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Directional Dominance for Low IgM and IgA Levels

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SUMMARY

A biometrical genetical analysis of IgG, IgM, and IgA levels in 134 sets of twins is reported. High heritabilities, around .8, are found for all three immunoglobulin levels, and possible reasons for lower heritabilities found in family studies are discussed. There is evidence for genetical dominance tending to decrease IgM and IgA levels, but there is no evidence for the importance of family environment although the presence of dominance may make its detection difficult. The causes of covariation in the three measurements are unclear in males but in females appear to be mainly environmental in correlations with IgA and equally genetical and environmental in the IgG-IgM correlation.

INTRODUCTION

While there have been a number of twin and family studies of plasma immunoglobulin concentrations, the numbers employed have been too small and the methods of analysis too inefficient to produce much consistency in their results.

Rowe et al. [1] studied IgG, IgA, and IgM levels in 128 pairs of twins. They split their sample into a < 21 years old age group (88 pairs) and a > 20 years old age group (140 pairs). Using the inefficient analysis proposed by Osborne and De George [2], which makes only partial use of the data, they concluded that there was genetic variation for all three immunoglobulins in adolescence, but in adults genetic

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variation was demonstrable only for IgG in males. However, with such small sample sizes in the adult group, heritabilities could have been anywhere between zero and unity [3] and no reliance can be placed on any differential effect of age from their data.

Kalff and Hijmans [4] carried out another study on 131 pairs of twins aged 14–70. Pooling data across sexes, they estimated the degree of genetic determination as .72 for IgG, .79 for IgA, and .71 for IgM. Finer analysis showed that those monozygotic (MZ) twins who had lived apart for more than 1 year had a significantly higher intrapair variance than those twins who lived together, indicating the importance of different environmental experiences in influencing immunoglobulin levels.

Allansmith et al. [5] carried out a further study of 45 pairs of same-sex twins aged 12–18 years. They detected substantial genetic variation for IgG and IgA but less variation for IgM. They also presented data on 15 subjects whose immunoglobulin levels were determined weekly for 25 weeks. For IgA and IgM, the variance of repeated weekly values for the same individual was significantly greater than measurement error and the variance within MZ twin pairs was significantly greater than repeat measurements at week 4 and week 5 on the same individual. However, for IgG there was no evidence that either form of environmental variance was significantly greater than measurement error.

Grundbacher [6] looked at immunoglobulin levels in 444 individuals from 64 families, half of them black and half of them white. He found lower heritabilities (.4–.5) based upon parent-offspring regressions than those based upon sib-sib correlations (.5–.6) and concluded that the latter were inflated by the effects of common environment. As further evidence for this point of view, he noted that these values based on sib correlations were themselves lower than previous estimates of heritability based on twins. However, it is equally possible that all these differences may arise from genotype × age interactions in which different genes affecting immunoglobulin levels are acting at different ages, so the greater the age difference between relatives the lower their genetic correlation.

Grundbacher [6] also considered the correlations between IgG, IgM, and IgA levels. He found significant correlations between IgG and IgA in both blacks and whites and slightly smaller correlations between IgG and IgM. The genetic correlation between IgG and IgA was around .4 for both races but negligible for the other comparisons.

Escobar et al. [7] studied immunoglobulin levels in families of 57 MZ female and 36 MZ male twin pairs taking advantage of the unique half-sib and other relationships generated by this design [8]. Their models for the data were unrealistic in that they fitted genetic dominance (V_D) components without additive genetic components (V_A), and their finding that only about 30% of variance in immunoglobulin levels was genetic should, therefore, be treated with caution.

It has been a universal finding that IgM levels are significantly higher in females than in males, and this led Grundbacher [6, 9] to speculate that there may be sex-linked genes involved in variation in IgM levels. However, his later study [6] and further data of Guízar-Vázquez et al. [10] and Escobar and Bixler [11] do not provide any strong support for this hypothesis.

