Am J Hum Genet 30:46–58, 1978

A Genetic Study of Immunoglobulin E

J. W. GERRARD,[1,2] D. C. RAO,[1] AND N. E. MORTON[1]

INTRODUCTION

It has been known for many years that allergic diseases tend to run in families [1–5], but the mode of inheritance has remained obscure. The discovery of immunoglobulin E (IgE) [6], high levels of which are frequently associated with atopic disease [7], suggested that factors controlling the level of serum IgE might play an important role in determining the prevalence of allergic diseases. This study was designed to determine whether the amount of IgE in the serum was under genetic control and if so, the nature of this control.

Bazaral et al. [8], the first to explore this field, measured serum IgE levels in normal infants and mothers, combined their data with certain published figures, and then postulated that serum levels of IgE were controlled by two alleles at a single locus. They then studied serum IgE levels in twins [9], estimating the heritability to be .592 in adults and .789 in children. Grundbacher [10] studied IgE levels in 326 individuals in 51 families (25 black and 26 white) from the Richmond, Virginia area and suggested a heritability between .49 and .60 for blacks and between .40 and .54 for whites. Marsh et al. [11] examined IgE levels in 205 highly allergic unrelated adults, in 106 nonallergic unrelated adults, and in 28 families. They also postulated that high levels of IgE were recessively inherited. Gerrard et al. [12] studied IgE levels in parents and children, without adjustment for age. By analyzing 80 normal families, they felt that the results were consistent with low levels of IgE being determined by two dominant genes, the absence of one or the other permitting high levels to occur.

Here, we apply path and complex segregation analyses to IgE levels in 173 nuclear families to ascertain the relative importance of environmental and genetic factors and to determine if the genetic component was due to a major locus in addition to polygenic heritability.

MATERIALS AND METHODS

Sera from 173 white families from the Saskatoon, Saskatchewan area were studied. Of these, 145 families were selected if (1) one child in each family had been born in University Hospital

Received April 4, 1977; revised July 20, 1977.

This work (PGL paper no. 172) was supported by grant GM 17173 from the National Institutes of Health. J. W. Gerrard was a visiting colleague under the sponsorship of the World Health Organization Collaborating Centre for Reference in Processing of Human Genetics Data. He was also supported by Canadian National Health grant no. 608-1010-28.

[1] Population Genetics Laboratory, University of Hawaii, Honolulu, Hawaii.

[2] Present address: Department of Pediatrics, University of Saskatchewan, University Hospital, Saskatoon, Saskatchewan, Canada S7N OW8.

between October 1967 and September 1969; (2) the child was originally under the care of a pediatrician; and (3) the family was still intact and living in Saskatoon 3 years later. The reason for the study, namely, the collection of sera from all members of the family for the purpose of determining if parents and children tended to have similar levels of IgE, was explained to the parents. Only four eligible families elected not to participate. The families which we studied were, we felt, representative of our population as a whole. A preliminary analysis [12], when the data from 80 families became available, indicated that more families in which either one or both parents had high levels of IgE were needed to determine the mode of inheritance of IgE. Because there is an association between high levels of IgE and atopic disease, 28 additional families with a high prevalence of atopic disease were included in the study, making a total of 173 families.

IgE levels (U/ml) were measured in duplicate by radio immunoassay using Phadebas kits; IgA, IgG, and IgM levels (mg/100 ml) were measured by radial immunodiffusion using Hyland plates. Because of extreme skewness and of the wide range in the distribution of IgE levels, ranging from 5 to 10,000 U/ml with a mean of 81 U/ml, the figures were first converted to natural logarithms by the senior author, who was also responsible for the data collection, prior to his collaboration with the Population Genetics Laboratory where the data were analyzed.

