Risk of Fetal Death to Mothers of Different ABO and Rh Blood Types

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ALTHOUGH THE MECHANISMS underlying selection against major blood group alleles at the ABO and Rh loci through maternal-fetal incompatibility and consequent fetal loss are understood qualitatively, information about the strengths of the selective forces is still limited.

Evidence of a possible threefold increase in the risk of stillbirth to ABO incompatible parents, for example, is based on the complete reproductive histories of 161 couples. Since only 13 stillbirths occurred, the observation is of borderline statistical significance (Reed and Kelly, 1958). Indications of a reduced fertility of ABO incompatible matings (Chung and Morton, 1961), although derived from larger numbers of parent-offspring groupings, is only indirectly applicable to estimations of mortality among the products of conception.

Still less is known about the strengths and directions of effects upon fetal mortality of various combinations of alleles at the ABO and Rh loci, although ABO incompatibility is believed to protect to some degree against sensitization of Rh-negative mothers by Rh-positive fetuses (Levine, 1958; Cohen, 1960). An apparent net increase in fertility among ABO incompatible couples has been reported from a study of 558 partial family groupings, the members of which had been ascertained in the course of a mass blood typing operation (Reed and Ahronheim, 1959). However, no quantitative measurements have yet been made of the effects on fetal mortality of simultaneous incompatibilities at both loci that would support or reject the assumption of a net favourable influence of ABO incompatibility on fetal survival arising out of interactions with the Rh system.

Some of the selective effects may be slight and may differ under varying circumstances, so that large quantities of data will perhaps be required for definitive studies of the various interactions. Precision in certain kinds of comparisons may thus be possible only when some systematic attempt has been made to interrelate the extensive blood group information currently being gathered with accurate family reproductive histories of the same individuals as set down in other records such as those of the vital statistics systems. In the meantime, however, further fragmentary evidence from additional sources can add substantially to what is now known.

The opportunity to obtain strictly relevant information on a rather large scale

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was provided by records of all reported fetal deaths occurring in the City of New York over the years 1954 through 1959, plus a ten per cent sample of all reported live births accumulated at Indiana University by Professor T. M. Sonneborn for the purpose of studying effects of paternal age on fetal loss. These records yielded 27,260 fetal deaths and 53,100 live births for which the maternal ABO and Rh blood types had both been recorded. The mother's age at the time of the birth was also available and was used in some of the analyses. Data of the kinds provided by these records allow comparisons to be made of the risks of fetal death to mothers who are capable, or incapable, of having fetuses incompatible with themselves because of ABO or Rh differences, singly or in combination.

MATERIALS

A total of 127,987 New York City fetal death cards representing all registrations of such events in the years 1954 through 1959, plus 101,013 cards for live births representing a systematic ten per cent sample, were read onto magnetic tape by an IBM 1401 computer, and tabulations were carried out by an IBM 709 computer using a generalized "101 Simulator Program" developed by the Indiana University Research Computing Center. The work was done at the Research Computing Center as part of a long-term study of paternal age effects initiated by Professor T. M. Sonneborn (1956).

The variables represented simultaneously in the tabulations used for the present analysis were ABO and Rh blood types of the mother, together with maternal age, separately for fetal deaths and for live births. No attempt was made to exhaust the relevant information content of the original punchcard records and the magnetic tape images of these cards. Still available for future study are details of sex, birth order, legitimacy, plurality, color, previous stillbirths and child deaths, gestation period, birthweight, and the delivery including operative procedures, maceration of the fetus, autopsy, and cause of death. Rh blood type of father is also recorded in a small proportion of cases, perhaps for 2 to 3 per cent of all live births and fetal deaths as indicated by a small sample.

Except where saved for specific scientific purposes, all such information, in its machine readable form, has in the past been systematically destroyed because of the difficulty of storing large quantities of punchcard records, a common practice in vital statistics systems. Information from current punchcards for births in New York City may perhaps be retained in more compact form as magnetic tape images. Unfortunately, however, blood types of parents have not been punched since 1959, presumably because of the limited use to which the information has been put.

