Inheritance of a Cardiac Arterial Asymmetry in Mice

Abstract. *A pair of coronary arteries supplies the interventricular septum of the heart of* Mus musculus. *The members of this pair tend to be of unequal size, which permits distinction between specimens displaying left asymmetry and those showing right asymmetry. Three inbred strains (C57BL/10, DBA/1, and Balb/c) differ with regard to this asymmetry. However, variation exists within strains, which suggests that nongenetic factors also influence the development of the asymmetry. Right arterial asymmetry is dominant over left asymmetry.*

Anatomical and functional asymmetries are quite common, but, in most cases, it is not known whether they are of genetic or environmental origin. Handedness, a functional asymmetry, has probably been studied most often. That handedness depends in part on learning is rather obvious, but it is a matter of controversy whether it is also influenced by heredity; Collins (*1*) has concluded that it is not. Our report deals with a demonstrably heritable coronary arterial asymmetry in mice. We observed that strains of mice differed with respect to this anatomical asymmetry.

Mice have two arteries supplying the interventricular septum of the heart. One septal artery originates from the left main coronary artery or from a separate ostium in the left sinus of Valsalva, and the other originates from the right main coronary artery or from a separate ostium in the right sinus of Valsalva. The left septal artery lies dorsal to the pulmonary artery, courses with a left-to-right, posterior-to-anterior, and apical orientation for a short distance, and enters the septum to descend in an anterior-to-posterior and apical direction. The right septal artery also lies dorsal to the pulmonary artery and enters the septum in an anterior-to-posterior and apical direction. The larger (dominant) septal artery courses in the right side of the interventricular septum, close to the endocardium, with an anterior-to-posterior and apical orientation. The smaller septal artery arises from the opposite side and enters the basal portion of the septum (*2, 3*). In the majority of mice the inequality of the two septal arteries is striking—one artery is readily visible and the other is diminutive and readily overlooked. In some cases both septal arteries are relatively large but still unequal. We decided to establish whether the asymmetry was of genetic origin.

We used 454 mice belonging to three inbred strains, three groups of F_1 hybrids, and four groups of backcross animals (Table 1). Since offspring of reciprocal crosses did not differ data from reciprocal crosses are presented together. Data from males and females were pooled. The mice were killed with ether, and the anatomic patterns of their coronary arteries were demonstrated by plastic casts (*4*). The casts were examined under a dissecting microscope, and each specimen was assigned to one of the following four septal artery patterns.

1) Pattern L!: one large septal artery originating from the left main coronary artery, or from a separate adjacent ostium in the left sinus of Valsalva, with a diminutive septal artery originating from the right.

2) Pattern L: two septal arteries, the left larger than the right.

3) Pattern R: two septal arteries, the right larger than the left.

4) Pattern R!: one large septal artery originating from the right main coronary artery, or from a separate adjacent ostium in the right sinus of Valsalva, with a diminutive septal artery originating from the left.

The choice of these four arterial patterns was dictated by convenience, that is, specimens could be readily classified by visual inspection. Although we assigned specimens to one of four classes, we want to stress that the four patterns do not represent qualitatively distinct anatomic configurations. On the contrary, in our view they belong to a continuous series of all degrees of asymmetry. The series stretches from extreme left asymmetry or sinistrality (L!) to extreme right asymmetry or dextrality (R!), and contains forms of medium sinistrality (L), and dextrality (R). Two of the authors (J.L. and H.K.H.) classified the mice independently, using the same criteria of asymmetry. The classifications were then compared, and agreement as to class was reached in the small number of cases where specimens had been placed in different categories by the two judges.

