Genetic control of severe pre-eclampsia

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SUMMARY A genetic analysis has been made of published and new data on the familial occurrence of severe pre-eclampsia in primigravid women. This has shown that the condition may be largely a Mendelian recessive one. Because the condition occurs only in pregnancy, and because susceptible women cannot otherwise be identified, it is difficult to decide whether the genotype of the parent or of the offspring carried *in utero* leads to the condition. Data on the incidence of severe pre-eclampsia in the relatives of women who have suffered eclampsia support the maternal genotype hypothesis, while similar data, in which the index cases were women who had had severe pre-eclampsia, are more compatible with the fetal genotype hypothesis. Data on the incidence of the condition in blood relatives of index cases compared to the incidence in their corresponding in-laws are now required. Such a comparison would allow a choice to be made between the two hypotheses if one or the other were correct, or would assess the contribution of each if a genotype $\times$ genotype interaction were involved. Recurrent severe pre-eclampsia seems to have the same genetic basis as the more common primigravid type. However, mild, that is non-proteinuric, pre-eclampsia usually seems to be inherited independently of the severe form.

Severe pre-eclampsia or pregnancy-induced severe hypertension is a common cause of perinatal death in Britain (Baird, 1977). Eclampsia, the epileptic-like seizure which occasionally results from severe pre-eclampsia, is an important cause of maternal death from child-bearing (DHSS, 1974). Despite much research effort throughout this century their primary cause remains unknown (Chesley, 1978). Several immunogenetic hypotheses on the aetiology of severe pre-eclampsia have been put forward (Kalmus, 1946; Penrose, 1946; Platt *et al.*, 1958). Very recently, reports have appeared showing that there is an unusual distribution of HLA types both in women who have had the condition and in their husbands (Jenkins *et al.*, 1978; Redman *et al.*, 1978). This has led Redman and his colleagues to suggest that recessive maternal immune response genes linked to HLA may predispose towards severe pre-eclampsia. Although close female relatives of sufferers from the condition also have a high incidence, no attempt seems to have been made to see if its inheritance is Mendelian. On the basis of our own and published family data we show here that severe pre-eclampsia could be largely a simple recessive trait, but we cannot say whether it is the genotype

of the mother or her fetus which predisposes towards the condition.

Materials and methods

All the data analysed are on women who have been examined clinically for blood pressure and urinary protein, and with the exception of the eclamptic index cases in Chesley *et al.* (1962, 1968) all women were primigravidae. The details of the definition of the condition and collection of data differ for the different bodies of data.

ABERDEEN DATA

In our own data and those of Adams and Finlayson (1961), the classification of Nelson (1955) is used. Nelson defined pre-eclampsia as the condition in which a rise of diastolic blood pressure to 90 mmHg or higher occurs after the 26th week of pregnancy on two occasions at least one day apart, or else shows a progressive increase during labour. He further defined severe pre-eclampsia as proteinuria exceeding 0.25 g/l in addition to the hypertension; non-proteinuric pre-eclampsia is referred to as mild pre-eclampsia. Applying this definition, Macgillivray (1958) found 5.6% of women in the Aberdeen

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Maternity Hospital in Scotland in the years 1948 to 1955 had severe pre-eclampsia in their first pregnancy, but only 0·3 % had it in their second pregnancy. Thus, severe pre-eclampsia as defined by Nelson occurs mainly in first pregnancy. More than 90% of all Aberdeen primigravidae were confined in this hospital during this period, and so the figures are probably representative of the whole population. We have used Macgillivray's data on the incidence in first pregnancy as the frequency of homozygotes for the putative gene for severe pre-eclampsia, *h* (normal allele *H*). The data of Adams and Finlayson appear to have been collected for women who were pregnant mainly in the 1950s, and so their figures may be compared with Macgillivray's.