New York City fetal death records are unique in that all products of conception are registerable by law, regardless of gestation period. Of the fetal deaths registered, approximately 30 per cent (27,270 of 92,075 for 1954-59) occurred in the period 0 to 9 weeks. Failures of mothers to be blood typed early in their pregnancies may considerably reduce the proportion of such early losses represented in the persent comparisons. Nevertheless, limited information on

the risk of loss to mothers of various blood types at different stages of pregnancy might perhaps be derived from the present files in quantities adequate for future investigation of the timings of selective fetal eliminations.

One of the purposes of the present account is to indicate the extent to which existing sources of genetic information, especially those relating to selection, are currently underutilized even where the facts are already in a form suitable for certain limited kinds of investigation.

STATISTICAL METHODS

The procedures used (a) to calculate the relative incidence of fetal death for one maternal blood type as compared with another, (b) for combining such values derived from different ages of mother into a single weighted mean relative incidence, and (c) for carrying out chi-square tests of significance of the deviations from unity of relative incidence and of mean relative incidence, are those developed by Woolf (1955) and described in detail by Roberts (1957). These methods were applied by the above authors to studies of associations of blood groups with susceptibility to disease, and have been adapted to their present use.

ABO AND RH DIFFERENCES, CONSIDERED SEPARATELY

As might be expected, mothers of blood type O, in whom fetuses of types A, B, or AB would be regarded as potentially at risk from ABO incompatibility, have more fetal losses than do mothers of non-O blood types (table 1). The effect is substantial, being equivalent to a 7 per cent increase, and is statistically significant. AB mothers have the fewest fetal deaths while those of types A and B fall between the two extremes as would be predicted on simple theory. The risk to AB, A and O mothers, in fact, varies linearly with the predicted numbers of incompatible fetuses (Fig. 1).

Unexpectedly, however, the relative risk to mothers of type B is much less than would be estimated. The effect is too large to be due to differences in the frequency of the B allele in different social or racial groups; when the predicted

TABLE 1. MATERNAL ABO BLOOD TYPE AND RISK OF FETAL DEATH

Blood Type of mother	Fetal Deaths	Live Births (10%)	% Fetal Deaths*	Relative Frequency	χ^2 (d.f. = 1)
O	13,454	25,341	5.31		
B	3,614	7,216	5.01		
A	9,133	18,394	4.97		
AB	1,059	2,149	4.92		
Combined	27,260	53,100	5.13		
Comparisons					
O/non-O			5.31/4.98 =	1.07	17.3
O/AB			5.31/4.92 =	1.08	3.9
B/AB			5.01/4.92 =	1.02	.2
A/AB			4.97/4.92 =	1.01	.1

*Among mothers who have been blood typed.

numbers of incompatible fetuses are based on allele frequencies for Negro populations, in which B is more common, the seeming anomaly remains.

The relative expectations of loss from ABO incompatibilities will differ from those shown in Fig. 1 if an interaction is assumed between the ABO and Rh loci such that Rh incompatibility protects against death due to ABO incompatibility. However, when only the single ABO incompatibilities are considered (ignoring cases of combined ABO-Rh incompatibility) the lower-than-expected risk to mothers of type B remains (Fig. 2).

