above them.

Membrane	γ_e	$\Delta p \times 10^{-6}$ (dyne/cm²)	$L_p \times 10^{13}$ (cm³/dyne • sec)
	Anion exchange controls		
A3	0	0.80	4.7
A4	0	.62	4.9
		.64	4.8
			(4.8)
	Cation exchange controls		
C3	1	1.00	3.5
		0.50	3.5
		1.00	3.3
		0.72	3.3
C4	1	1.00	3.0
			(3.3)
	Mosaic membranes		
M6	0.51	1.00	3.3
		1.00	3.6*
		0.54	3.0
M7	0.48	1.00	3.0
		0.80	2.5
			(3.1)

* One experimental run with 0.14*M* KCl.

counted for only 1 to 2 percent of the overall flux.

The results given in Table 2 indicate that the reflection coefficients of the mosaic membranes are all negative. The proximity of some of the reflection coefficients to -1 is fortuitous since this value, unlike $+1$, has no special significance.

It can be shown, on the basis of Onsager's reciprocal relations, that membranes capable of negative osmosis may in principle be used for "piezo-dialysis," that is, extrusion through the membrane of a salt solution which is more concentrated than that on the high-pressure side. This process could possibly have important applications in the field of desalination, but its practicability has yet to be demonstrated. Charge-mosaic membranes may be of use in applications requiring high electrolyte permeability in an otherwise relatively impermeable structure.

Table 2. Experimentally determined values of the KCl permeability, ω, and reflection coefficient, σ, for the mosaic and control membranes. The fraction of active membrane surface area occupied by cation exchanger, γ_e, is indicated.

Membrane	γ_e	$\omega \times 10^{15}$ (mole/dyne • sec)	σ
	Anion exchange controls		
A1	0	0.07	+ 0.43
A2	0	.05	+ .46
		.10	+ .42
	Cation exchange controls		
C1	1	.10	+ .96
C2	1	.09	+ .86
		.10	+ .88
		.13	+ .84
	Mosaic membranes		
M1	0.52	5.6	− 1.15
M2	.51	4.6	− 0.96
M3	.51	5.2	− 1.24
M4	.51	5.4	− 1.13
		4.8	− 1.04
M5	.52	5.2	− 1.07

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9. Volume flow, J_v, and salt flow, J_s, are considered positive if they take place from side I to side II of the membrane, when $\Delta p = p^{I} - p^{II}$ and $\Delta\pi = \pi^{I} - \pi^{II}$.
10. The KCl permeability obtained directly from the experiments is ω^*, defined by

$$\omega^* = \left(\frac{J_s}{\Delta\pi}\right)_{\Delta p = 0,\ I = 0}$$

Since the mean salt concentration changes only slightly during an experimental run, ω^* is assumed constant and its value calculated (with a correction for volume flow) from the relation

$$\omega^* = \frac{V}{4ARTt} \ln\left(\frac{\Delta\pi_{initial}}{\Delta\pi_{final}}\right)$$

where A represents the active membrane area, t the time of the experiment, T the temperature, R the gas constant, and V the volume of one compartment. The parameter ω is related to ω^* by the expression

$$\omega = \omega^* + c_s L_p \sigma (1 - \sigma)$$

where c_s is the logarithmic mean of the concentrations in the two compartments. The two salt permeabilities differed by no more than 2 percent in any of the experiments reported here.
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Genetic Control of Drug Levels in Man: Antipyrine

Abstract. *Antipyrine was administered to identical or monozygotic twins and to fraternal or dizygotic twins. Individuals with identical genotypes (monozygotic twins) exhibited significantly less variability in antipyrine half-life than did genetically different individuals (dizygotic twins). Therefore variations in antipyrine metabolism appear to be determined genetically rather than environmentally. In the 36 twins tested, antipyrine half-lives varied between 5.1 and 16.7 hours. No significant correlation occurred between half-lives for phenylbutazone and antipyrine in the 28 twins who received both drugs.*

Large differences among individuals in the half-lives of phenylbutazone (*1*) and dicumarol (*2*) have been reported, but the basis for this variability remains obscure. Variability in the metabolism of antipyrine has been described in rats and in man (*4*).

This study extends previous observations of the half-life of phenylbutazone in human twins (*5*). Large variations in normal individuals not receiving other drugs depend on genetic rather than environmental factors (*5*). Since phenylbutazone is bound almost entirely to albumin (*1*), the results could not exclude individual differences in binding to albumin or in catabolism of albumin (*5*). Antipyrine was selected as the second drug because structurally it resembles phenylbutazone, both being phenylpyrazolon derivatives, but it is bound only 10 percent by albumin (*6*). Since renal excretion of antipyrine is negligible (*4*), variability in half-life suggests difference in metabolism—that is, in levels of the hepatic microsomal enzyme that hydroxylates antipyrine (*4*).

The subjects were 18 pairs of volunteer twins from the Washington, D.C., area; determined by blood grouping, nine twinships were identical and nine were fraternal. The subjects included 14 pairs who participated in an earlier study of phenylbutazone (*5*). All 36 volunteers were Caucasian, over 21 years of age, and in good health; they had not received drugs for several weeks before administration of antipyrine. The individual identical twins of six of the nine pairs studied lived in different households, so that in this respect similarity of the external environment seems an unlikely explanation for the results in identical twins.