PATH ANALYSIS

Log-transformed immunoglobulin E (ln IgE) was adjusted for age and sex effects by regressing ln IgE on sex, age, age^2, age^3, sex $\times$ age, sex $\times$age^2, and sex $\times$ age^3. The adjusted ln IgE was then normalized as best as possible using the power transform (1) described in the next section: we used $p = -0.639$ for this (see table 4). The transformed variable we call phenotype (P). We then created an environmental index (I) for each individual by regressing phenotype on IgG, IgA, and IgM; this index was separately adjusted for age and sex effects as above. We thus created the following six basic variables: P_F = phenotype of father; I_F= environmental index of father; P_M = phenotype of mother; I_M = environmental index of mother; P_C = phenotype of child; and I_C = environmental index of child (average of index values for a sibship). These variables generate 15 correlations, and sibling phenotypes generate an additional correlation, making a total of 16 correlations. These 16 correlations are estimated by maximum likelihood methods [13]. Approximate sample sizes are taken as the integer parts of

$$n_{ij} = \begin{cases} \sum_k N_{ik} N_{jk} & : \quad i,j = 1,2,3,4,6 \; (i \neq j) \\ \sum_k N_{ik} \sqrt{f(s_k)} & : \quad i = 1\,2,3,4,6 \; (j = 5) \\ \sum_k f(s_k) & : \quad i = j = 5 \end{cases}$$

Where the six variables P_F, I_F, P_M, I_M, P_C, I_C are denoted by 1, 2, 3, 4, 5, 6, respectively, and N_{ik} = number of individuals measured for the ith variable in the kth family (= 0 or 1 or s_k, number of children in the kth family),

$$f(s_k) = \frac{s_k}{1 + (s_k - 1)r_{55}} = \frac{\text{variance of one X value}}{\text{variance of the mean of the X values of } s_k \text{ sibs}}$$

r_{55} = estimated sibling correlation.This way we adjust the sample size by the ratio of variances, $f(s_k)$. Thus, n_{ij} is larger than the number of families for correlations involving P_C, because $f(s_k) > 1$ whenever $r_{55} < 1$. These 16 correlations (see table 1) are analyzed here according to the general path model developed for nuclear families [13]. Although the general model [13] involves 10 parameters, we consider the special case shown in figure 1, which involves only the following seven parameters, as adequate for IgE: h = effect of genotype on phenotype (square-root of heritability); c = effect of indexed environment on the phenotype; u = correlation between indexed environments of spouses; i = effect of indexed environment on child's index; i_F = effect of indexed environment on father's index; i_M = effect of indexed environment on mother's index; and f = effect of parent's indexed environment on child's indexed environment (same for father and mother).

Previously the term 'family environment' was used instead of indexed environment, when we assumed that family environment (typified by socioeconomic status) was entirely determined before reproduction. This is appropriate for behavioral traits like IQ where the phenotype is not easily resolved from adult habits and attitudes. However, a different approach is more suitable for physiological traits. We consider that the indexed environment is a constellation of many manipulable states which affect the phenotype and are not themselves a product of the relevant genotype. In the present study, IgG, IgA, and IgM define the indexed environment.

The expected correlations (ρ_i), derived from figure 1, are also presented in table 1. The log-likelihood function is taken as $\ln L = -\chi^2/2 + \text{constant}$; $\chi^2 = (\underset{\sim}{z} - \underset{\sim}{\bar{z}})'\Sigma^{-1}(\underset{\sim}{z} - \underset{\sim}{\bar{z}})$. Where $\underset{\sim}{z}$ is the column vector of 16 bias-corrected z-transforms of the observed correlations, $\underset{\sim}{\bar{z}}$ is the corresponding vector for expected correlations, and Σ is the covariance matrix (16×16) of the z-transforms. Σ incorporates correlations between observed correlations [14]. The residual χ^2 after estimating κ parameters follows a chi-square distribution with $16 - \kappa$ df. By specifying ρ_i's as functions of parameters