Our study presents further data on IgG, IgM, and IgA levels in 134 pairs of twins. While this data set is no more extensive than those previously reported, a more efficient analysis of the data can be provided based on the techniques of biometrical genetics first introduced to the study of human quantitative variation by Jinks and Fulker [12].

MATERIALS AND METHODS

A sample of 134 twin pairs was obtained in the Sydney, Australia, area by appeals in the press. The sex, zygosity, and age distribution of the sample is shown in table 1. There is the familiar excess of female pairs over male pairs observed in all volunteer twin studies (e.g., [13]), so there is better discrimination between alternative models for variation in females. Most of the twins are in their 20s, but there is a sufficient number of older pairs to create some problems in the analysis of variables heavily dependent on age. Inferences about the causes of variation can really apply only to this young age group. The twins are mainly of Northern European ancestry but the inclusion of a small proportion of twins of Southern European ancestry may inflate genetic variance between pairs out of proportion to within pair variance.

Zygosity was diagnosed by blood typing with the following antisera: anti A, A_1, B, C, c, D, E, e, M, N, S, s, Fy^a, K, and P_1. In addition, twin pairs were typed for HLA using up to 29 antisera and for the serum protein haptoglobin, the red cell enzyme acid phosphatase, and the Gc group. Secretor, color vision, and phenylthiocarbamide tasting status were also determined. Eye and hair color and ear lobe form were noted. It is very unlikely, therefore, that any twins have been misclassified with respect to zygosity. Anthropometric and skin reflectance data collected on the same sample have been analyzed elsewhere [14, 15].

Immunoglobulin concentrations were determined by a single radial immunodiffusion (R.I.D.) method using commercially available R.I.D. plates (Behringwerke, LG, Germany). Five microliters (5 μl) of standard solutions (Behringwerke) or serum was placed in circular holes in the agar plates, and after 80 hrs at room temperature, the diameter of the circular precipitate that formed was measured using an obliquely lighted viewer equipped with a vernier scale. A standard curve was constructed by using the squares of the diameters of three standards, and immunoglobulin levels were considered to be valid only if the measurement fell within the straight portion of the standard curve. Accuracy was considered to be within 10% with a single operator. Immunoglobulin levels were expressed as mg/100 ml.

One extreme outlying value of 540 mg/100 ml for IgM (> 6 SD above the mean) for a dizygotic (DZ) male was rejected, and this pair was excluded from the analysis. Some immunoglobulin levels were not available for all twins, and these pairs have also been excluded from the analysis. The number of pairs used in the genetic analysis can be seen from the degrees of freedom in table 6.

METHODS OF ANALYSIS

Scaling

There seems to be some uncertainty as to the most appropriate scale to use in the quantitative analysis of immunoglobulin levels. Rowe et al. [1] converted their

TABLE 1

AGE, SEX, AND ZYGOSITY COMPOSITION OF THE SAMPLE

	MZ males	MZ females	DZ males	DZ females	DZ opposite sex
No. pairs	23	45	20	33	13
Mean age (yrs)	24.39	26.16	20.95	25.52	20.85
Age range	17–53	15–64	17–37	16–47	17–31

concentrations to logarithms because they found the error of the technique of estimation to be a constant proportion of the concentration.

With Behringwerke R.I.D. plates, the error over the normal ranges for immunoglobulins G, A, and M is quoted as ±10%. All other studies quoted have worked with the untransformed concentrations expressed either as mg/100 ml or W.H.O. international units.

The most appropriate scale for a genetical analysis is the one that shows a linear relationship between the variable in question and genetic fitness, which in the present case could presumably be approximated by some measure of disease resistance or morbidity. In the absence of precise data on this point, it is most convenient to choose a scale that minimizes genotype (G) × environment (E) interaction. There is little point in quoting global heritabilities if the relative importance of genotype and environment varies at different immunoglobulin concentrations.