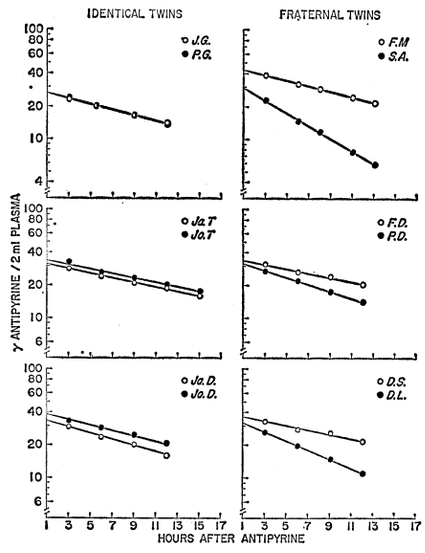

Fig. 1. Decline of antipyrine in the plasma of three sets of identical twins (left) and three sets of fraternal twins (right). The log of the antipyrine concentration in 2 ml of plasma is shown at intervals after a single oral dose (18 mg/kg).

Table 1. Half-life of antipyrine in plasma. The difference between monozygotic and dizygotic twins in intrapair variance is significant: $P < .001$ ($F = 64.5$, $N_1 = N_2 = 9$).

Twin	Age, sex	Half-life (hr)
	Identical twins	
JG	22,M	11.5
PG	22,M	11.5
DH	26,F	11.0
DW	26,F	11.0
JaD	29,M	11.0
JoD	29,M	12.0
SD	34,F	11.1
ML	34,F	11.5
DT	43,F	10.3
UW	43,F	9.6
JaT	44,M	14.9
JoT	44,M	14.9
GeL	45,M	12.3
GuL	45,M	12.8
HeM	48,M	11.3
HoM	48,M	11.3
CJ	56,F	6.9
FJ	56,F	7.1
	Fraternal twins	
AM	21,F	15.1
SM	21,M	6.3
LD	21,F	8.2
LW	21,F	6.9
JaH	24,F	12.0
JeH	24,F	6.0
EK	31,F	7.7
RK	31,M	7.3
SA	33,F	5.1
FM	33,F	12.5
DL	36,F	7.2
DS	36,F	15.0
NM	39,F	16.7
JR	39,F	13.4
LL	44,F	12.0
LR	44,F	16.7
FD	48,M	14.7
PD	48,M	9.3

Each twin received at 0830 hours a single oral dose of antipyrine (18 mg/kg); at intervals of 3, 6, 9, and 12 hours thereafter blood samples were drawn in tubes containing oxalate, and the plasma was assayed for antipyrine by the method of Brodie *et al.* (*7*). After 12 hours the levels in blood in certain twins were so low that measurement was inaccurate.

Figure 1 shows the decay of antipyrine in plasma from three sets of identical and three sets of fraternal twins. Table 1 gives the half-lives determined from such curves for each subject; the lines were fitted by eye. Threefold variations in antipyrine half-life occurred in these 36 subjects; the range was from 16.7 to 5.1 hours (Table 1). Antipyrine half-life appears to be a stable trait; in two individuals given a second dose 6 weeks after the first, the half-lives were unchanged.

The contribution of heredity was calculated from a formula in which the difference between the variance within pairs of fraternal twins and the variance within pairs of identical twins is divided by the variance within pairs of fraternal twins (*8*). The value of 0.98 indicates that control of antipyrine variability in normal humans not receiving other drugs depends on hereditary rather than environmental factors; the formula permits a range of values from 0 (suggesting negligible contribution by heredity) to 1 (indicating strong hereditary influence). Variance within pairs was calculated from a formula in which the sum of the squares of the difference between twins is divided by twice the number of pairs of twins (*8*).

The intrapair correlation coefficient was 1.0 for identical and 0 for fraternal twins. Differences between fraternal twins in the half-life of antipyrine varied from 0.4 hours in E.K. and R.K. (values in the range of those observed in identical twins) to 8.8 hours in A.M. and S.M. This result probably depends on the degree of genetic similarity between the parents of each pair of twins.

The antipyrine half-life in the 36 subjects was 10.9 ± 0.5 hours (mean $\pm$ S.E.); a value of 10 hours appears in the literature (*3, 4*). The half-lives in the 22 female and 14 male subjects were 10.6 ± 0.7 and 11.5 ± 0.7 hours (means $\pm$ S.E.), respectively. Similarity of half-lives for males and females makes unlikely any strong contribution by Y-linked genes to the control of antipyrine half-life.

For the 28 individuals receiving both antipyrine and phenylbutazone, the possibility of correlation in their rates of metabolism was studied, particularly in view of the drugs' close resemblance in structure. No correlation between half-lives of antipyrine and phenylbutazone in an individual was found by Bartlett's method (*9*). This lack of correlation suggests that antipyrine and phenylbutazone are metabolized by two functionally distinct enzymes, a conclusion supported by differences between the drugs in the chemical sites at which hydroxylation occurs (*1, 4*). Knowledge of an individual's genetically dependent half-life might be utilized to improve the therapeutic effectiveness and to avoid the toxic side effects of many drugs.

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Retrograde Amnesia Produced by Hippocampal Spreading Depression

Abstract. *Injection of potassium chloride into the hippocampus produces a disruption of electrical activity; a concomitant of this disruption is a deficit in retention of conditioned suppression learned 24 hours before injection.*

A marked decrease in the amplitude of the electrical activity of the hippocampus is seen after injection of puromycin (*1*). Puromycin is a potent inhibitor of protein synthesis and produces retrograde amnesia (*2*). The