TABLE 1

OBSERVED AND EXPECTED CORRELATIONS FOR TRANSFORMED ln IgE IN 173 NUCLEAR FAMILIES

Variables	Expected Correlation (ρ)	Observed Correlation (r)	Sample Size (n)
P_F, P_M	c^2u	.077	164
P_F, I_M	cui_M	−.063	164
P_M, I_F	cui_F	.042	164
I_F, I_M	ui_Fi_M	.123	164
P_F, I_F	ci_F	.121	164
P_M, I_M	ci_M	.240	172
P_F, P_C	$h^2/2 + c^2f(1+u)$	.313	220
P_F, I_C	$icf(1+u)$	.163	164
I_F, P_C	$i_Fcf(1+u)$	.100	220
I_F, I_C	$ii_Ff(1+u)$	.314	164
P_M, P_C	$h^2/2 + c^2f(1+u)$	.222	230
P_M, I_C	$icf(1+u)$	.180	172
I_M, P_C	$i_Mcf(1+u)$	.119	230
I_M, I_C	$ii_Mf(1+u)$	.436	172
P_C, P_C	$h^2/2 + c^2$	.264	317
P_C, I_C	ic	.230	231

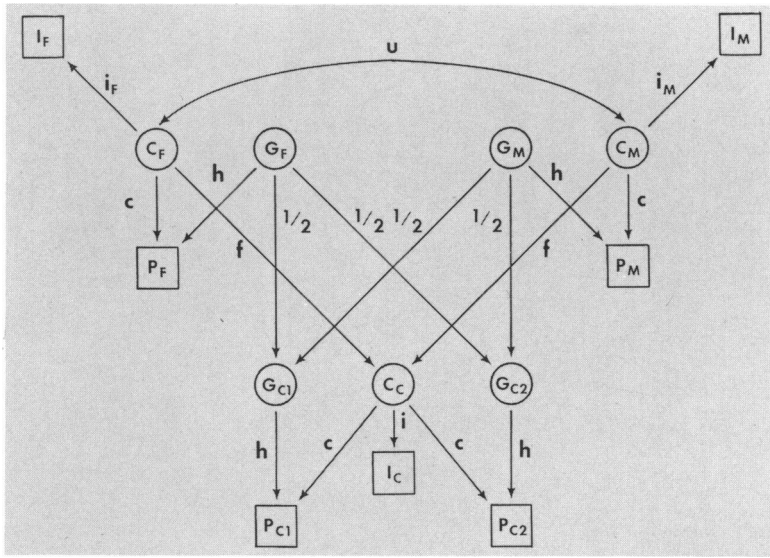

FIG. 1.—Path diagram. The subscripts *F*, *M*, *C*1, *C*2 denote father, mother, and children respectively. *G* is genotype, *P* is phenotype, and *C* is indexed environment with index *I* (environment estimated by an index is called indexed environment).

(table 1), we make χ^2 a function of the parameters. Therefore, by minimizing χ^2 or maximizing ln L, we can estimate all or some parameters and use the residual χ^2 for tests of hypotheses. If $\chi^2_{16-\kappa-\omega}$ is the value of χ^2 after estimating $\kappa + \omega$ parameters, and $\chi^2_{16-\kappa}$ is another value after estimating only κ of the $\kappa + \omega$ parameters, the other ω parameters being fixed under a null hypothesis, $\chi^2_\omega = \chi^2_{16-\kappa} - \chi^2_{16-\kappa-\omega}$ provides the likelihood-ratio test for the null hypothesis on the other ω parameters. The general model, in seven parameters, is tested by the residual χ^2 with $16 - 7 = 9$ df.

The following important assumptions underlie this model. (1) Genotype and indexed environment are uncorrelated. (2) Marital correlation, if any, is solely due to correlated indexed environments of the spouses. (3) The IgE levels of parents do not directly contribute to the indexed environment they provide to their children. (4) Specific maternal effects are negligible. (5) Intergenerational differences are negligible for genetic and environmental effects. (6) Relationships between all variables are linear.