Jinks and Fulker [12] have shown that MZ twins provide a unique opportunity to test for one such important type of G × E interaction. Because MZ twins are genetically identical, the absolute difference between cotwins is a measure of the specific environmental influences to which that pair has been subjected (E_1) while the pair sum is a measure of their genetic value (G) and/or the environmental influences that they have shared and that make them different from other twin pairs. Correlating pair sums and absolute pair differences of MZ twins will, therefore, test for any systematic linear interaction between genotype and individual environmental influences. Thus, if immunoglobulin concentrations of genotypes tending to produce low levels were less responsive to environmental stimuli than those of genotypes tending to produce high levels, a positive correlation between pair sums and absolute differences would be expected. If "genetically low" individuals tended to have larger fluctuations in response to environmental challenges than "genetically high" individuals, a negative correlation would be expected. If there were any marked relationship between measurement error and concentration, this would generate a sum-|difference| correlation. Table 2 shows these correlations for MZ male and female twins in this sample. There is no evidence for any systematic G × E interaction for immunoglobulin levels except for IgA in females where there is a high positive correlation. Transformation of IgA values to logarithms removed this correlation in females but introduced an equally large negative correlation in males. It is possible that there is a genuine interaction such that females who tend to

TABLE 2

CORRELATIONS BETWEEN PAIR SUMS AND ABSOLUTE PAIR DIFFERENCES FOR IMMUNOGLOBULIN LEVELS

	MZ males	MZ females	DZ males	DZ females
IgG	.32	−.05	.11	.11
IgM	.26	.05	.51*	.42†
IgA	−.06	.55‡	.56†	.59‡

*$.01 < P < .05$.
†$.001 < P < .01$.
‡$P < .001$.

produce high IgA levels are more susceptible to environmental stimuli. However, confirmation of this finding will have to await further data and for the moment this result must be regarded as anomalous. Previous experience [13] has shown that transformation to remove such interactions usually makes little difference to the results of genetic analysis.

Of course, interactions could be other than linear, and quadratic associations were checked for by correlating absolute pair differences with the square of pair sums, but no extra information was gained. Higher order, or nonsystematic, interactions would be difficult to interpret and even more difficult to take account of in a global genetic analysis. It appears that, apart from the anomalous case of IgA in females, there is no case for transformation of the raw measurements.

Martin et al. [3] have shown that in the absence of G × E interaction, it is possible to detect the presence of genetical nonadditivity by carrying out the same analysis on DZ twins. If there is no sum-|difference| correlation in MZ twins but this is found in DZ twins, this is an indication that there is either directional dominance for the trait or that there is an inequality in the number of alleles tending to increase or decrease expression of the trait, or that both phenomena are present. More specifically, they showed that if there is a negative correlation there is a predominance of dominant alleles tending to increase expression at loci affecting the trait, while if the correlation is positive, dominance is in the decreasing direction. A negative correlation could also mean that alleles tending to increase expression are more frequent at loci affecting the trait than are decreasing alleles, while a higher frequency of decreasing alleles produces a positive correlation.

These relationships are also expressed in the phenotypic distribution of the trait. Dominance or gene frequencies in the increasing direction are reflected in negative skewness of the distribution, while decreasing dominance or gene frequencies are expressed as positive skewness. As will be seen below, these relationships are found in these and in previous data.

The sum-|difference| correlations for same-sex DZ pairs are shown in table 2. There are large and significant positive correlations for IgM and IgA in both sexes. In view of the equally high correlation in MZ females for IgA, one should be wary of interpreting the corresponding DZ correlation, but otherwise there is surprisingly strong evidence for dominant alleles tending to decrease levels of IgM and IgA in both males and females. Alternatively, alleles for low expression are more frequent than those for high expression.

Relationships with Sex and Age

Since it is not necessary to transform the raw immunoglobulin concentrations, let us now consider the distribution of the sample values. Before attempting to fit models to explain trait variation, it is important to ensure that MZ and DZ groups have been sampled in the same range, that is, that subgroup means and variances are comparable. No significant differences between MZ and DZ means and total variances were found in females. In males, the same is also true except that the total variance for IgA is significantly greater in DZ twins than in MZ twins. This probably reflects an inadequacy of sampling but may also be caused by some sort of

genotype-environment covariation [16]. The models fitted below to the data assume equality of total MZ and DZ variances, so if the inequality here is important it will cause model failure.