Our data are for primigravid women in the Aberdeen Maternity Hospital in the years 1968 to 1972, during which the incidence of severe pre-eclampsia was 5·3% (W. A. Liston, unpublished data). During this period also, more than 90% of pregnant women in the area were confined there. All women who had had severe pre-eclampsia in this hospital in 1968 to 1972 were included in the survey, together with an approximately equal number of mild pre-eclamptic and normal women. Data on the incidence in their mothers were obtainable if the mothers had also been delivered in this hospital. No attempt was made to obtain data on those who delivered elsewhere. Sisters were identified by writing to the index cases and asking them for information on their sisters' married name. The index cases were told that the survey concerned pregnancy-induced hypertension. Information on the incidence in sisters was obtained only if the index cases responded to the questionnaire and their sisters were delivered in the hospital. The percentages of index cases for whom information concerning mother or sister was obtained are shown in Table 1.

Adams and Finlayson (1961) identified sisters

from (1) records of a previous sociological study of the Aberdeen area; (2) interviews with index cases in wards; and (3) by writing to index cases.

DATA OF CHESLEY ET AL. (1962, 1968)
Chesley and his colleagues studied a group of 270 North American women (mainly white) who had had eclampsia, 60% in their first pregnancies. Of all the daughters, 96% were traced and their reproductive histories recorded. Hospital records were obtained for the 187 daughters (of 122 mothers) who had had at least one completed pregnancy. Of these, only 13 had insufficient information to decide whether the first pregnancy was toxæmic or not; these were counted as normal by Chesley *et al.* in their analysis and we follow suit in this paper. The 270 index cases had 171 sisters, 147 of whom delivered in the same hospital (Margaret Hague Maternity in New York). Chesley *et al.* (1962) presented data on these 147.

They state that their toxæmia 'includes pre-eclampsia, essential hypertension and unrecognised cases of renal disease', in proportions which could not be determined (Chesley *et al.*, 1968). Of the toxæmic daughters, 80% had proteinuria in their first pregnancy. Chesley's primigravid toxæmics presumably include all severe pre-eclampsics by Nelson's definition, plus a smaller proportion of other conditions. We have therefore retained the term toxæmia when referring to Chesley's patients in order to distinguish them from the severe pre-eclampsics by Nelson's slightly narrower definition.

Possible hypotheses: maternal genotype or fetal genotype?

Severe pre-eclampsia presents an unusual problem in human genetics: it is not clear whether the mother or the fetus should be regarded as the index case. Women susceptible to severe pre-eclampsia cannot be identified when they are not pregnant, and offspring born alive from a severe pre-eclamptic pregnancy do not have any known characteristic which separates them from other offspring (Jenkins, 1976). In principle, the condition could be the result of either genetic variation in the mother, or in the fetus, or in both together (a genotype × genotype interaction).

This problem is made more difficult because for mother-first born daughter data the expectations for simple recessive inheritance are the same no matter whether the genotype of the mother or the genotype of her fetus is regarded as causing the condition (Fig. 1, Table 2). Thus, these data may show agreement with a simple mode of inheritance, but they cannot for this condition reveal in which generation the genes are acting.

Table 1 Percentage of index cases for which information on the occurrence of pre-eclampsia in the first pregnancy of a relative was obtained

Phenotype of index cases	(a) Mothers of index cases		
	No of index cases	No of mothers	Percentage
Normal	253	72	28
Mild	280	85	30
Severe	253	70	28
(b) Sisters of index cases			
	No of index cases	No of sisters	Percentage
Normal	253	28	11
Mild	291	42	14
Severe	253	55	22

Fig. 1 Maternal vs fetal genotypic causation of severe pre-eclampsia; examples of the equivalent expectations for mother-daughter data.

Circles are females, diamonds are of either sex. *h* = gene for severe pre-eclampsia, which has a frequency of *p*. (a) Maternal genotype hypothesis. Under this hypothesis the mother is considered to be the index case, and to have the recessive genotype *hh*. That is, the *hh* genotype in the mother causes her to suffer pre-eclampsia. The ratio of *HH* plus *Hh* to *hh* among her daughters will be $1 - p:p$ (see Table 1) and so *p* of her daughters will be susceptible to severe pre-eclampsia. (b) Fetal genotype hypothesis. Under this hypothesis, the fetus is considered to be the index case, and to have the recessive genotype *hh*. That is, the *hh* genotype in the fetus leads to severe pre-eclampsia in the mother. The ratio of *HH* plus *Hh* to *hh* among the fetuses of daughters of the original pre-eclamptic mother will be $1 - p:p$ and so *p* of these daughters will develop severe pre-eclampsia. As noted in the text, this rule applies only if the daughter is first born.