The general model fits very well ($\chi^2_9 = 6.73$, table 2). There is, therefore, no evidence against the assumptions of the model. There is overwhelming evidence that genetic factors contribute significantly to the inheritance of IgE ($\chi^2_1 = 53.35 - 6.73 = 46.62$), and the indexed environment is also indispensable ($\chi^2_4 = 33.03 - 6.73 = 26.30$). The variance components under the general model are given in table 3. Because heritability is substantial, we decided to look for major genes.

COMPLEX SEGREGATION ANALYSIS

Path analysis can only distinguish between polygenic and environmental effects. Complex segregation analysis as Morton and MacLean [15] have developed is required to detect major genes in the presence of polygenic heritability and sibling environmental correlation. Morton and MacLean's model contains the following parameters: $V =$

TABLE 2

PATH ANALYSIS OF TRANSFORMED ln IgE

Hypothesis	df	χ^2	h	c	i	i_F	i_M	u	f
$h = 0$*	10	53.35	0	.502	.409	.240	.432	.270	.627
$c = 0$	13	33.03	.706	0	1	1	1	.092	.323
General	9	6.73	.652 ± .045	.265 ± .050	.844 ± .096	.477 ± .142	.725 ± .146	.185 ± .219	.604 ± .125

* This solution is restricted to have $2(1 + u)f^2 = 1$. The unrestricted solution yields $\chi^2 = 39.78$ with $2(1 + u)f^2 = 2.250$.

TABLE 3

VARIANCE COMPONENTS FOR TRANSFORMED ln IgE AS FRACTIONS OF TOTAL PHENOTYPIC VARIANCE

SOURCE	VARIANCE COMPONENT ± SE FROM	
	Path Analysis (general)	Segregation Analysis ($q = t = d = 0$)
Heritability	.425 ± .058	.485 ± .078
Indexed environment	.070 ± .026	.024 ± .030
Residual	.505 ± .059	.491 ± .082

variance of liability; U = mean liability; H = polygenic heritability; B = sibling environmental correlation; q = gene frequency of the major locus; d = degree of dominance at the major locus; and t = displacement due to major locus (measured in standard deviation units on the liability scale).

This segregation model assumes that there is no parent-offspring environmental correlation, whereas in path analysis, the parent-offspring environmental correlation is $c^2f(1 + u) = 0.050$ which is 19% of the total parent-offspring correlation. This would lead to an overestimate of heritability in segregation analysis. The general model contains seven parameters, whereas under subhypotheses certain parameters are fixed, and only the remaining ones are estimated. For each hypothesis we shall calculate $-2 \ln L + c$, where $\ln L$ is the log-likelihood of the sample and c is a constant; if $-2 \ln L_1 + c$ is the value when $m + k$ parameters are estimated, and $-2 \ln L_2 + c$ when only m of the $m + k$ parameters are estimated, then $(-2 \ln L_2 + c) - (-2 \ln L_1 + c) = 2 \ln (L_1/L_2)$ follows a χ^2 distribution with k df testing a null hypothesis on these k parameters. These likelihood ratio tests are carried out below to test subhypotheses.

Skewness in the distribution of quantitative traits is a major source of difficulty in detecting major loci, for skewed distributions, unless correctly transformed prior to complex segregation analysis, can simulate a major locus. We therefore transformed ln IgE in two steps: (1) We standardized ln IgE within generations by first subtracting the mean from every observation, and then by dividing by the standard deviation within each generation; this guarantees that parents and children have variance 1 and mean 0. (2) We then applied a general theory for removing skewness [16] through the transformation

$$Y = \frac{r}{p}\left[\left(\frac{X}{r} + 1\right)^p - 1\right] \quad \ldots \quad \ldots \qquad (1)$$