Table 3 shows the distribution of immunoglobulin concentrations for the total sample of males and females. There is no significant difference between the means of IgG levels in males and females, but IgM levels are significantly higher ($P < .001$) in females than in males and slightly higher ($P < .05$) for IgA in males than in females. These results are similar to those of other workers [6]. The skewness and range of the samples are also shown in table 3. The significant positive skewness of both males and females for IgM and IgA is evident from these statistics, and the distributions here look similar to the histogram distributions previously published [1, 6].

The importance of skewness in the IgM and IgA distributions has already been mentioned, for it is another manifestation of the directional dominance already detected by the sum-|difference| correlation test in DZ twins.

The correlations of immunoglobulin concentrations with age are shown in table 4, and none of these is significant. Other workers [6, 7] report a high correlation between IgA levels and age but their samples had wider and more even age distributions. Age correlations can inflate the variance between pairs, and it is important to correct for this where it occurs but is clearly not necessary here.

While there are no significant correlations of immunoglobulin levels with age, it is possible that with increasing age, accumulated different environmental experiences may tend to make MZ twins less similar, while accumulated differences in the activation of different genes may additionally tend to increase variance within DZ pairs. This is the reasoning that caused Rowe et al. [1] to partition their sample into two age groups, Kalff and Hijmans [4] to partition their sample into those living apart and those living together, and Allansmith et al. [5] to restrict their sample to a 12–18 years age group. Such partitioning of the sample, however, may produce cell sizes too small to make worthwhile comparisons. The age distribution of the present sample is too weighted toward the 20–30 age group to give much chance of detecting any age effect, but it is possible to test for any that are present by correlating absolute pair differences with age, and these correlations are shown in table 5. The only significant correlation is for IgA in MZ females. A correlation of sums and |differences| for IgA has already been detected in this group, and the fact that there is no consistent correlation with age in DZ females tends to suggest that the data are anomalous. However, it is an effect that would be worth checking in future data sets.

TABLE 3

DISTRIBUTION OF IMMUNOGLOBULIN VALUES (MG/100 ML) FOR MALES AND FEMALES

	MALES (No. = 96)				FEMALES (No. = 163)			
	Mean	SD	Skewness (g_1)	Range	Mean	SD	Skewness (g_1)	Range
IgG	1049.58	267.58	.184	410–1740	985.73	291.76	.100	220–1920
IgM	126.26	50.59	.580	38–279	155.28	57.06	.723	45–368
IgA	146.24	62.56	.879	30–400	130.98	53.19	.763	34–346

TABLE 4

CORRELATIONS OF IMMUNOGLOBULIN LEVELS WITH AGE

	Males	Females
IgG	.16	−.07
IgM	.06	−.15
IgA	.14	.12

Fitting Models

The statistics to which models of variation are fitted are the between and within pairs mean squares (WMS) from an analysis of variance of each separate group of n twin pairs.

Source	Degrees of freedom	Expected mean squares
Between pairs	$n - 1$	$\sigma^2_w + 2\sigma^2_b$
Within pairs	n	σ^2_w

The 10 mean squares and their degrees of freedom for each variable are shown in table 6. A similar analysis of the covariances between the three variables produces the three sets of mean products that are also shown in table 6.

A large difference in the means of males and females will inflate the WMS of DZ opposite sex (DZOS) pairs by an amount $(n/2\,(\overline{M} - \overline{F})^2$, where there are n pairs, $\overline{M}$ is the male mean, and $\overline{F}$ is the female mean. Because there were only 12 DZOS pairs, it was decided that a more reliable correction would be obtained by using the total sample values of $\overline{M}$ and $\overline{F}$. The residual WMS (now with $n - 1$ df) is given by $(n/n - 1)$ [WMS $- \frac{1}{2}\,(\overline{M} - \overline{F})^2$]. The DZOS within pairs mean products are corrected by subtracting the corresponding product of mean sex differences. Although there was no significant difference in male and female means for IgG, for consistency, all DZOS WMS and mean products have been corrected for the sex differences using the values of $\overline{M}$ and $\overline{F}$ shown in table 3.

