PLASMA ENZYME ACTIVITIES IN INBRED MICE[1]

JOHN M. YUHAS, CHARLES R. ANGEL, DORSEY T. MAHIN, RICHARD D. FARRIS, KENT T. WOODWARD, AND JOHN B. STORER

The Jackson Laboratory, Bar Harbor, Maine, 04609, and the Division of Nuclear Medicine, Walter Reed Army Institute of Research, Washington, D.C. 20012

Received May 31, 1967

WITH the exception of those enzymes concerned directly with coagulation, plasma enzymes do not play a major functional role, but are released into the blood as products of cellular degradation (WHITE, HANDLER, and SMITH 1964). Elevations in plasma enzyme activity levels are well recognized in certain diseased states associated with cellular damage or destruction. In the normal, or nondiseased state, however, plasma activity levels may be maintained by a variety of influences. Differences in the activity levels of plasma enzymes may be attributed to greater or lesser concentrations, alterations in the activity of the enzyme molecules *per se*, or differences in the relative concentration or quality of enzyme inhibitors. The functional activity of a plasma enzyme is defined, therefore, both by its qualitative structure and quantitative concentration relative to the concentration and quality of inhibitors.

Variation in normal activity levels may be related to the genetic background of an animal in at least two ways: primary and secondary relationships. Genetic variations may express themselves through alterations in the molecular structure of the enzyme, and would, therefore, constitute primary relationships between the genotype and the observed activity level. On the other hand, the genotype may regulate plasma enzyme activities by secondary mechanisms, as for example through differences in the rates of synthesis, destruction, or cellular degradation. An example of genetic control of the rate of enzyme destruction in the liver has recently been provided by RECHCIGL and HESTON (1967).

Clearly, few methods now exist which permit exact determination of genetic control over these possible influences upon plasma enzyme activity levels. Strains of mice are available, however, whose breeding history and genetic inter-relationships are known in considerable detail. A large scale survey was therefore designed to measure plasma enzyme levels of many such strains of presumably normal mice, in order to reveal possible relationships between enzyme activity and genetic control. After establishment of genetic control of functional differences, appropriate investigations may proceed as to the mechanism of these differences.

The four enzymes tested in these studies, cholinesterase, alkaline phosphatase, acid phosphatase, and glutamic-oxaloacetic transaminase, have all been shown to possess quantifiable genetic control. Heritabilities ranged from 0.18 to 0.70. The distribution of means of the 23 strains tested has allowed formulation of pre-

[1] This study was supported in part by the Department of the Army under Contract DA-49-193-MD-2289.

liminary estimates of the number of controlling genetic elements for three of the four enzymes.

MATERIALS AND METHODS

Twenty-three inbred strains of mice were employed in these studies. All were born, raised, and maintained in the same mouse breeding facility (The Jackson Laboratory). At weaning they were transferred from individual breeding rooms to a single room where they remained until the time of assay. Automated analytical equipment was transported (Walter Reed Army Institute of Research) and assembled in an adjacent room and utilized to perform assays as soon as possible after the mice were killed.

Mice were provided with water and Old Guilford laboratory chow *ad libitum*, and were housed in groups of 4 to 6 per cage with the exception of the males of the AKR/J, BALB/cJ, RF/J, and SJL/J strains. These mice fight vigorously and therefore were housed individually. All mice were 3½ to 4½ months old at the time assay.

Under light ether anesthesia the femoral artery and vein were dissected free and transected. The freely flowing blood was aspirated into heparinized pipettes. It was then placed into 0.4 ml plastic cones and centrifuged sufficiently to separate the plasma from the formed elements. Plasma aliquots of 0.2 ml were placed in sample cups and diluted with distilled water to a final volume of 0.5 ml. In many cases, two such samples were obtained from a single mouse. One sample provided enough plasma for cholinesterase and one of the transaminases, or for both phosphatase determinations. When only one sample was obtained from an individual mouse, samples within the strain and sex were equally divided and directed to determination of one group of enzymes or the other. Technical difficulties prevented the analysis of all 23 strains for both transaminases. The data given below show glutamic oxaloacetic transaminase levels for 15 strains and glutamic pyruvic transaminase levels for eight strains. Owing to the small number of strains used for the latter, no analysis was attempted, and the data are appended at the end of RESULTS (Table 10).