By maximum likelihood estimation, we then find a value of p that transforms a skewed X into an unskewed Y (r is a constant so chosen that $X/r + 1$ is positive). It should be pointed out that while the p values needed to remove the skewness in IgE and ln IgE are different, it makes no difference as to which variable (IgE or ln IgE) is used; under appropriate p-transformation, both variables give rise to distributions with zero skewness. Different values of p can be obtained by assuming 1, 2, or 3 components in the distribution of X. The objective is to test the number of significant components and then to take the p value corresponding to the appropriate number of significant

components. We fitted a mixture of one, two, and three distributions. Their p values and the corresponding values of $-2 \ln L + c$ ($\ln L$ = log-likelihood, and c is a constant) are given in table 4. It can be seen that two distributions fit significantly better than one ($\chi^2_2 = 2102.12 - 2091.87 = 10.25$); a third distribution fails to improve the fit significantly, and is therefore redundant ($\chi^2_1 = 2091.87 - 2088.92 = 2.95$). The evidence therefore supports the hypothesis that there is a mixture of two equally skewed distributions, both of which would be unskewed if $p = 0.245$ in equation (1). A tentative genetic interpretation of this phenotypic analysis is that there is a major locus, either completely recessive or completely dominant, which contributes to the inheritance of IgE.

We then carried out complex segregation analysis on Y of equation (1) with $p = 0.245$. The results are given in table 5. The following subhypotheses are considered: $q = t = d = 0$ (corresponds to no major locus); $H = 0$ (no polygenic heritability); $d = B = 0$ (complete recessivity at the major locus and no sibling environmental resemblance); $d = 1$ (complete dominance at the major locus); and $d = .5$ (additivity at the major locus). The results support the hypothesis that levels of IgE are determined by both a major locus ($\chi^2_3 = 1135.67 - 1104.73 = 30.94$) and by polygenes ($\chi^2_1 = 1113.22 - 1104.73 = 8.49$). The data are consistent with a completely recessive gene determining high levels of IgE together with polygenic heritability ($\chi^2_2 = 1104.73 - 1104.73 = 0.00$); they are not consistent with a dominant gene ($\chi^2_1 = 1117.42 - 1104.73 = 12.69$) nor with additivity ($\chi^2_1 = 1124.11 - 1104.73 = 19.38$). Variance components for $q = t = d = 0$ are presented in table 3. As expected, heritability is somewhat higher than from path analysis. Still, there is good agreement between the variance components obtained from path analysis and segregation analysis.

Ordinarily, segregation analysis would stop here with the claim of having detected a major locus for IgE. However, we prefer a conservative approach requiring additional tests of consistency: we believe that failure to detect a true major locus is less serious than asserting a nonexistant major locus. One advantage of the Morton-MacLean method [15] is that one can test for homogeneity among mating types; different mating types are expected to be homogeneous because the likelihood function is conditional on parental phenotypes. Mating types may be generated by arbitrarily polychotomizing the phenotypic scale. In addition to homogeneity of mating types, one can also test for major locus within each mating type, provided there are enough families for each mating type. While heterogeneity of data is one of several possible interpretations of results inconsistent over mating types, consistency over mating types is an added assurance for our conclusions. Since the total number of families in this study is rather

TABLE 4

FITTING COMMINGLED DISTRIBUTIONS TO ln IgE

Hypothesis	No. Parameters Estimated	$-2 \ln L + C$	p
One distribution	3	2102.12	−0.639
Two distributions	5	2091.87	0.245
Three distributions	6	2088.92	0.765

TABLE 5

COMPLEX SEGREGATION ANALYSIS OF TRANSFORMED ln IgE ASSUMING TWO COMPONENTS IN THE DISTRIBUTION OF ln IgE (p = .245)