Models of variation for these mean squares and mean products can now be fitted using the method of weighted least squares that has been described extensively [17, 18].

TABLE 5

CORRELATIONS BETWEEN ABSOLUTE PAIR DIFFERENCES AND AGE

	MZ males	MZ females	DZ males	DZ females
IgG	.05	.21	−.01	.02
IgM	.07	−.10	−.13	.29
IgA	−.20	.35*	−.02	.19

*$.01 < P < .05$.

TABLE 6

OBSERVED MEAN SQUARES AND MEAN PRODUCTS USED FOR MODEL FITTING

Statistic	Degrees of freedom	IgG	IgM	IgA	IgG/IgM	IgG/IgA	IgM/IgA
MZ males:							
Between	19	84049.89	3566.15	5554.11	3532.04	4906.39	1402.46
Within	20	27057.50	785.43	541.25	1456.25	−4.00	303.55
MZ females:							
Between	43	149209.21	6047.70	4869.82	12476.11	11886.91	1447.30
Within	44	20945.43	571.06	846.76	1574.52	2743.13	262.78
DZ males:							
Between	18	151178.17	5653.03	9610.13	20592.97	28923.99	4514.43
Within	19	36138.16	812.66	1855.55	847.89	840.53	−281.37
DZ females:							
Between	30	109950.78	4170.25	2955.19	11074.84	6490.61	616.54
Within	31	58305.65	1540.44	2510.69	4648.71	7754.68	390.87
DZ opposite sex:							
Between	11	95949.64	5058.30	5606.03	1004.39	5686.06	848.79
Within	11	79544.46	2721.19	738.58	5643.41	−206.92	133.28

A simple model for variation in MZ and DZ mean squares is shown in table 7. E_1 is environmental variance within families, and as such it is specific to the individual and will include error variance. E_2, on the other hand, includes sources of environmental variance shared by members of a family but differing between families. It will, thus, include the lasting effects of cultural and class differences and parental rearing practices. Here it may include disease experience and other challenges to the immune response that both members of a twin pair share in common, but which differ between pairs. V_A is that part of the genetic variation due to the additive effects of genes in the absence of assortative mating. If assortative mating occurs for immunoglobulin levels, it will increase the additive genetic variance between pairs, but in proportions such that it is completely confounded with estimates of E_2. As Grundbacher [6] reports negligible marital correlations for immunoglobulin levels, this potential complication will not be considered further. V_D is genetic variance due to the effects of dominance. In practice, it is extremely difficult to detect in classical twin studies, even under ideal conditions, and where it occurs, it will usually be confounded with V_A and E_2 [3]. Thus, even though there is evidence for directional dominance acting in IgA and IgM levels, it is most unlikely that it can be detected by fitting models to variance components.

A sensible hierarchy of models is to first fit E_1 alone. Failure of this most simple model will indicate that there is significant between families variation. A model incorporating E_1 and E_2 will test whether the between families variation is entirely environmental in origin, while the E_1V_A model will test whether it is entirely genetic. If both two parameter models fail, then a model incorporating all three sources of variation must be considered. As indicated, the model is not of full rank so a model comprising E_1, V_A, and V_D will yield the same chi square as the $E_1E_2V_A$ model, the remaining degree of freedom simply testing the equality of MZ and DZ variances. The more appropriate of these two models must be selected by seeing which

TABLE 7

MODEL FOR TWIN MEAN SQUARES

Mean squares	E_1	E_2	V_A	V_D
MZ females				
Between	1	2	2	2
Within	1	0	0	0
MZ males				
Between	1	2	2	2
Within	1	0	0	0
DZ females				
Between	1	2	½	¼
Within	1	0	½	¾
DZ males				
Between	1	2	½	¼
Within	1	0	½	¾
DZ opposite-sex				
Between	1	2	½	¼
Within	1	0	½	¾

parameter estimates are more sensible. Because it is so difficult to detect dominance in classical twin studies, in nearly all cases the $E_1E_2V_A$ model will be of most interest.