Table 2 Expected proportions of women with severe pre-eclampsia among relatives of normal and affected index cases, derived on the hypotheses of recessive inheritance

Phenotype of index case	(a) Maternal recessive, relatives of index cases		
	Mothers and daughters ¹	Sisters	All in-laws
Normal	$\frac{p^2}{1 + p}$	$\frac{p^2(3 + p)}{4(1 + p)}$	p^2
Affected	p	$\frac{(1 + p)^2}{4}$	p^2

(b) Fetal recessive, relatives of index cases			
Mothers, mothers-in-law, daughters, daughters-in-law, if daughter or son was first born ^{1 2}	Mothers, mothers-in-law, daughters, daughters-in-law, if daughter or son was not first born ^{1 3}	Sisters, sisters-in-law	
Normal	$\frac{p^2}{1 + p}$	$\frac{p^2(2 + p)}{2(1 + p)}$	$\frac{p^2(4 + 3p)}{4(1 + p)}$
Affected	p	$\frac{1}{2}p(1 + p)$	$\frac{1}{2}p(1 + 3p)$

Here *p* is the pregnancy of the putative gene for severe pre-eclampsia, ie the population frequency of the condition itself is p^2 . The derivation of the expectations assume random mating. The proportion of affected subjects can be obtained by subtracting the proportion of affected subjects from one.

- (1) Note that if there is more than one daughter per family, these ratios are only valid if a mother is counted each time one of her daughters is used as an index case.
- (2) In the data of Chesley *et al.* (1962, 1968) where many eclamptic index cases experienced their eclampsia in later pregnancies, these ratios would apply to the daughters born in the eclamptic pregnancy.
- (3) For the Chesley data these apply to daughters not born in the eclamptic pregnancy.

Some discrimination between the two hypotheses is possible for sister-pair data. There will be a high correlation between phenotypes of sisters if the maternal genotype hypothesis is correct, but for the fetal genotype hypothesis the predicted correlation is much lower, because the fetus of the index case and the fetus of her sister are merely cousins.

In addition, data on the incidence of the condition in blood relatives of index cases compared to their in-laws also discriminate between the two hypotheses (Fig. 2, Table 2). If the fetal genotype hypothesis is

Fig. 2 Predictions of the fetal genotype hypothesis for severe pre-eclampsia; identity of expectations for blood relatives of affected index cases and their corresponding in-laws, using mother and mother-in-law as an example.

Hatching and arrow indicate affected index case. Squares are males, circles females, and diamonds may be of either sex. All women with an *hh* fetus in their first pregnancy will have severe pre-eclampsia. (Strictly speaking the *hh* offspring should be regarded as the index case under the fetal genotype hypothesis, but here we maintain the usual convention of regarding the affected mother as the index case.) The gene frequency is *p*, and *h* is the gene for the condition. Expectations for the different classes of relative are given in Table 2. E is *hh*. Prob (C is *hh*) = prob (D is *hh*) = *p*. Hence prob (A has condition) = prob (B has condition) = *p*. Similar relationships hold for daughters and daughters-in-law, and sisters and sisters-in-law.

correct the incidence in mothers should equal that in mothers-in-law, the incidence in sisters should equal that in sisters-in-law, and the incidence in daughters should equal that in daughters-in-law. If the maternal genotype hypothesis is correct, the incidence in the in-laws should equal that in the general population. (The usefulness of a comparison between data on blood relatives and corresponding in-laws is not confined to severe pre-eclampsia; the approach could provide a general method for assessing the relative contribution of maternal and fetal genotypes in any characteristic of pregnancy, for example gestation length and maternal hormonal levels.)

Because severe pre-eclampsia manifests itself predominantly in first pregnancies, the birth order of daughters in a pedigree affects the expected ratios for the fetal genotype hypothesis, irrespective of whether the daughters are index cases or daughters of index cases (Table 2). This dependence on birth order means that the identity of expectations depicted in Fig. 1 for mother-daughter data for the two hypotheses holds only if the daughter is first born. If the daughter is born of a later pregnancy, the

probability that the relative of the affected index case will be affected is $\frac{1}{2}p(1+p)$ rather than $\frac{1}{2}p$ (Table 2).