Hypothesis	$-2 \ln L + C$	V	U	H	B	q	t	d
General	1104.73	0.951 ± .085	−0.064 ± .110	.187 ± .068	.000 ± .035	.489 ± .055	1.628 ± .184	.000 ± .129
$q = t = d = 0$	1135.67	0.922	−0.061	.485	.024	0	0	0
$H = 0$	1113.22	0.929	−0.063	0	.027	.478	1.820	.197
$d = B = 0$	1104.73	0.951	−0.064	.188	0	.488	1.630	0
$d = 1$	1117.42	0.958	−0.026	.109	.000	.130	1.468	1.000
$d = .5$	1124.11	0.933	−0.065	.130	.000	.122	2.515	.500

NOTE. — In standard deviation units, $t = 1.628/\sqrt{.951} = 1.67$.

small, we decided to generate mating types by dichotomizing the phenotype. While there are an infinite number of ways to dichotomize, we chose a cutoff point to guarantee a large enough number of families within each mating type (or groups of mating types) to be analyzed separately. The cutoff point we thus chose is 0.4 on the standardized ln IgE scale (which corresponds to 0.39 on the transformed scale with $p = 0.245$): low (L): ln IgE < 0.4; high (H): ln IgE ≥ 0.4; and unknown (U): IgE level not known. These three states generate six mating types if the two parents are not distinguished: $H \times H$, $L \times L$, $U \times U$, $H \times L$, $H \times U$, and $L \times U$. Number of families is a great limitation for analyzing these six mating types separately. We, therefore, decided to pool the six matings into two groups. One group consists of all families without an H parent (mating types $L \times L$, $U \times U$, and $L \times U$ belong to this group), and the remaining families each with at least one H parent form the other group (consisting of mating types $H \times H$, $H \times L$, and $H \times U$). There are 87 families in the former group and 86 in the latter. Several cutoff points were tried, but the one we chose (0.4) gave an adequate number of families in each of the two groups considered above. These two groups are analyzed separately, and the results are given in table 6. For the first group of 87 families, those without an H parent, the hypothesis $q = t = d = 0$ (no major locus) is untenable ($\chi^2_3 = 569.15 - 552.27 = 16.88$), but not $H = 0$ ($\chi^2_1 = 555.34 - 552.27 = 3.07$). For the other group as well, those with at least one H parent, $q = t = d = 0$ is unacceptable ($\chi^2_3 = 562.25 - 550.82 = 11.43$) but not H = 0 ($\chi^2_1 = 554.51 - 550.82 = 3.69$). Each group is consistent with $B = d = 0$. The two groups of matings are homogeneous with respect to the estimated parameters (table 6).

As a last check, we repeated the analysis by assuming only one distribution and hence used $p = -0.639$. This is a conservative test which minimizes evidence for a major locus. Therefore failure of significance for a major locus would not necessarily disprove a major locus, but persistence is strong evidence in favor of a major locus. The results are given in table 7. Again, there is significant evidence for a major locus ($q = t = d = 0$: $\chi^2_3 = 1129.24 - 1116.99 = 12.25$), as well as for polygenic heritability ($H = 0$: $\chi^2_1 = 1124.47 - 1116.99 = 7.48$). As before, $d = B = 0$ is not falsified, nor is there any evidence for nonrecessivity.

Our analysis therefore suggests that levels of IgE are controlled not only by polygenes, but also by a recessive gene which, when present, boosts the general level of IgE.

DISCUSSION

Our data support the hypothesis of a regulatory locus for IgE occupied by two alleles, say *RE* and *re*, with the dominant allele suppressing persistently high levels of IgE. If this hypothesis is correct, the locus should be mappable, since the displacement of the homozygote *re/re* is 1.67 standard deviations. Apparently the antigens and allergens which stimulate IgE production are common enough in this population to sensitize all individuals, but those with an *RE* allele regulate IgE production.