Rh-negative mothers, like those of blood type O, are more prone to fetal deaths than are their antigen positive counterparts (table 2). However, the over all difference in the case of the Rh blood types is surprisingly small,

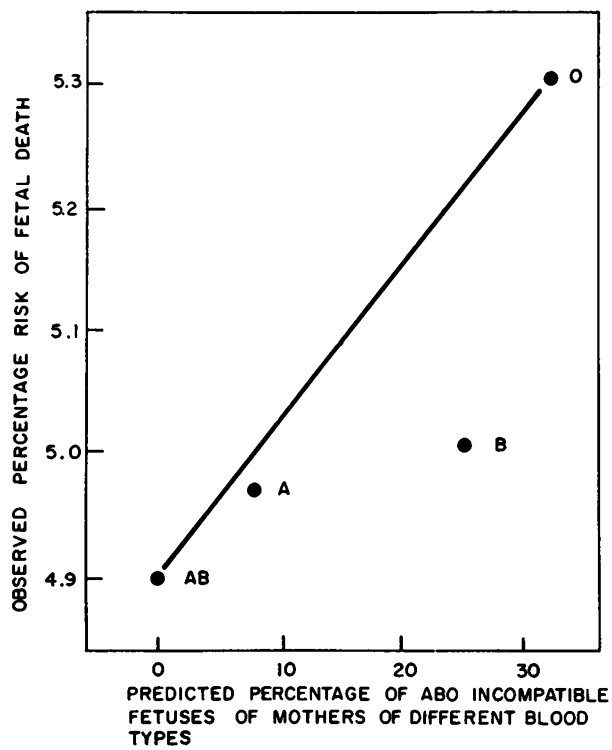

FIG. 1. Observed fetal death risk and predicted ABO incompatibility frequency for mothers of different ABO blood types.

TABLE 2. MATERNAL Rh BLOOD TYPE RISK OF FETAL DEATH

Blood Type of Mother	Fetal Deaths	Live Births (10%)	% Fetal Deaths	Relative Frequency	χ^2
Rh-neg	4,594	8,786	5.23		
Rh-pos	22,666	44,314	5.12		
Comparison Rh-neg/Rh-pos			5.23/5.12 =	1.02	1.1

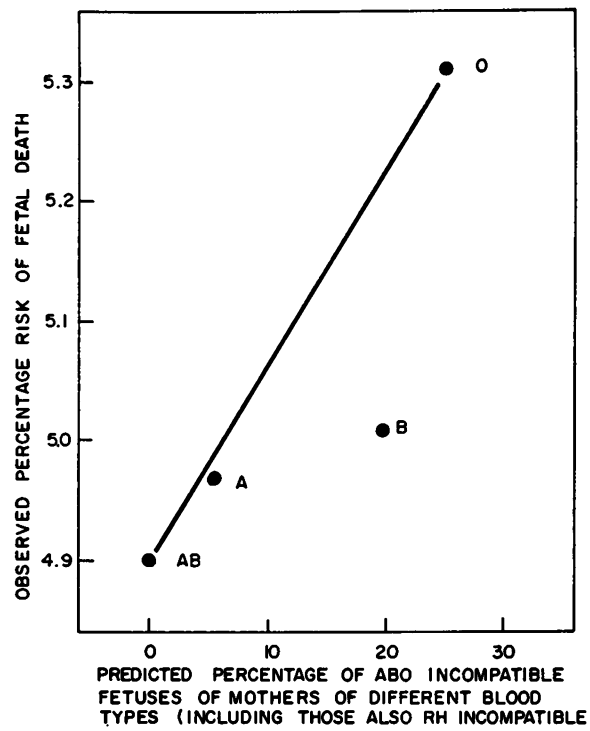

FIG. 2. Observed fetal death risk and predicted ABO incompatibility frequency for mothers of different ABO blood types, excluding cases of combined ABO and Rh incompatibility.

amounting to less than one-third that found in comparisons involving the ABO locus, and is statistically insignificant despite the large numbers of observations. The net importance of major allele differences at the Rh locus would thus seem to have been overestimated in comparison with that of major ABO differences.