There is no necessary reason why the components of variation will be the same in both males and females, so models are first fitted to the sexes separately and then to the eight statistics together. At this stage, a heterogeneity chi square for k df can be calculated by adding the two male and female chi squares for $4 - k$ df and subtracting from the chi square ($8 - k$ df) for the corresponding model of parameters fitted to all eight statistics. The heterogeneity chi square for k df will indicate whether the same parameters are appropriate for both sexes. If it is not significant, then the DZOS data may be added and the same model fitted to all 10 statistics.

RESULTS

For IgG and IgM, there was no heterogeneity in the fit of models to the male and female data so models of variation may be fitted to all 10 mean squares. For IgA, the chi square testing the adequacy of the purely environmental E_1E_2 model was significant in both sexes, indicating that the model was inadequate while the simple genetical model including E_1 and V_A fitted well in both males ($\chi^2_2 = 4.17$) and females ($\chi^2_2 = 2.57$). However, when this model was fitted to the male and female data jointly, it failed badly ($\chi^2_6 = 14.42$), indicating significant heterogeneity ($\chi^2_2 = 7.78$) in the parameters required to account for variation in IgA levels in males and females. This complication will be considered below, but for consistency, the results of model fitting to the 10 statistics for all three variables are shown in table 8.

For both IgG and IgM, the purely environmental model fails badly while the E_1V_A model gives a good fit to the data. Addition of a third parameter to the model causes no improvement, indicating that the effects of family environment (E_2) are negligible, or in the case of IgM are counter-balanced: $h^2 = \hat{V}_A/(\hat{E}_1 + \hat{V}_A)$ is high for both variables (.72 for IgG and .79) for IgM, indicating that most of the variance is genetically determined.

TABLE 8

RESULTS OF MODEL FITTING TO 10 STATISTICS FOR IMMUNOGLOBULIN LEVELS

	$\hat{E}_1$	$\hat{E}_2$	$\hat{V}_A$	χ^2*	h^2
IgG	38654.70†	43020.25†	...	18.47‡	...
	23250.03†	...	59366.60†	5.83	.72 ± .05
	23186.67†	−1043.42	60401.35†	5.80	...
IgM	1071.70†	1986.10†	...	24.31§	...
	617.88†	...	2380.21†	8.23	.79 ± .04
	640.84†	690.25	1739.12§	8.36	...
IgA‖	1354.35†	1960.16†	...	29.59†	...
	750.59†	...	2592.94†	17.54‡	♂ = .88 ± .04
	...	...	...	...	♀ = .68 ± .07
	765.63†	350.60	2258.45§	16.65‡	...

*Degrees of freedom are 8 for the E_1E_2 and E_1V_A models and 7 for the $E_1E_2V_A$ model.
†$P < .001$.
‡$.01 < P < .05$.
§$.001 < P < .01$.
‖Significant heterogeneity of fit between sexes.

In the case of IgA, while an E_1V_A model is most appropriate for both males and females, the heterogeneity reported above suggests that genetical and environmental influences are responsible for different proportions of the variance in the two sexes. The heritability of IgA in males is .88 ± .04, and for females, .68 ± .07, indicating a significantly higher degree of genetic determination of variation in males.

The correlations for males and females are shown in table 9. All are significant and considerably higher than those reported by Grundbacher [6]. To investigate the basis of this covariation, models were fitted to the mean products shown in table 6. No model fitted any of the male data, and the pattern of mean products for this sex is difficult to interpret and may simply reflect an anomaly of small sample size. However, for the female data, the E_1E_2 model failed badly for all three covariances, but the E_1V_A model gave a very adequate fit.