Essentially, this difference between the expectations arises because not all daughters can be tested for their capacity to cause severe pre-eclampsia by being born in a first pregnancy, but all mothers must have a first pregnancy and so be tested for their susceptibility. The expectations for in-laws on the fetal hypothesis are also correspondingly different for first born sons as opposed to later born sons.

Dominant inheritance in either the maternal or the fetal generation seems unlikely; the nature of the evidence against it is illustrated in the footnote to Table 3.

Results

INHERITANCE

In Tables 3, 4, and 5 we present analyses of data published by Adams and Finlayson (1961) and of our own family data on Nelson's type of severe pre-eclampsia in Aberdeen women. The mother-daughter data are compatible with both recessive hypotheses. The sister pair data in Table 5 suggest, but do not conclusively prove, that the genotypic variation lies in the fetus. For the two bodies of data combined, the ratio of normal to severely pre-eclamptic among sisters of severely pre-eclamptic index cases is 95:5 (15.9%). This is much higher than the general population figure (2×2 contingency table $\chi^2_1 = 18.76$, $P < 0.001$), much lower than the expectation on the maternal genotype hypothesis (using $p = 0.2368$ from Table 3, $\chi^2_1 = 23.82$, $P < 0.001$), and slightly greater than the expectation predicted by the fetal genotype hypothesis (using $p = 0.2368$ from Table 3, $\chi^2_1 = 4.19$, $P = 0.05$ to 0.01). Also the incidence of severe pre-eclampsia among sisters of pre-eclamptic index cases is lower than among mothers of pre-eclamptic index cases (15.9% vs. 22.8%), but this difference is not significant (2×2 contingency table $\chi^2_1 = 1.37$, $P = 0.20$ to 0.30).

An analysis showing the agreement of Chesley's family data with the maternal hypothesis is summarised in Table 6. Sisters and sisters-in-law have

Table 3 Severe pre-eclampsia in mothers of index cases; test of agreement with maternal recessive hypothesis. Aberdeen data of this paper

Mothers of index cases	Index cases			
	Normal		Affected	
	Observed	Expected	Observed	Expected
Normal	147	149.88	54	53.43
Affected	10	7.12	16	16.57
χ^2_1	1.22 ns		0.03 ns	

ns, not significant.

Expectations were calculated from the formulae of Table 2. The value of $p = 0.2368$, $SE = 0.0091$, was derived from the square root of the frequency of severe pre-eclampsia in women in first pregnancy in the data of Macgillivray (1958), who found 161 severe pre-eclampsia in 2872 consecutive pregnancies. The definition of severe pre-eclampsia is that of Nelson (1955) (see text). (Note also that these data are incompatible with the hypothesis that severe pre-eclampsia is a dominant trait. At least 50% of the mothers of severe pre-eclamptics would have to have the condition if this were so, and their departure from 50% is highly significant $\chi^2_1 = 20.63$, $P < 0.001$.)

Table 4 Severe pre-eclampsia in mothers of index cases; test of agreement with fetal recessive hypothesis

Mothers of index cases	First born index cases				Later born index cases			
	Normal		Affected		Normal		Affected	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Normal	89	89.74	25	26.71	58	59.81	29	29.88
Affected	5	4.26	10	8.29	5	3.19	6	5.12
χ^2_1	0.13 ns		0.46 ns		1.08 ns		0.18 ns	

Method of analysis and origins of data as in Table 3.