Assay for plasma enzyme activity levels was performed with automatic wet chemical analysis equipment. The analytical principles for each of the five assay methods will be described briefly. (a) *Cholinesterase* (CHE): Assay is based upon the release of free sulfhydryl from acetylthiocholine. Enzymatic activity is expressed as micromoles of free sulfhydryl released per minute per 100 ml of plasma (GARRY and ROUTH 1965; LEVINE, SCHEIDT, and NELSON 1965). (b) *Alkaline phosphatase* (ALK-P): Assay is based on hydrolysis of the substrate, phenyldisodium phosphate, at pH 10.0. Phenolic residues of this hydrolysis are condensed with 4-amino antipyrine, oxidized with ferricyanide, and measured colorimetrically. Activity is expressed in King Armstrong units per 100 ml of plasma (MARSH, FINGERHUT, and KIRSCH 1959; Technicon Methodology, 1965a). (c) *Acid phosphatase* (ACID-P): Assay is identical to (b) except that all reactions are carried out at pH 5.0. Activity is again expressed in King Armstrong units per 100 ml of plasma (Marsh *et al.* 1959; Technicon Methodology, 1965a). (d) *Glutamic oxaloacetic (*or *pyruvic) transaminase* (GOT or GPT): Assay is based on the decrease in fluorescence produced by the interaction of oxaloacetic (or pyruvic) acid with diphosphopyridine nucleotide. Activity is expressed in Karmen units per 100 ml of plasma (Technicon Methodology, 1965b).

All assays were controlled by measurement of suitable standards and control sera. Standards were measured daily, and the calibration curves plotted. Assays were compared to their simultaneous standards in order to minimize the errors due to variations between runs and batches of reagents.

Enzyme activities were measured on approximately 1000 individual mice within a five-day period to minimize environmental and age variations. Approximately 2700 enzyme assays were performed during this period. Individual values were recorded for enzyme activity levels in each mouse.

Standard statistical methods were employed in the analysis of the data (SNEDECOR 1956).

Genetic determination, or heritability in the broad sense was calculated according to methods described by FALCONER (1960), according to the relation:

$$h^2 = (V_B - V_W)/[V_B + (2K - 1)V_W]$$

where V_B = variance between strains,
V_W = variance within strains, and
K = harmonic mean of number of mice per strain. The values represent estimates of total hereditary effects rather than only the additively genetic effects. The derivation of this formula has been given by STORER (1966).

RESULTS

Strain differences and heritabilities: The results of the plasma cholinesterase (CHE) assay for 23 inbred strains are presented in Table 1. These data have been reported earlier in abbreviated form (ANGEL *et al.* 1967), and are included for further analysis and comparison with the other enzymes. Mean activities cover an approximate twofold range in females and a threefold range in males. The AKR/J and the AU/SsJ strains have the lowest and highest activities, respectively, in both sexes. Analysis of variance for strain, sex, and (strain × sex) effects (Table 2) confirmed significance in all three cases. Male and female strain means are highly correlated ($r = +0.799$; $P < .01$). Within-strain variance, as estimated by