Let us first compare the three inbred strains C57BL/10 [C], DBA/1 [D], and Balb/c [B]. The majority of C-mice displayed left asymmetry: 69.7 + 6.1 = 75.8 percent. C-mice occupied positions L! and L on the left-right continuum of arterial patterns. Because of this high frequency of left asymmetry in C-mice, we will call strain C a sinistral strain. Strain C differs from strains D and B, two dextral strains: 80.6 percent of D-mice and 96.8 percent of B-mice occupied the right side of the arterial trait

Table 1. Septal artery patterns in ten genotypes of mice.

Genotype	*N*	Septal artery pattern (%)			
		L!	L	R	R!
C57BL/10 [C]	33	69.7	6.1	3.0	21.2
DBA/1 [D]	31	19.4	0.0	16.1	64.5
Balb/c [B]	31	3.2	0.0	9.7	87.1
F_1 (C×D)	103	21.4	1.9	9.7	67.0
F_1 (C×B)	76	18.4	0.0	7.9	73.7
F_1 (D×B)	45	8.9	0.0	0.0	91.1
BX[(C×D)×C]	38	60.5	0.0	7.9	31.6
BX[(C×D)×D]	36	16.7	0.0	13.9	69.4
BX[(C×B)×C]	32	43.8	3.1	12.5	40.6
BX[(C×B)×B]	29	3.4	3.4	0.0	93.1

Table 2. Septal artery patterns. Comparisons of ten populations of mice. Shown are χ^2 values. With 3 degrees of freedom, critical values of χ^2 are: for $P < .10$, 6.25; for $P < .05$, 7.82; for $P < .02$, 9.84; for $P < .01$, 11.34; and for $P < .001$, 16.27.

Genotype	C	D	B	C×D	C×B	D×B
C57BL/10 [C]		20.83	33.99	29.82	34.20	39.18
DBA/1 [D]	20.83		5.12	1.55	1.73	10.39
Balb/c [B]	33.99	5.12		6.51	4.23	5.31
C×D	29.82	1.55	6.51		2.27	9.73
C×B	34.20	1.73	4.23	2.27		5.29
D×B	39.18	10.39	5.31	9.73	5.29	
BX[(C×D)×C]	3.98	11.87	25.48	20.23	21.37	31.90
BX[(C×D)×D]	24.65	0.18	20.29	1.45	0.99	8.40
BX[C×B)×C]	6.12	5.76	17.29	7.72	11.54	23.53
BX[(C×B)×B]	33.18	10.57	3.95	9.34	9.16	2.33

continuum. The difference between C-mice and D-mice was highly significant (Table 2) ($\chi^2 = 20.83$, 3 d.f., $P < .001$), and the difference between C-mice and B-mice was even more significant ($\chi^2 = 33.99$) (*5*). Only the difference between the two dextral strains, D and B, was not significant ($\chi^2 = 5.12$, $P < .20$), although inspection of Table 1 suggests a greater degree of dextral asymmetry in strain B than in strain D.

When sinistral strain C was mated to dextral strain D, the F_1 hybrids were predominantly dextral. When sinistral strain C was mated to dextral strain B, the majority of the F_1 hybrids were dextral. In cross C × D the hybrids differed significantly ($\chi^2 = 29.82$, $P < .001$) from their C-parent, and resembled their D-parent ($\chi^2 = 1.55$). In cross C × B the situation was analogous—the hybrids differed significantly ($\chi^2 = 34.20$) from parent C, but resembled parent B ($\chi^2 = 4.23$). Cross D × B is of interest because they are both dextral strains. If parent B were more dextral than parent D, one would expect that hybrids would resemble parent B rather than D. This was the case; the hybrids resembled parent B ($\chi^2 = 5.31$) but not their less dextral parent D ($\chi^2 = 10.39$, $P < .02$). Thus, septal artery dextrality appears to be a dominant trait. In the three strains we worked with, arterial sinistrality was recessive to dextrality.