INTERACTIONS OF ABO AND RH ALLELES

A belief that the capacity of a mother to eliminate ABO incompatible fetal red cells from her blood stream may serve to protect her against fetal deaths due to simultaneous Rh incompatibility is borne out by detailed comparisons of risks to mothers having different ABO and Rh blood type combinations (table 3). Fetal deaths are most frequent for AB Rh-negative mothers, who may be regarded as most unprotected against Rh sensitization, and least frequent to AB Rh-positive mothers whose offspring are unlikely to be incompatible with respect to either blood group system. The effect is large and statistically significant. Other ABO-Rh maternal constitutions fall in intermediate positions on the scale, although not necessarily in these positions which might be predicted for them.

When mothers below age 25 are excluded, such differences in risks become more striking (table 4) as would be expected since the opportunity for Rh sensitization increases with the number of pregnancies. The AB mothers, when

also in possession of an Rh-positive allele, are exposed to the lowest risk of any of the blood group combinations. Where they lack the Rh-positive allele, however, they become the most vulnerable of all. The difference is large, equivalent to a 66 per cent increase, and is statistically highly significant.

The singular vulnerability of AB Rh-negative mothers is observed consistently at ages from 25 years upward, but is not detected in younger mothers as might be expected where prior sensitization must be involved (table 5). A gradual decline in relative risk with increasing age of mother above age 29 might perhaps be attributed to failure of sensitized mothers to continue having children in the latter part of their reproductive period, a possibility which will be considered again later in another connection.

For mothers of A, B, or O blood type, presence or absence of the Rh-positive gene makes much less difference, amounting to about one-seventh to one-twelfth the effect observed for AB mothers. The degree of protection afforded to Rh-negative mothers by absence of A or absence of B from their own genotypes is

TABLE 3. RISK OF FETAL DEATH BY COMBINED ABO AND Rh TYPE OF MOTHER

Blood Type of Mother	Fetal Deaths	Live Births (10%)	% Fetal Deaths	Relative Incidence	χ^2
AB Rh-neg	199	320	6.22		
O Rh-pos	11,282	21,189	5.32		
B Rh-neg	613	1,152	5.32		
O Rh-neg	2,172	4,152	5.22		
A Rh-neg	1,610	3,162	5.09		
B Rh-pos	3,001	6,064	4.95		
A Rh-pos	7,523	15,232	4.94		
AB Rh-pos	860	1,829	4.70		
Comparisons					
AB, Rh-neg/Rh-pos			6.22/4.70 =	1.32	7.8
B, Rh-neg/Rh-pos			5.32/4.95 =	1.08	1.9
A, Rh-neg/Rh-pos			5.09/4.94 =	1.03	.8
O, Rh-neg/Rh-pos			5.22/5.32 =	.98	.5

TABLE 4. RISKS OF FETAL DEATH TO OLDER MOTHERS OF DIFFERENT BLOOD TYPES

Blood Type of Mother	Fetal Deaths	Live Births (10%)	% Fetal Deaths	Relative Frequency	χ^2
Mothers age 25 and over					
AB Rh-neg	164	200	8.20	1.66	18.9
AB Rh-pos	618	1,247	4.95		
B Rh-neg	459	756	6.07	1.09	1.7
B Rh-pos	2,152	3,860	5.58		
O Rh-neg	1,621	2,647	6.37	1.06	2.8
O Rh-pos	8,211	13,615	6.03		
A Rh-neg	1,174	2,020	5.83	1.05	1.5
A Rh-pos	5,512	9,969	5.54		

thus not so very different from that enjoyed when both are absent simultaneously. This might seem, superficially, to suggest a capacity on the part of type A mothers to get rid of fetal red cells of type A that have entered the maternal blood stream (as well as to get rid of those of type B) and a corresponding capacity of type B mothers to get rid of fetal cells of type B, and for each to do so with almost as much dispatch as would a mother of blood group O. Such responses are inherently unlikely, however, and an alternative explanation must be sought.