TABLE 1

Plasma cholinesterase activity in 23 inbred mouse strains

Strain	Females		Males	
	N	Mean* ± SE	N	Mean* ± SE
A/J	10	37.2 ± 1.20	13	28.7 ± 1.08
AKR/J	16	29.8 ± 0.57	18	16.1 ± 0.71
AU/SsJ	6	67.7 ± 2.97	5	47.2 ± 2.92
BALB/cJ	10	33.1 ± 1.08	12	26.5 ± 0.93
CBA/J	12	41.8 ± 0.87	16	28.1 ± 0.82
CE/J	9	37.1 ± 0.94	17	27.9 ± 1.45
C57BL/6J	11	34.5 ± 1.06	10	30.3 ± 0.78
C57BR/cdJ	10	31.9 ± 0.82	18	26.2 ± 0.49
C57L/J	11	33.8 ± 0.42	15	26.6 ± 0.49
C58/J	9	37.8 ± 1.13	16	29.5 ± 0.65
C3HeB/FeJ	15	33.3 ± 0.67	14	26.1 ± 0.50
DBA/1J	9	52.9 ± 1.71		....
DBA/2J	10	44.7 ± 0.84	10	29.8 ± 0.29
LP/J		....	7	20.7 ± 1.41
MA/J	23	45.6 ± 0.78	21	23.3 ± 0.25
PL/J	15	46.0 ± 1.20	16	30.9 ± 0.82
RF/J	12	31.0 ± 0.44	17	17.8 ± 0.30
RIII/J	8	42.8 ± 3.07	11	32.7 ± 1.18
SEC/1ReJ	10	42.6 ± 1.07	10	36.0 ± 1.03
SJL/J	12	34.0 ± 0.60	10	19.4 ± 0.88
SM/J	11	35.5 ± 0.55	13	25.2 ± 0.58
ST/bJ	11	35.6 ± 0.93	13	26.8 ± 0.48
129/J	11	39.1 ± 0.83	10	35.8 ± 0.81

* Enzyme activity expressed as micromoles of sulfhydryl released per minute per 100 ml of plasma.

TABLE 2

Statistical analysis of plasma cholinesterase activity in both sexes of 23 inbred mouse strains

Source	df	MS	F	P
Strain mean analysis of variance				
Strains	20	937.2	8.6	$<.01$
Sex	1	16,916.0	154.3	$<.01$
S × S	20	109.7	10.5	$<.01$
Error	485	10.5		
Male analysis of variance				
Strains	21	445.5	49.2	$<.01$
Error	270	9.1		
Female analysis of variance				
Strains	21	651.7	51.1	$<.01$
Error	229	12.8		
	Heritability (h^2)	Males = 0.67	Females = 0.70	

the error mean square, is slightly higher in the females. Estimated heritabilities are 0.70 for females and 0.67 for males. These values are in close agreement with the intraclass correlation of 0.82 obtained by WETSTONE, HONEYMAN, and MCCOMB (1965) for serum cholinesterase in human monozygotic twins.

Plasma glutamic oxaloacetic transaminase (GOT) activity levels for 15 inbred strains are shown in Table 3. Mean activities cover a threefold range in both males and females. The distribution of means is characterized by clustering at both extremes, and assignment of highest and lowest ranks is, therefore, arbitrary.

TABLE 3

Plasma glutamic oxaloacetic transaminase activity for males and females of 15 inbred mouse strains

Strain	Females		Males	
	N	Mean* ± SE	N	Mean* ± SE
AKR/J	10	108.2 ± 3.61	18	100.1 ± 2.90
CBA/J	11	109.6 ± 4.45	15	102.7 ± 4.77
CE/J	9	37.1 ± 2.47	14	34.2 ± 2.32
C57BL/6J	11	55.9 ± 3.11	10	56.4 ± 3.47
C57BR/cdJ	10	45.0 ± 2.56	18	44.8 ± 2.66
C57L/J	11	47.4 ± 4.27	14	33.4 ± 3.12
C58/J	10	48.3 ± 5.03	16	32.3 ± 3.78
MA/J	23	61.7 ± 3.63	23	57.3 ± 4.78
PL/J	15	99.5 ± 4.14	16	90.5 ± 3.42
RF/J	12	55.5 ± 2.37	17	51.6 ± 1.13
RIII/J	8	44.8 ± 2.45	11	36.9 ± 3.76
SEC/1ReJ	10	121.3 ± 4.04	10	104.8 ± 2.14
SJL/J	12	101.4 ± 4.18	13	75.6 ± 2.82
SM/J	10	74.9 ± 7.48	12	85.4 ± 7.37
129/J	11	66.0 ± 4.57	10	54.0 ± 4.10

* Activity is expressed in Karmen units per 100 ml of plasma.