Path analysis can resolve dominance from environment common to sibs only through unusual relationships (halfsibs, foster children, and MZ twins) under environmental assumptions of questionable validity. If dominance is limited to genes of megaphenic effect (i.e., large relative to the phenotypic standard deviation), then

TABLE 6

COMPLEX SEGREGATION ANALYSIS OF MATING TYPES FOR TRANSFORMED ln IgE (p = 0.245)

Mating type*	Hypothesis	$-2\ln L + C$	V	U	H	B	q	t	d
$L \times L$, $L \times U$, $U \times L$, $U \times U$	general	552.27	0.912 ± .175	−0.158 ± .184	.162 ± .105	.000 ± .055	.380 ± .107	1.834 ± .341	.000 ± .263
	$B = d = 0$	552.29	0.907	−0.161	.160	0	.373	1.846	0
	$q = t = d = 0$	569.15	0.785	−0.201	.311	.069	0	0	0
	$H = 0$	555.34	0.847	−0.214	0	.001	.253	2.355	.205
$H \times H$, $H \times L$, $L \times H$, $H \times U$, $U \times H$	general	550.82	0.962 ± .128	−0.091 ± .222	.202 ± .130	.000 ± .100	.501 ± .084	1.645 ± .309	.057 ± .190
	$B = d = 0$	550.94	0.955	−0.057	.204	0	.509	1.569	0
	$q = t = d = 0$	562.25	1.110	−0.271	.638	.000	0	0	0
	$H = 0$	554.51	0.957	−0.030	0	.020	.505	1.874	.242

* ln terms of standardized ln IgE, low (L): ln IgE < 0.4; high (H): ln IgE ≥ 0.4; unknown (U): ln IgE unknown. Heterogeneity over mating types: for general, $\chi^2_7 = 1104.73 - (552.27 + 550.82) = 1.64$; $B = d = 0$, $\chi^2_5 = 1104.73 - (552.29 + 550.94) = 1.50$.

TABLE 7

COMPLEX SEGREGATION ANALYSIS OF TRANSFORMED ln IgE ASSUMING ONE COMPONENT IN THE DISTRIBUTION OF ln IgE ($p = -0.639$)

Hypothesis	$-2 \ln L + C$	V	U	H	B	q	t	d
General	1116.99	0.923 ± .073	−0.142 ± .109	.189 ±.078	.000 ± .033	.547 ± .061	1.394 ± .248	.000 ± .204
$q = t = d = 0$	1129.24	0.908	−0.132	.487	.012	0	0	0
$d = B = 0$	1116.99	0.923	−0.141	.190	0	.547	1.395	0
$H = 0$	1124.47	0.911	−0.133	0	.016	.532	1.686	.270
$d = 1$	1123.88	0.916	−0.125	.176	.000	.135	1.254	1
$d = .5$	1128.07	0.900	−0.139	.253	.000	.151	1.771	.5

segregation analysis can make a critical distinction between dominance and common environment. In the present case dominance appears complete. The estimate of environmental component from path analysis (0.070 ± .026) is confounded with this dominance, approaching zero in segregation analysis when the major locus is allowed for. The information from path and segregation analyses is clearly complementary, although extension of segregation analysis can in principle make path analysis redundant. Such an advance has yet to be made and would require forbidding computations with present techniques of numerical analysis.

Before complex segregation analysis is attempted, path analysis is helpful, and transformation to control skewness is essential. The analysis illustrates the sensitivity of complex segregation analysis to skewness. Homogeneity among mating types, expected under the Morton-MacLean method [15], provides an additional safeguard against a false assertion. The next step is to characterize the *RE* locus in molecular terms and to determine its location on the chromosome map.

SUMMARY

Path analysis gives evidence of genetic heritability (.425) for serum IgE levels. Complex segregation analysis indicates, in addition to significant polygenic heritability, a major regulatory locus *RE*, with homozygotes *re/re* maintaining persistently high levels of IgE. The gene frequency of *re* is .489, and the displacement is 1.67 standard deviations.