The same sort of comparison may be made the other way round. Among Rh-positive mothers the risk of fetal death is lowest when A and B are both present in the maternal genotype. An increase of 12 to 13 per cent is observed when either A or B is absent, and of 22 per cent when both are absent simultaneously (table 6). The increases in risk for the two types of absence are thus almost strictly additive. The same conclusion cannot be drawn, however, for Rh-negative mothers. Among these, the simultaneous absence of the A and the B

TABLE 5. EFFECT OF MATERNAL AGE ON RELATIVE FREQUENCY OF FETAL DEATHS TO AB Rh-NEGATIVE AND AB Rh-POSITIVE MOTHERS

Age Group of Mother	AB Rh-negative Mothers		AB Rh-positive Mothers		Relative Frequency	χ^2
	Fetal Deaths	Live Births (10%)	Fetal Deaths	Live Births (10%)		
0-19	8	20	39	106	1.09	
20-24	27	100	203	476	.63	
25-29	65	98	227	637	1.86	
30-34	54	70	206	432	1.62	
35-39	34	27	138	149	1.36	
40-49	11	5	47	27	1.24	
Weighted mean (all ages)					1.34	8.0
Weighted mean (ages 25 and up)					1.65	17.9

TABLE 6. EFFECT OF ABSENCE OF ABO BLOOD FACTORS IN Rh-NEGATIVE AND Rh-POSITIVE MOTHERS AGE 25 AND OVER ON THE RISK OF FETAL DEATH

ABO Factor Missing from Mother	Risk of Fetal Death (per 100 live births)	Difference as Compared with "Neither Missing"	% Change in Risk
Rh-negative mothers			
neither missing	8.20	—	—
A missing	6.07	—2.13	26 % decrease
B missing	5.82	—2.38	30 % decrease
both missing	6.37	—1.83	22 % decrease
Rh-positive mothers			
neither missing	4.96	—	—
A missing	5.58	+0.62	13 % increase
B missing	5.54	+0.58	12 % increase
both missing	6.03	+1.07	22 % increase

allele has, if anything, less effect (in this case observed as a reduction in risk) than absence of either allele alone.

The source of the anomaly in both kinds of comparison may be identified as associated almost wholly with the AB Rh-negative maternal phenotype. When all other maternal phenotypes are arrayed in order of risk of fetal death, this risk is found to rise smoothly with the number of antigenically active alleles that are unrepresented in the maternal genotype (Fig. 3) although there is no apparent theoretical reason why this should be so. Only the AB Rh-negative blood type fails to fit neatly into the scheme so as to appear as a special case.

The known interactions between the ABO and Rh systems might, at first sight, seem adequate to account for the relationships apparent in Fig. 3. AB Rh-negative mothers would be most strongly prone to fetal loss from Rh incompatibility, where fathers are unselected for ABO blood type, owing to the absence of possible protection from ABO incompatibilities. AB Rh-positive mothers would not be susceptible to loss from either ABO or Rh incompatibilities. It is difficult, however, to account for the more striking features of the observed relationship.

The expected percentages of fetuses rendered incompatible by the A, B, and Rh-positive genes, and combinations thereof, may be calculated separately for each maternal phenotype from the known gene frequencies (table 7). Such