TABLE 4

Statistical analysis of plasma glutamic oxaloacetic transaminase activity in males and females of 15 inbred mouse strains

Source	df	MS	F	P
Strain mean analysis of variance				
Strains	14	18,461.6	89.3	<.01
Sex	1	7,360.0	35.6	<.01
S × S	14	309.5	1.5	NS
Error	360	206.7		
Male analysis of variance				
Strains	14	10,182	48.9	<.01
Error	202	208		
Female analysis of variance				
Strains	14	8,589	41.9	<.01
Error	158	204.9		
	Heritability (h^2):	Males = 0.64	Females = 0.65	

TABLE 5

Plasma alkaline phosphatase activity in males and females of 23 inbred mouse strains

Strain	Females		Males	
	N	Mean* ± SE	N	Mean* ± SE
A/J	10	16.65 ± 0.47	12	13.67 ± 0.63
AKR/J	16	10.56 ± 0.33	20	9.55 ± 0.66
AU/SsJ	4	15.25 ± 2.05	4	12.13 ± 1.25
BALB/cJ	10	17.05 ± 1.28	13	15.42 ± 0.61
CBA/J	11	17.22 ± 0.76	16	13.88 ± 0.51
CE/J	7	6.63 ± 0.47	10	9.40 ± 0.70
C3HeB/FeJ	8	14.87 ± 1.18	18	10.53 ± 0.53
C57BL/6J	15	15.67 ± 0.41	11	15.90 ± 1.52
C57BR/cdJ	10	6.45 ± 0.29	19	5.45 ± 0.30
C57L/J	11	6.27 ± 0.27	16	5.41 ± 0.35
C58/J	8	11.63 ± 0.74	16	8.87 ± 0.48
DBA/1J	10	18.55 ± 0.86	10	15.55 ± 0.93
DBA/2J	10	16.65 ± 1.08	10	17.05 ± 0.76
LP/J	..	....	8	7.44 ± 0.50
MA/J	18	11.08 ± 0.74	24	11.83 ± 1.08
PL/J	15	12.10 ± 0.22	16	13.12 ± 0.45
RF/J	12	7.25 ± 0.84	15	7.07 ± 0.38
RIII/J	6	11.0 ± 2.04	11	9.32 ± 0.75
SEC/1ReJ	10	15.40 ± 0.73	9	16.33 ± 1.03
SJL/J	13	11.77 ± 0.51	13	8.69 ± 0.68
SM/J	12	14.16 ± 0.63	11	11.86 ± 0.92
ST/bJ	10	15.90 ± 0.67	12	15.83 ± 0.58
129/J	11	7.59 ± 0.49	10	7.10 ± 0.42

* Activity is expressed in King-Armstrong units per 100 ml of plasma.

Analysis of variance of the GOT data is given in Table 4. Significant strain and sex effects are demonstrated but their interaction could not be shown to be significant. Mean activities for males and females are highly correlated ($r = +0.953$; $P < .01$), with estimated heritabilities of 0.65 for females and 0.64 for males. Within-strain variance is approximately equal in the two sexes.

Plasma alkaline phosphatase (ALK-P) activities in both sexes of 23 inbred strains are shown in Table 5. Mean differences cover an approximate threefold range in both sexes. The C57L/J strain possesses the lowest mean activity in both sexes, while the DBA/1J and DBA/2J possess the highest mean activity for females and males, respectively. Statistical analyses of these data are shown in Table 6. Strain, sex, and their interaction exert significant effects on the ALK-P activity of the plasma. Male and female means are highly correlated ($r = +0.888$; $P < .01$). In females, within-strain variance is slightly greater, and estimated heritability is 0.35 compared to 0.49 for males.