Table 5 Severe pre-eclampsia in sisters of index cases; tests of agreement with maternal recessive genotype hypothesis (Expected A) and the fetal recessive genotype hypothesis (Expected B)

Sisters of index cases	(a) Data of Adams and Finlayson (1961)					
	Index cases					
	Normal			Affected		
	Observed	Expected A	Expected B	Observed	Expected A	Expected B
Normal	469	478.77	470.47	50	35.82	52.13
Affected	28	18.23	26.53	8	22.18	5.87
χ^2_1		5.44*	0.09 ns		14.68***	0.86 ns
Sisters of index cases	(b) Data of this paper					
	Index cases					
	Normal			Affected		
	Observed	Expected A	Expected B	Observed	Expected A	Expected B
Normal	64	67.43	66.26	45	33.97	49.43
Affected	6	2.57	3.74	10	21.03	5.57
χ^2_1		nd	1.45 ns		9.37**	3.93*

The method of calculation is given in the footnote to Table 3. ns, not significant; nd, not done because expectation was too low; *, significant at 5% level; **, significant at 1% level; ***, significant at 0.001% level.

Table 6 Toxaemia in first pregnancy of sisters, daughters, and sisters-in-law of eclamptic women; maximum likelihood test of the maternal genotype hypothesis

Phenotype of non-index cases	Sisters-in-law		Sisters		Daughters	
	Observed	Expected	Observed	Expected	Observed	Expected
Normal	69	70.09	93	89.03	139	139.13
Affected	6	4.91	54	57.97	48	47.87

From Chesley (1978) it would seem that 6% is the probable frequency of toxaemia in primigravid North American whites. But in view of Chesley's expressed doubts about the consistency with which the diagnosis of toxaemia was made from hospital to hospital, it seems preferable not to use this figure, even though it is very similar to that obtained by Macgillivray (1958) for Aberdeen. Instead, the values of p have been estimated from the data itself by the maximum likelihood procedure of Fisher as outlined in Mather (1964). The expectations are given in Table 2. After estimation, the particular value of p is then substituted back into these formulae and agreement with the observed values tested by χ^2 . Data are from Chesley *et al.* (1962, 1968). See text for relation between severe pre-eclampsia and toxaemia. Maternal genotype hypothesis, $p = 0.256$, $\chi^2_2 = 0.71$, $P = 0.70$.

Table 7 Toxaemia in families of eclamptic women; further test of the hypothesis of maternal recessive inheritance using the data of Chesley *et al.* (1968)

Daughters per family	Total families	Families with at least one toxaemic daughter in first pregnancy	
		Observed	Expected*
1	72	18	18.43
2	28	13	12.50
(3-5)**	12	8	8.32

Since these data were used in another form in Table 6 to help estimate p, a degree of freedom is lost and $\chi^2_2 = 0.09$, $P > 0.90$, a non-significant departure. See text for relationship between severe pre-eclampsia and toxaemia.

*Expected proportion of families with at least one pre-eclamptic daughter = $1 - (1-p)^n$ where n = number of daughters and p = gene frequency = 0.256 (Table 6). **Expectation was calculated using $n = 4$.

very different incidences (2×2 contingency $\chi^2_1 = 20.79$, $P < 0.001$). The incidence in sisters-in-law is low (8%). The correlation between sisters is much higher than in the Scottish data; 54/147 (36.7%) sisters of eclamptic index cases had severe pre-eclampsia. Thus, the analysis unequivocally supports the maternal genotype hypothesis.

In Table 7 an analysis is made of Chesley's data on the incidence of families of eclamptic women in which there is at least one toxaemic daughter. They exhibit the pattern typical of maternal recessive inheritance. Assessment of their agreement with fetal recessive inheritance is not possible in the absence of information on whether the daughters were born of the toxaemic pregnancy or not.

RELATION BETWEEN MILD AND SEVERE PRE-ECLAMPSIA

Table 8 shows the incidence of mild pre-eclampsia among relatives of normal, mild, and severe index cases. The incidence of the mild form is highest among the relatives of the mild index cases, although it is only in the Adams and Finlayson (1961) sister data that this reaches statistical significance. There is a very slight suggestion that less mild pre-eclampsia occurs among the relatives of normal as opposed to severe index cases, but in none of the three bodies of data is the difference between them significant. The 2×2 contingency table χ^2 values are: mothers 0.64, $P = 0.5$ to 0.3; sisters (this paper) 0.53, $P = 0.5$ to 0.3; sisters (Adams and Finlayson, 1961) 3.07, $P = 0.10$ to 0.05. We conclude that severe pre-eclampsia and mild pre-eclampsia are usually inherited independently of each other.