It is now possible to calculate the genetical and environmental correlations between the three measurements in females. For example, the genetical correlation between IgG and IgM can be calculated as:

$$r_{V_{A_{GM}}} = \frac{\hat{V}_{A_{GM}}}{\sqrt{\hat{V}_{A_G} \cdot \hat{V}_{A_M}}} ,$$

and other genetical and environmental correlations can be similarly calculated. These are shown in table 10, and it can be seen that genetical and environmental influences are equally responsible for the covariation in IgG and IgM levels but that environmental influences seem more important in producing the correlations between IgG and IgA and IgM and IgA. By contrast, Grundbacher [6] found that the environmental correlation was higher and the genetical correlation negligible except for the IgG/IgA correlation in which the genetical correlation was equally important. Resolution of these inconsistencies must await larger and more comprehensive studies.

DISCUSSION

Findings of high heritabilities, around .8, for IgG, IgM, and IgA levels are consistent with earlier twin studies. That these estimates are higher than those from family studies [6, 7] may reflect the inability of the twin design to separate satisfac-

TABLE 9

PHENOTYPIC CORRELATIONS BETWEEN IMMUNOGLOBULIN LEVELS IN MALES AND FEMALES

	IgG	IgM	IgA
	Females		
Males	...	.40	.45
	.41	...	.19
	.44	.40	...

TABLE 10

GENETICAL AND ENVIRONMENTAL CORRELATIONS BETWEEN IMMUNOGLOBULIN LEVELS IN FEMALES

	IgG	IgM	IgA
		Genetical	
Environmental.....	...	.46	.38
	.46	...	.20
	.72	.35	...

torily additive genetic variance from family environmental variance when dominance variance is also present. However, another possible explanation is that different genes affect immunoglobulin levels at different ages so that comparisons of relatives of widely differing ages may underestimate the genetic variance acting at any one time. If this were an important factor, some effect of age-specific gene activation might be found by regressing absolute differences of DZ pairs on age. Because DZ twins are the same age, this would only be a weak test, and the results in table 5 do not lend much support to this hypothesis. However, the data are scant and the hypothesis needs testing on a larger sample covering a wider age range.

The most striking finding from these data, however, is the evidence for dominance acting to decrease levels of IgM and IgA. Mather [19] discusses the concept of "genetic architecture" in which selection in a given direction causes the evolution of nonadditive genetical effects acting in the same direction. On this theory, one would predict that selection has acted to keep IgM and IgA levels low. Failure to detect dominance for IgG levels does not mean that it is not present, for it is almost impossible to detect V_D from an analysis of twin variance components [3]. It is possible that IgG levels have been selected for an intermediate optimum with dominant alleles acting equally in both directions.

Directional dominance acting to decrease the levels of immunoglobulin might arise from an interaction of alleles at antibody V region loci with antigenic stimuli of environmental origin. Thus heterozygous individuals may have larger repertoires of antibody V region genes, and for a given set of antigenic stimuli, it would be easier for them to produce adequate concentrations of specific antibody at lower concentrations of total immunoglobulin. In contrast, homozygous individuals, with smaller V region repertoires, may need to produce larger amounts of less specific immunoglobulin in order to produce adequate concentrations of specific antibody [20].

Martin et al. [3] have also shown that the possibility of detecting directional nonadditivity decreases as the number of loci affecting the trait increases. Our finding of such striking directional nonadditivity in IgM and IgA may indicate that these levels are influenced by a relatively small number of genes and measurements might be more successful than in other variables.

In conclusion, the biometrical genetical analysis of these twin data has shown that while many of the findings are not substantially different from previous studies

there are certain new findings and also some anomalies that would not have been detected with less efficient analyses. Application of these techniques to more extensive data sets may confirm some of the findings, particularly of dominance, and resolve the anomalies such as the age effects and the causes of covariation in male immunoglobulin levels.

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