REFERENCES

1. COOKE RA, VANDER VA: Human sensitisation. *J Immunol* 1:201–305, 1916
2. ADKINSON J: The behaviour of bronchial asthma as an inherited character. *Genetics* 5:363–418, 1920
3. SPAIN WC, COOKE RA: Studies in specific hypersensitiveness. XI. The familial occurrence of hay fever and bronchial asthma. *J Immunol* 9:521–569, 1924
4. BUCHER CS, KEELER CE: The inheritance of allergy. *J Allergy* 5:611–614, 1934
5. WIENER AS, ZIEVE I, FRIES JH: The inheritance of allergic disease. *Hum Genet* 7:141–162, 1936
6. ISHIZAKA K, ISHIZAKA T, HORNBROOK MM: Physico-chemical properties of reaginic antibody. V. Correlation of reaginic activity with E-globulin antibody. *J Immunol* 97:840–853, 1966
7. JOHANSSON SGO: Raised levels of a new immunoglobulin class (IgND) in asthma. *Lancet* 2:951–953, 1967
8. BAZARAL M, ORGEL HA, HAMBURGER RN: IgE levels in normal infants and mothers and an inheritance hypothesis. *J Immunol* 107:794–801, 1971
9. BAZARAL M, ORGEL HA HAMBURGER RN: Genetics of IgE and allergy: serum IgE levels in twins. *J Allergy Clin Immunol* 54:288–304, 1974
10. GRUNDBACHER FJ: Causes of variation in serum IgE levels in normal populations. *J Allergy Clin Immunol* 56:104–111, 1975
11. MARSH DG, BIAS WB, ISHIZAKA K: Genetic control of basal serum immunoglobulin E level and its effect on specific reaginic sensitivity. *Proc Natl Acad Sci USA* 71:3588–3592, *1974*
12. GERRARD JW, HORNE S, VICKERS P, MACKENZIE JWA, GOLUBOFF N, GARSON JZ, MANINGAS C: Serum IgE levels in parents and children. *J Pediatr* 85:660–663, 1974
13. RAO DC, MORTON NE, GULBRANDSEN CL, RHOADS GG, KAGAN A, YEE S: Familial determinants of lipoprotein concentrations. *Ann Hum Genet*. In press, 1978

14. ELSTON RC: Correlations between correlations. *Biometrika* 62:133–148, 1975
15. MORTON NE, MACLEAN CJ: Analysis of family resemblance. III. Complex segregation of quantitative traits. *Am J Hum Genet* 26:489–503, 1974
16. MACLEAN CJ, MORTON NE, ELSTON RC, YEE S: Skewness in commingled distributions. *Biometrics* 32:695–699, 1976

Clinical Genetics for the Pediatrician

The 17th annual postgraduate course entitled "Clinical Genetics for the Pediatrician," sponsored by the Department of Pediatrics of Emory University School of Medicine, will be held April 3–5, 1978. The course will cover a fundamental review of human genetics, the genetics of common disorders, cytogenetics, and inherited metabolic disorders. Recent advances in treatment and control of heritable disorders will also be covered. Guest faculty will include: Dr. James Hanson, University of Iowa; Dr. Lewis B. Holmes, Harvard University; Dr. Arthur Robinson, University of Colorado, Dr. Leon E. Rosenberg, Yale University; and Dr. Louis J. Elsas, II, coordinator, Emory University. Direct queries to Postgraduate Education, Department of Pediatrics, Emory University School of Medicine, 69 Butler Street, S.E., Atlanta, Georgia 30303.

Postgraduate Course in Medical Genetics

A postgraduate course, entitled "Diagnosis, Treatment and Prevention of Genetic Disease" and sponsored by the Harbor General Hospital Campus of the UCLA School of Medicine, the American College of Physicians, and the National Foundation–March of Dimes, will be held at the Riviera Hotel, Palm Springs, California from March 6–8, 1978. This course is designed to familiarize the clinician with the principles of medical genetics and their relevance to clinical practice. For further information write to Dr. D. L. Rimoin, Harbor General Hospital, 1000 W. Carson, Torrance, California 90509.