These findings regarding dominance were confirmed by data obtained from backcross populations. If an F_1 hybrid is backcrossed to one of its parents, P, one expects one half of the backcross progeny, BX, to resemble that parent, and the other half to resemble the hybrid, that is, BX = ½ P + ½ F_1. In the case of traits displaying dominance this leads to two predictions: (i) Populations resulting from a backcross of F_1 to the dominant parent, P_D, will show little phenotypic variation and will tend to be unimodal. Such populations will resemble both the F_1 and the dominant parent population which, because of dominance, resemble each other, that is, BX = P_D = F_1. (ii) In contrast, populations resulting from a backcross to the recessive parent, P_R, will show maximum phenotypic variation. Such populations will tend to be bimodal since half of the animals will be like the recessive parent and the other half will be like F_1, and P_R and F_1 differ, that is, BX = ½ P_R + ½ F_1.

Our data bear out these two predictions. Population BX[(C × D) × D] resemble both the dominant parent D ($\chi^2 = 0.18$), and the hybrid parent F_1 (C × D) ($\chi^2 = 1.45$). Population BX [(C × B) × B] also resembled the dominant parent B ($\chi^2 = 3.95$); it differed though from its hybrid parent F_1 (C × B) ($\chi^2 = 9.16$, $P < .05$) by being even more "dextral" and unimodal—93.1 percent of all animals were R!. The situation was quite different in population BX[(C × B) × C]. As predicted, this backcross of F_1 (C × B) to the recessive parent C was clearly bimodal—43.8 percent of the animals were L! and 40.6 percent were R!. The situation was similar though not as striking in the case of population BX[(C × D) × C].

In general, dominance appears to evolve where in some way the dominant condition is of greater adaptive value than the recessive one. It is not known how septal artery dextrality is of benefit to mice as opposed to arterial sinistrality.

Phenotypic variation within an inbred strain or within an F_1 population of inbred strains points to nongenetic, "environmental" sources of variation. The three inbred strains and the three F_1 groups of this study displayed much phenotypic variation, forcing us to conclude that asymmetry, while undoubtedly influenced by heredity, is readily influenced by nongenetic factors. Bloor and associates (*3*) have arrived at a similar opinion in their genetic study of coronary anatomic patterns (accessory coronary ostia) in three inbred strains of rats. The demonstration that genetic factors play a role in the determination of coronary artery patterns in the mouse and in the rat adds support to reports of racial and familial similarities of coronary anatomy in man (*6*). The presence of an additional primary coronary artery or main branch to the septum could serve as a potential source of collateral circulation upon occlusion of a main coronary artery. The low incidence of myocardial infarction in Bantus has been explained on this basis (*3*).

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References and Notes

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5. All χ^2 values were computed from actual numbers of specimens and not from percentages shown in Table 1.
6. W. J. Pepler and B. J. Meyer, *Circulation* **22**, 14 (1960); J. J. Sidd, A. A. Sasahara, D. Littmann, *N. Engl. J. Med.* **274**, 55 (1966).
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Atropinesterase and Cocainesterase of Rabbit Serum: Localization of the Enzyme Activity in Isozymes

Abstract. *Zymograms reveal a multiplicity of esterase isozymes in rabbit serum. Most of the staining activity is concentrated in a region of the gels just anodal to the albumins where six phenotypes (A, AF, F, M, P, and S) are distinguished. The atropinesterase activity is associated with phenotypes A and AF and appears to be restricted to a single isozyme, zone A. Cocainesterase activity is limited to isozyme S, a zone common to all phenotypes except M.*

It has long been known that some but not all rabbits possess in their serum an enzyme capable of hydrolyzing atropine (DL-hyoscyamine) and other tropine esters. This enzyme, commonly referred to as atropinesterase (atropine acyl-hydrolase, E.C. 3.1.1.0), has been the subject of an extensive literature (*1*, *2*) which traces to a report in 1852 that rabbits can thrive on a diet of belladonna leaves. According to Kalow (*2*), the discovery of atropinesterase represents the first fully documented observation of a heritable modification of a pharmacological response. It is also known that the serum