RELATION BETWEEN SEVERE PRE-ECLAMPSIA IN FIRST AND LATER PREGNANCIES

In agreement with Macgillivray (1958) our data show that severe pre-eclampsia is much less common in second pregnancies (Table 9). The incidence of the condition in the second pregnancies of those who have had it in the first pregnancy is 11%. This is significantly higher than the incidence in the second pregnancies of those who had mild pre-eclampsia (2×2 contingency χ^2 with Yates's correction = 4.72, $P = 0.05$ to 0.02). This suggests that the severe pre-eclampsia of later pregnancies is the result of the same genetic predisposition which leads to the condition in first pregnancies. Chesley's data agree with this (Table 10). The incidence of toxæmia in daughters of the index cases who had their eclampsia in first pregnancy is almost identical to the incidence in daughters of those who had their eclampsia in a later pregnancy (2×2 contingency $\chi^2_1 = 0.03$, $P > 0.90$).

Discussion

All hospital data are subject to possible ascertainment bias. In the Aberdeen data only 30% ascertainment of mothers was obtained, and we do not

Table 9 Incidence of severe pre-eclampsia in second viable pregnancy in women who had normal, mild, or severe pre-eclampsia in first pregnancy (percentages in brackets). Aberdeen data

First pregnancy	Second pregnancy		
	Normal	Mild	Severe
Normal	100 (97)	3 (3)	0 (0)
Mild	81 (60)	51 (37)	4 (3)
Severe	58 (56)	34 (33)	11 (11)

Table 10 Incidence of toxæmia in first pregnancy of daughters of eclamptic index cases according to pregnancy in which eclampsia occurred (percentages in brackets). Data of Chesley *et al.* (1968)

	First pregnancy	Later pregnancy
Total daughters	107	80
Toxaemic daughters	28 (26)	20 (25)

Following Chesley's own analysis, 13 daughters upon whom there was insufficient information to make a definite diagnosis have been counted as normal.

know if the remaining 70% delivered at home or in hospital. If women with the condition tend to enter hospital relatively more frequently than women with normal pregnancies, our incidence figures could be biased upwards. However, since mothers of normal daughters and sisters of normal sisters had incidences very close to the population figure, as predicted by the expectations in Table 2, it is unlikely that this particular bias has distorted the Aberdeen figures. Ascertainment in Chesley's data was 96% for daughters and 86% for sisters, and so a significant bias for these data is unlikely also.

Although figures are lacking, there is a widespread clinical impression that the incidence of severe pre-eclampsia in Western countries has declined in recent years (Scott *et al.*, 1978). If this were true it would cast doubt on any simple genetic hypothesis. However, as indicated above, in the Aberdeen area of Scotland the incidence of severe pre-eclampsia as defined by Nelson in 1968 to 1972 was 5.3% as compared to the 5.6% found by Macgillivray for the years 1948 to 1955. Nelson's criteria are proteinuria

Table 8 Incidence of mild (non-proteinuric) pre-eclampsia among relatives of normal, mild pre-eclamptic, and severe pre-eclamptic index cases (percentages in brackets)

Relatives and source of data	Index case phenotypes			χ^2_2 for heterogeneity
	Normal	Mild	Severe	
Mothers. This paper	24/72 (33)	34/85 (40)	19/70 (27)	2.85 ns
Sisters. This paper	7/28 (25)	15/42 (36)	18/55 (35)	0.91 ns
Sisters. Adams and Finlayson (1961)	90/379 (24)	47/118 (39)	20/58 (34)	12.70**

ns, not significant; **, significant at the 1% level.

and hypertension, and do not directly measure the clinical status of the women. Perhaps the practice of early induced delivery of potential sufferers has reduced the incidence of what is recognised by clinicians as severe pre-eclampsia, without affecting the incidence of proteinuria and hypertension.

The North American data support the maternal genotype hypothesis, but the Scottish data point towards the fetal genotype hypothesis. The resolution of this paradox may lie in the fact that two rather different groups of index cases were considered, primigravid and multigravid eclamptics for the North American series and Nelson's type of severe pre-eclampsia for the Scottish series. We suggest two possible explanations consistent with the available data.

