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THE HERITABILITY OF PLASMA CHOLESTEROL CONCENTRATION IN THE RABBIT

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SUMMARY

The heritability of the plasma total cholesterol concentration in rabbits has been estimated by the paternal half-sibling method. In female rabbits, the heritability is $62 \pm 38{\cdot}8$ per cent ($h^2 \pm$ S.E.) indicating that this trait is highly heritable. In male rabbits, the heritability is $22 \pm 20{\cdot}2$ per cent. The large error involved makes it difficult to state if the trait is heritable in male rabbits.

1. INTRODUCTION

THE inheritance of plasma cholesterol concentration has been reported in chickens, mice, beef cattle and rats (Estep, Fanguy and Ferguson, 1969; Stufflebean and Lasley, 1969; Imai and Matsumura, 1973; Weibust, 1973). In a previous publication from this laboratory the heritability of dietary induced hypercholesterolaemia in the rabbit has been demonstrated (Roberts, West, Redgrave and Smith, 1974). In that paper, considerable variation in plasma cholesterol concentration was shown for both male and female rabbits in the non-cholesterol-fed state. Part of this variation in males but not females was attributable to a decrease in plasma cholesterol concentration with age. Some of the variation could be genetically determined. Accurate records of the parents, age and litter size of these animals had been kept and thus it has been possible to analyse the data for heritability by the paternal half-sibling method. In this paper the heritability of plasma cholesterol concentration in the non cholesterol-fed rabbit is reported.

2. MATERIAL AND METHODS

(i) *Animals and diets*

Data were collected from 267 male and 219 female offspring produced by 20 sires and 59 dams over a 2-year period. The rabbits were from a randomly outbred closed colony maintained in the Animal Breeding Establishment of the Australian National University. Details of the diet, which contained no added cholesterol, have been reported earlier (Roberts *et al.*, 1974).

All rabbits shared a common environment. Matings took place on the same day each week (Tuesday) and the young were usually born during the quiet of the weekend. The offspring were weaned at 6 weeks, caged up to four to a cage and allowed access to feed and water at all times. The temperature was maintained at 20°-22° C. throughout the year.

(ii) *Estimation of plasma cholesterol concentration*

At approximately 3-month intervals the plasma cholesterol concentrations of all offspring between 6 and 20 weeks of age were determined.