Plasma acid phosphatase (ACID-P) activities in both sexes of 23 inbred strains are shown in Table 7. Distribution of means is relatively uniform, and no grouping of strains occurs at high or low values. Table 8 gives the variance analyses of ACID-P activity in males and females. Male and female means demonstrate a high degree of correlation ($r = +0.914$; $P < .01$). Statistically significant strain and sex effects are demonstrated, but their interaction is not significant. In females within-strain variance is lower and the estimated heritability is 0.30. In males, the estimated heritability is 0.18, the lowest value found in the entire study.

Enzyme correlations: Table 9 summarizes the correlation coefficients between enzymes based on the 15 strains which yielded data for all four enzymes. Simple as well as partial correlations have been calculated for each sex separately. In the simple correlations, ALK-P and GOT demonstrate a positive correlation in both sexes, while a significant negative correlation between CHE and ACID-P is seen only in the females.

TABLE 6

Statistical analyses for plasma alkaline phosphatase activities in males and females of 23 inbred mouse strains

Source	df	MS	F	P
Strain mean analysis of variance				
Strains	21	324.3	27.8	<.01
Sex	1	283.0	24.2	<.01
S × S	21	11.7	1.8	<.05
Error	489	6.7		
Male analysis of variance				
Strains	22	171.0	23.4	<.01
Error	281	7.3		
Female analysis of variance				
Strains	21	115.0	11.3	<.01
Error	215	10.2		
	Heritability (h^2):	Males = 0.50	Females = 0.35	

TABLE 7

Plasma acid phosphatase activity for males and females of 21 inbred mouse strains

Strain	Females		Males	
	N	Mean* ± SE	N	Mean* ± SE
A/J	10	5.10 ± 0.22	12	5.69 ± 0.33
AKR/J	16	4.88 ± 0.32	20	2.85 ± 0.48
BALB/cJ	10	6.90 ± 0.69	13	7.67 ± 0.61
CBA/J	11	6.27 ± 0.48	16	6.14 ± 0.76
CE/J	7	2.89 ± 0.55	10	3.04 ± 0.32
C3HeB/FeJ	8	4.69 ± 0.40	19	4.86 ± 0.60
C57BL/6J	15	6.50 ± 0.44	9	6.96 ± 1.53
C57BR/cdJ	10	5.63 ± 0.28	19	5.37 ± 0.22
C57L/J	11	4.84 ± 0.12	16	5.41 ± 0.35
C58/J	8	4.88 ± 0.49	16	5.63 ± 0.49
DBA/1J	10	6.53 ± 0.51	10	6.53 ± 0.65
DBA/2J	10	5.93 ± 0.44	10	5.63 ± 0.55
LP/J	..	....	8	4.49 ± 0.50
MA/J	15	3.68 ± 0.27	21	2.66 ± 0.43
PL/J	12	3.50 ± 0.21	15	3.28 ± 0.24
RF/J	15	6.00 ± 0.37	16	5.10 ± 0.31
RIII/J	6	2.56 ± 0.58	11	2.76 ± 0.49
SEC/1ReJ	10	4.43 ± 0.62	9	5.08 ± 0.74
SJL/J	13	5.08 ± 0.32	13	4.62 ± 0.39
SM/J	12	5.04 ± 0.42	11	4.43 ± 0.49
129/J	11	2.46 ± 0.23	10	3.38 ± 0.44

* Activity is expressed in King-Armstrong units per 100 ml of plasma.

The partial correlations provide an insight into the above-mentioned relations. The correlation between ALK-P and GOT is not affected in either sex by holding CHE constant ($r_{24.1}$), by holding ACID-P constant ($r_{24.3}$), or by holding their combined effects constant ($r_{24.13}$). This would seem to indicate that a specific

TABLE 8

Statistical analysis of plasma acid phosphatase activity in male and female mice of 21 inbred strains

Source	df	MS	F	P
Strain mean analysis of variance				
Strains	19	45.3	14.8	<.01
Sex	1	5.9	1.9	<.05
S × S	19	1.4	0.4	NS
Error	456	3.1		
Male analysis of variance				
Strains	20	27.2	6.8	<.01
Error	263	4.0		
Female analysis of variance				
Strains	19	17.8	10.0	<.01
Error	20	1.8		
	Heritability (h^2):	Males = 0.18	Females = 0.30	