- (1) For most cases the fetal genotype hypothesis may be correct, but in order for eclampsia to result, other genes may have to be present in the maternal genome. These maternal genes may by themselves also predispose towards severe pre-eclampsia, hence the high correlation between sisters in the North American data (Tables 6 and 7). Eclampsia is a rare condition, and so these genes would also presumably be a less common cause of severe pre-eclampsia in the general population. This genotype $\times$ genotype interaction is depicted diagrammatically in Fig. 3. The Aberdeen data, which show a slightly greater proportion of affected sisters of severely pre-eclamptic index cases than that predicted by the fetal genotype hypothesis, are also compatible with the idea that the maternal genotype may sometimes contribute towards the development of severe pre-eclampsia.
- (2) The maternal genotype hypothesis for severe pre-eclampsia may be correct, but not all bearers of the recessive homozygous genotype

may develop in their first pregnancy the condition defined by Nelson's criteria, that is penetrance may not be complete. This implies that mild pre-eclampsia (hypertension in pregnancy without significant proteinuria) may sometimes be a manifestation of the genes which cause severe pre-eclampsia. However, our analysis shows that most cases of mild pre-eclampsia seem to be inherited independently of the severe form. This is in agreement with other data which show that mild pre-eclampsia is distinct from severe pre-eclampsia in at least three ways. (i) Its incidence increases sharply after the age of 30 whereas that of severe pre-eclampsia is constant with age (Nelson, 1955). (ii) Women who have had mild pre-eclampsia have an increased incidence of hypertension in later life while severe pre-eclampsia is uncorrelated with later hypertension (Adams and Macgillivray, 1961; Chesley *et al.*, 1962). (iii) Mild pre-eclampsia occurs in the second pregnancies of about a third of the women who have either severe or mild pre-eclampsia in their first pregnancy, while severe pre-eclampsia is uncommon in later pregnancies (Macgillivray, 1958, and Table 9).

Severe pre-eclampsia is said to be very common in women with hydatidiform moles, which are derived from trophoblast tissue (Scott *et al.*, 1978). Such moles have recently been shown to be androgenetic in origin, that is, they possess two identical sets of paternal chromosomes and have no maternal contribution (Kajii and Ohama, 1977). They are therefore haploid or largely haploid from a population genetics standpoint. On the fetal genotype hypothesis, the expected incidence of severe pre-eclampsia should be much higher than in the general population (p vs p^2), and so these observations support this hypothesis rather than the maternal hypothesis.

The suggestion that the phenotype of the mother may be influenced by the genotype of the offspring she carries *in utero* has a precedent. Milk yield in cattle is influenced by the genotype of the sire of the calf whose birth initiated the lactation (Skjervold and Fimland, 1975). In goats, placental lactogen levels in pregnancy are correlated with the degree of mammary gland development (Hayden *et al.*, 1978). It may be that in cattle the sire's genetic contribution could affect placental lactogen production which in turn could affect mammary gland development and milk yield.

There is some debate as to whether the severe pre-eclampsia which occurs in later pregnancies has the same cause as the more common primigravid condition (Chesley, 1978). The data in Table 9 and the

Fig. 3 Possible relation between genetic control of predisposition to pre-eclampsia and genetic control of predisposition to eclampsia.

equivalent incidences in daughters of primigravid and multigravid eclamptic index cases (Table 10) suggest that most cases in parous women are the result of the same genetic predisposition which affects nulliparous women.

Recessive inheritance usually implies absent or defective gene product. A number of writers have discussed the idea that severe pre-eclampsia may be the result of an aberrant immune reaction initiated by first exposure to the foreign paternal antigens of the placenta (Jenkins, 1976; Scott and Beer, 1976; Redman *et al.*, 1978; Scott *et al.*, 1978). How such an aberrant immune response could lead to severe pre-eclampsia is still conjectural. If either of the two simple genetic hypotheses are correct, it may be possible by immunological techniques to recognise the phenotype of women at risk before they become pregnant. Prior immunisation with the relevant paternal antigens could then prevent severe pre-eclampsia. Since they hold out this possibility of treatment, the simple genetic hypotheses should be thoroughly investigated.

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