TABLE 1

Mean plasma cholesterol concentration of offspring

Dam (Sire)	Plasma cholesterol concentration* Male†	Female
(Bl 1)		
853	42 ± 2·8 (2)	94 ± 15·3 (3)
897	70 ± 25·9 (9)	55 ± 5·0 (12)
907	—	51 ± 0·8 (3)
920	48 ± 1·2 (4)	—
(Bl 3)		
889	47 ± 1·2 (2)	—
897	74 ± 5.1 (3)	—
970	63 ± 11.6 (3)	94 ± 13·5 (2)
916	—	91 (1)
925	78 ± 7·6 (3)	90 ± 12·0 (2)
931	59 ± 2.2 (5)	105 ± 10·0 (2)
945	70 (1)	81 (1)
(Bl 4)		
877	55 (1)	—
894	48 (1)	53 ± 4.4 (4)
934	—	68 ± 20·5 (2)
(Bl 5)		
894	—	95 ± 13·0 (2)
912	—	44 ± 4·8 (4)
(Br 5)		
894	59 ± 6.6 (5)	—
912	46 ± 4.1 (5)	—
(Br 8)		
873	50 ± 13·7 (3)	—
896	69 ± 16·0 (2)	—
898	50 ± 4·0 (2)	—
905	44 (1)	—
924	71 ± 2·6 (3)	—
936	34 (1)	—
938	—	88 ± 14·7 (3)
954	79 ± 7·1 (5)	127 ± 21·1 (3)
968	89 ± 3·5 (2)	91 ± 16·0 (2)
(Br 9)		
873	—	50 ± 15·2 (2)
938	79 (1)	42 ± 3·6 (6)
956	—	63 (1)
962	70 ± 9·8 (5)	81 ± 3·0 (2)
967	72 ± 7·1 (7)	68 ± 7·9 (3)
977	96 ± 7·7 (3)	119 ± 7·5 (5)
(Br 13)		
878	36 ± 3·6 (2)	—
(Gr 5)		
834	66 ± 13·6 (3)	86 ± 14·1 (3)
944	65 ± 2·1 (6)	—
954	41 ± 2·2 (2)	—
968	—	217 ± 50·9 (4)
971	—	98 ± 1·5 (2)
978	70 ± 8·7 (3)	86 ± 16·3 (3)
(Gr 6)		
865	83 ± 17·6 (4)	—
882	34 ± 4.5 (6)	70 ± 32.0 (2)
887	75 ± 3·9 (4)	—
(Gr 7)		
871	—	104 ± 16·7 (5)
903	—	94 ± 21·8 (3)
923	67 ± 3·1 (4)	123 ± 13·8 (4)
929	106 (1)	55 (1)
932	88 ± 11.5 (2)	105 ± 11.1 (3)
937	—	70 ± 16·5 (2)
940	—	64 ± 0·5 (2)
(Gr 8)		
907	71 ± 1·0 (2)	44 ± 4·9 (3)
922	59 ± 3·3 (4)	82 ± 9·1 (4)
925	98 ± 15·4 (3)	—
931	83 ± 6·0 (10)‡	—
(Gr 9)		
859	65 ± 25·0 (3)	42 (1)
874	71 ± 4·3 (4)	81 ± 7·0 (5)
878	56 ± 5·7 (7)‡	89 ± 10·0 (4)
886	—	104 ± 10·3 (5)
887	74 ± 6.9 (9)‡	91 ± 6.5 (3)
913	61 ± 8·8 (4)	67 ± 2·0 (2)
919	—	86 ± 9·5 (2)
928	—	68 ± 7·5 (2)
(Gr 11)		
894	51 ± 8·6 (2)	81 ± 8·0 (3)
963	—	67 ± 2·5 (2)
965	98 ± 13·0 (2)	68 ± 13·0 (2)
969	—	75 (1)
(Re 5)		
871	83 ± 18·5 (3)	146 (1)
918	67 ± 15·7 (6)	98 ± 9·7 (9)
923	62 (1)	—
929	73 ± 4·9 (3)	86 ± 15·6 (2)
965	—	82 ± 22·6 (3)
965	—	86 ± 22·6 (3)
(Re 6)		
963	75 ± 10·4 (4)	150 ± 37·4 (4)
970	—	97 ± 7·9 (3)
981	62 (1)	167 (1)
(Sm 2)		
839	88 (1)	93 ± 8·5 (2)
849	56 ± 8 1 (3)	—
894	—	81 ± 12·8 (3)
908	63 ± 45·0 (2)	—
912	58 ± 3.9 (10)‡	—
(Sm 3)		
897	87 ± 12·1 (2)	81 ± 11.4 (3)
907	80 ± 9·8 (4)	96 ± 13·0 (2)
920	58 ± 12·6 (2)	138 ± 66.0 (2)
925	62 ± 2·3 (7)	70 ± 4·0 (2)
945	86 ± 13·0 (2)	111 ± 5·0 (2)
973	—	88 ± 13·9 (3)
(Wh 3)		
859	79 ± 37·0 (2)	—
865	32 (1)	—
874	88 ± 13·4 (5)	155 ± 21·5 (2)
878	54 (1)	—
886	113 ± 15·1 (10)‡	—
887	—	113 ± 16·1 (4)
913	58 ± 9·9 (7)	107 ± 9·1 (8)‡
928	66 ± 31·0 (2)	—
933	56 ± 5·4 (5)	48 ± 7·5 (3)
(Wh 4)		
871	104 (1)	131 ± 8·0 (3)
912	—	90 ± 10·1 (4)
918	74 ± 13·9 (2)	105 ± 11·6 (6)
932	101 (1)	183 ± 10·1 (3)
937	82 ± 20·6 (5)	191 ± 22·0 (3)
939	124 ± 11·2 (6)	98 (1)

* Plasma cholesterol concentration of offspring: mean ± S.E. mg/dl (*n*).

† Due to the decrease in plasma cholesterol with age previously reported (Roberts *et al.*, 1974), the male values have been adjusted to their mean age (10·77 weeks) using the regression equation:

$$\log Y = 2{\cdot}0807 - 0{\cdot}02445X$$

where X = age in weeks and Y = plasma cholesterol concentration as mg/dl.

‡ Data for two litters.

Samples of blood (3 ml) were removed from the marginal ear vein into tubes containing 0·05 ml of 0·4 M EDTA, *p*H 7·4 as anticoagulant and the plasma was separated from the chilled blood by centrifugation. The cholesterol was extracted by the method of Mann (1961) and estimated using the σ-phthaldialdehyde colour reagent of Zlatkis and Zak (1969).

(iii) *Statistical analysis and estimation of heritability*

As parental values of plasma cholesterol concentration were not obtained, heritability was estimated by the paternal half-sibling method described by Falconer (1963). Briefly, this involves an analysis of variance leading to the estimation of three components of variance, attributable to sires (between half-sib families) to dams (between dams within sires) and to individuals (within dams). These values are equated to the expected composition of the variances which are dependent on the number of offspring per litter

and per half-sib family. From these equations the correlation between half-sib families can be obtained and this, multiplied by four, provides an estimate of the heritability.