TABLE 9

Correlation coefficients for pairs of enzymes based on 15 strains in which data was obtained for all four enzymes. CHE = 1; ALK-P = 2; ACID-P = 3; and GOT = 4

r†	Females	Males
12	+0.39	+0.33
12·3	+0.72**	+0.33
12·4	+0.34	+0.50
12·34	+0.68*	+0.50
13	—0.52*	+0.08
13·2	—0.78**	+0.02
13·4	—0.58*	+0.08
13·24	—0.77**	—0.04
14	+0.21	—0.10
14·2	—0.05	—0.41
14·3	+0.36	—0.10
14·23	—0.02	—0.41
23	+0.35	+0.18
23·1	+0.71**	+0.17
23·4	+0.31	+0.23
23·14	+0.67*	+0.22
24	+0.62*	+0.62*
24·1	+0.60*	+0.70**
24·3	+0.60*	+0.63*
24·13	+0.63*	+0.70**
34	+0.18	+0.01
34·1	+0.34	+0·01
34·2	—0.05	—0.14
34·12	—0.14	—0.16

* P<.05. ** P<.01.
†AB·C is the correlation between A and B with C held constant.

factor tends to raise the plasma activities of these two enzymes, and has little, if any, effect on the others.

The remainder of the partial correlations do not provide significance in any of the male comparisons, but do add significance to certain of the female data.

When the significant ($P < .05$) simple correlation between CHE and ACID-P ($r = -0.523$) is corrected to a constant ALK-P level ($r_{13.2}$), the correlation becomes more negative. This would seem to indicate that ALK-P is involved in the correlation between CHE and ACID-P. Partial correlations demonstrate that ALK-P is, in fact, significantly positively correlated with both CHE and ACID-P ($r_{12.34}$ and $r_{23.14}$, respectively), and therefore serves to reduce the negative correlation between CHE and ACID-P.

Genetic control of enzyme activity levels: The mean activities for the enzymes studied have been plotted in Figures 1 to 3. The data for each enzyme are grouped into a number of classes (25–29.9 units, 30.0–34.9 units, etc.) according to the total range observed (~10 groups per enzyme).

The mean activities for CHE (Figure 1) are distributed approximately normally, with the exception of the AU/SsJ strain. Aside from the fact that this strain

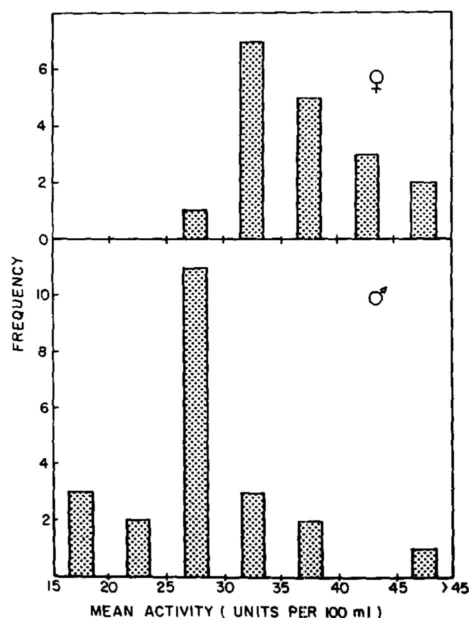

FIGURE 1.—Distribution of mean cholinesterase activity levels in the plasma of males and females of 23 inbred strains.

was brought to The Jackson Laboratory precisely for its independent origin (T. H. RODERICK, personal communication 1967) no explanation is obvious for this strain being far removed from the values obtained with the others. The possibility that an altered major allele is present in this strain demands further investigation.

Female ALK-P mean values distribute themselves into three major groups—high, intermediate, and low (Figure 2). The males do not show such a definitive grouping. Both the males and the females show similar GOT mean activity groupings, with the female distribution shifted toward the higher values (Figure 3). Two groupings are seen in the 15 strains: high and low. If the high and low mean activities are taken as defining the range, the two groups are separated by 26% of the range in males, and 27% of the range in females.

ACID-P mean activity values distribute themselves in a random manner and give no indication of a control mechanism. The low heritabilities preclude further analysis of the genetic control mechanism of this enzyme.

GENERAL DISCUSSION

The inbred strains of mice employed in these studies have been shown to possess large between strain variations in enzyme activity coupled with variable degrees of within-strain variation. The within-strain variance operates as a function of the enzyme and sex in question and therefore controls the estimated heritabilities (0.18 to 0.70). Since sex has an effect on the mean activity, it is not surprising that it also affects the within strain variance and correlations.

The distributions of mean activities provide an insight into the mechanism of genetic control (Figures 1 to 3). CHE (Figure 1) shows a wide range of activity

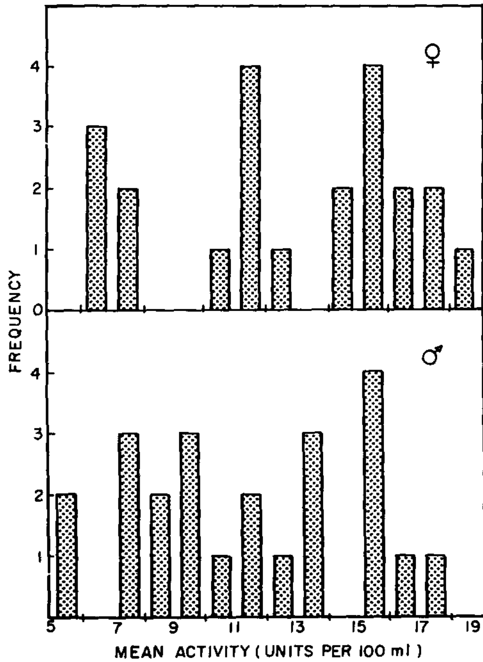

FIGURE 2.—Distribution of mean alkaline phosphatase activity levels in the plasma of males and females of 23 inbred strains.

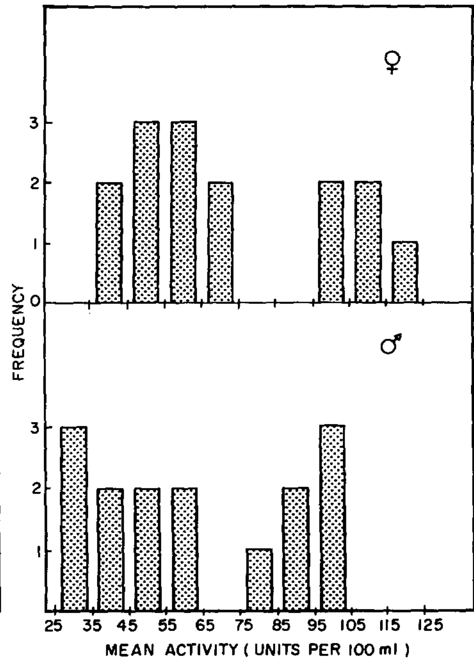

FIGURE 3.—Distribution of mean glutamic oxaloacetic transaminase activity levels in the plasma of males and females of 15 inbred strains.

levels and would appear to be subject to the effects of many loci. ALK-P, at least in the females, demonstrates a three level distribution, which would be compatible with an additive two locus system (Figure 2). GOT mean activities distribute themselves into two levels, high and low (Figure 3), in both males and females, and may represent alternate alleles at a single locus.

TABLE 10

Plasma glutamic pyruvic transaminase activity levels for males and females of eight inbred mouse strains

Strain	Females		Males	
	N	Mean* ± SE	N	Mean* ± SE
A/J	10	111.0 ± 2.96	7	121.4 ± 6.53
AU/SsJ	6	104.0 ± 8.26	..	....
BALB/cJ	10	90.8 ± 7.36	12	92.3 ± 2.91
C3HeB/FeJ	10	112.7 ± 4.15	14	128.1 ± 6.68
DBA/1J	9	99.8 ± 3.75	10	94.9 ± 3.63
DBA/2J	10	83.0 ± 2.38	10	101.4 ± 3.95
LP/J	..	....	7	93.6 ± 4.59
ST/bJ	..	....	10	107.9 ± 7.05

* Activity is expressed in Karmen units per 100 ml of plasma.