3. Results and discussion

The mean plasma cholesterol concentration of the offspring of the various half-sibling families is shown in table 1. These data have been

Table 2

Components of variance of offspring plasma cholesterol concentration

Source	Sum of squares	d.f.	Mean square	V.R.	Expected mean square†
			Males		
Between litters	91,008	74	1230	1·60*	—
Between sires	32,728	18	1818	1·74	$W+4{\cdot}488D+13{\cdot}822S$
Within sires (between dams)	58,280	56	1041	—	$W+3{\cdot}234D$
Within litters	*147,322*	*192*	767	—	W
Total	236,330	266			
			Females		
Between litters	265,639	72	3689	4·25***	—
Between sires	112,476	17	6616	2·40**	$W+3{\cdot}505D+11{\cdot}973S$
Within sires (between dams)	153,163	55	2785	—	$W+2{\cdot}829D$
Within litters	*126,771*	*146*	868	—	W
Total	392,410	218			

† Expected mean square required for sib analysis of heritability where:

W = component of variance attributable to individuals within full sib families.
D = component of variance attributable to dams.
S = component of variance attributable to sires.

The coefficients of D and S are calculated by the method of Falconer (1963) for unequal family size.

*P < 0·05. **P < 0·01. ***P < 0·001.

published previously in a different form showing that female plasma cholesterol concentration is higher than male and that male but not female plasma cholesterol concentration decreases with age (Roberts *et al.*, 1974). For these reasons the females were analysed separately from the males and the male values were adjusted to their mean age (see equation in legend to table 1). As there were so few observations for the ages 15-20 weeks the regression was calculated on ages 6-14 weeks only (mean age 10·77 weeks) and those animals older than this were excluded from the calculation of male heritability and not reported in table 1. The components of variance of offspring plasma cholesterol concentration for males and females are shown in table 2. Variation between litters is significantly greater than within litters for both male ($F_{74,\ 192} = 1{\cdot}60$, $P < 0{\cdot}05$) and female ($F_{72,\ 146} = 4{\cdot}25$, $P < 0{\cdot}001$) offspring indicating that the dam is contributing to the variation. This contribution could be both genetic and environmental. Variation between sires is significantly greater than within sires for females ($F_{17,\ 55} = 2{\cdot}40$, $P < 0{\cdot}01$) but not for males ($F_{18,\ 56} = 1{\cdot}74$, N.S.). Thus,

the sire is not having a significant effect on the male offspring plasma cholesterol concentration. This is reflected in the estimate of the heritability for males and females shown in table 3. The male heritability is low and has a large standard error with respect to the estimate of heritability. In females the heritability of plasma cholesterol concentration is $62 \pm 38{\cdot}8$ per cent ($h^2 \pm$ S.E.).

Additive inheritance has been shown in man (Schaeffer, Adlersberg and Steinberg, 1958), rats (Imai and Matsumura, 1973), mice (Bruell, 1963; Weibust, 1973) and beef cattle (Stufflebean and Lasley, 1969). In a previous study of the inheritance of dietary induced hypercholesterolaemia in rabbits (Roberts *et al.*, 1974) it was suggested that the mode of inheritance was additive. Sufficient data are not present in this study to make any conclusions concerning the mode of inheritance of plasma cholesterol concentration in the normal rabbit. Heritability estimates of 26 per cent in male chickens (Estep *et al.*, 1969), 50 per cent in male and female mice (Weibust, 1973) and 73 per cent in male mice (Eapen, Goswami and Pillai, 1971), and 80 per cent in beef cattle (Stufflebean and Lasley, 1969) have been reported. In this paper the heritability in female rabbits is shown to be $62 \pm 38{\cdot}8$ per cent. The low value for the male heritability ($22 \pm 20{\cdot}2$ per cent) is difficult to interpret because of the large standard error. It is possible that this particular trait is not heritable in male rabbits. Certainly, the analysis of variance shows that there is no significant sire effect on the male offspring (table 2). However, in view of the large error of estimation, the experimental design may not have been appropriate for the assessment of heritability in male rabbits. Clearly, further experiments are necessary to establish whether the plasma cholesterol concentration is a heritable trait in the male rabbit.

TABLE 3

Heritability of plasma cholesterol concentration in rabbits

	Components of variance†	
	Male	Female
W	767	868
D	85	678
S	49	282
heritability $h^2 \pm$ S.E.	$0{\cdot}22 \pm 0{\cdot}202$	$0{\cdot}62 \pm 0{\cdot}388$

† See legend to table 2 for explanation of W, D and S.

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