These preliminary estimates must be viewed as hypotheses subject to further testing rather than as conclusions. Each of the estimates has an internal inconsistency which must be resolved. The hypothesis that CHE is under the control of many loci is compatible with the data for all strains except the AU/SsJ. The correlation between ALK-P and GOT offers the possibility that the mean distributions are the product of a strain effect (viral damage to the liver) rather than a locus effect. The fact that ALK-P and GOT are both elevated in certain types of liver pathology (WHITE *et al.* 1964) seems to offer a mechanism of this strain effect. The advantage of the inconsistencies is that they are all subject to experimental testing.

We hope that the activity data presented in this paper provide a basis for the rational approach to the genetic control of plasma enzyme levels. Appropriate hybrids obtained from the strains given above will allow direct testing of genetic control of activity, at least with respect to those enzymes which appear to be under the control of a few major loci.

SUMMARY

Plasma activity levels of four enzymes (cholinesterase, alkaline phosphatase, acid phosphatase, and glutamic oxaloacetic transaminase) have been determined in males and females of 23 inbred mouse strains. All four enzymes have demonstrated a wide range of activity levels among these strains, but the within-strain variance is dependent on the enzyme analyzed. Cholinesterase and glutamic oxaloacetic transaminase have been shown to possess a high level of genetic determination (60 to 70%), while the two phosphatases range from 20 to 50%. A correlation has been demonstrated between the acitvity of alkaline phosphatase and that of glutamic oxaloacetic transaminase. This correlation is presumably due to factors controlling the amount of the enzyme in the plasma rather than an effect on the enzyme molecules themselves. The distributions of mean activities have been employed to give gross estimates of the underlying genetic control mechanisms.

LITERATURE CITED

ANGEL, C., D. T. MAHIN, R. D. FARRIS, K. T. WOODWARD, J. M. YUHAS, and J. B. STORER, 1967 Heritability of plasma cholinesterase in inbred mouse strains. Science **156**: 529–530.

FALCONER, D. S., 1960 *Introduction to Quantitative Genetics.* Ronald, New York.

GARRY, P. J., and J. I. ROUTH, 1965 A micro-method for serum cholinesterase. Clin. Chem. **11**: 91–96.

LEVINE, J. B., R. A. SCHEIDT, and V. A. NELSON, 1965 An automated microdetermination method for serum cholinesterase. In Technicon Symposium: *Automation in Analytical Chemistry*. Mediad Inc., New York.

MARSH, W. H., B. FINGERHUT, and E. KIRSCH, 1959 Adaptation of an alkaline phosphatase method for automatic colorimetric analysis. Clin. Chem. **5**: 119–126.

RECHCIGL, M., and W. E. HESTON, 1967 Genetic regulation of enzyme activity in mammalian system by the alteration of the rates of enzyme degradation. Biochem. Biophys. Res. Comm. **27**:119–124.

SNEDECOR, G. W., 1956 *Statistical Methods.* 5th edition. Iowa State College Press, Ames.

STORER, J. B., 1966 Longevity and gross pathology at death in 22 inbred mouse strains. J. Gerontol. **21:** 404–409.

Technicon Methodology, 1965a N-6A and N-7A. Technicon Instruments Corporation, Ardsley, New York.

Technicon Methodology, 1965b N-53P and N-54P. Technicon Instruments Corporation. Ardsley, New York.

WETSTONE, H. J., M. S. HONEYMAN, and R. B. MCCOMB, 1965 Genetic control of the quantitative activity of a serum enzyme in man. J. Am. Med. Assoc. **192:** 1007–1009.

WHITE, A., P. HANDLER, and E. SMITH, 1964 *Principles of Biochemistry.* 3rd edition. McGraw-Hill, New York.