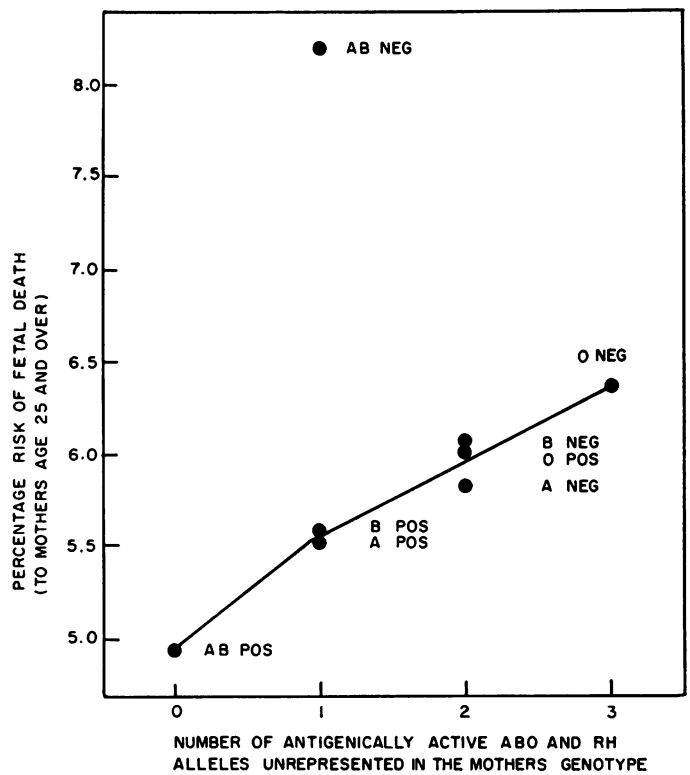

FIG. 3. Effect of absences of antigenically active alleles.

calculations show that for no one sort of incompatibility, and for no simple combination of incompatibilities and protective effects, would one expect either (a) the observed close correlation of risk of fetal loss with number of antigenically active alleles unrepresented in the mother, or (b) the very large difference in risk to AB Rh-negative mothers as compared with other high risk maternal phenotypes.

The proportions of fetuses at risk from either kind of single incompatibility (ABO or Rh) may be plotted in a similar manner, excluding those at risk from double incompatibilities (ABO and Rh) as not being especially vulnerable (Fig. 4). The relative risk to mothers of the various blood types that would be expected on these assumptions are seen to differ widely from the observed risks shown in Fig. 3, in the respects noted above. This is true whether the predictions are based on gene frequencies for whites or for negroes. No set of assumptions concerning the nature of the possible locus and allele interactions has been found that provides anything approaching quantitative agreement between the observed and expected relative risks to fetuses of mothers of the different blood groups.

Differences in allele frequencies associated with various social and racial groups within the population having widely different fetal death rates and opportunities for ascertainment of such deaths might, of course, modify predictions made on simple theory. However, the essential similarity between predictions based on allele frequencies for whites and for Negroes argues against an interpretation in these terms. Added to this, the precision with which observed risk of fetal death is correlated with the number of antigenically active ABO and Rh alleles unrepresented in the mother's genotype (when the AB Rh-negative mothers are excluded), where no such precision is predicted on present theory, would seem hardly to be possible if it were merely fortuitous and secondary to population inhomogeneities of a social or racial kind.

Perhaps the number of antigenically active ABO and Rh alleles unrepresented in the mother's genotype is, in fact, the important underlying variable for all

TABLE 7. EXPECTED PROPORTIONS OF INCOMPATIBLE FETUSES TO WHITE AND NEGRO MOTHERS OF DIFFERENT PHENOTYPES

Race, and Kind of Incompatibility	% of Fetuses Incompatible, by Maternal ABO and Rh Phenotype							
	O Rh-neg.	O Rh-pos.	A Rh-neg.	A Rh-pos.	B Rh-neg.	B Rh-pos.	AB Rh-neg.	AB Rh-pos.
White Mothers[1]								
ABO only (single)	12.5	32.6	3.0	7.8	9.5	24.8	0.0	0.0
Rh only (single)	41.6	0.0	56.9	0.0	46.4	0.0	61.7	0.0
ABO and Rh (double)	20.1	0.0	4.8	0.0	15.3	0.0	0.0	0.0
Negro Mothers[2]								
ABO only (single)	8.5	31.4	3.6	13.3	4.9	28.1	0.0	0.0
Rh only (single)	49.9	0.0	63.1	0.0	59.6	0.0	72.8	0.0
ABO and Rh (double)	22.9	0.0	9.7	0.0	13.2	0.0	0.0	0.0

[1]Based on allele frequencies. O = .674, A = .248, B = .078 (Glass and Li, 1953); Rh-negative = .383, Rh-positive = .617 (Sinnott, Dunn and Dobzhansky, 1958).

[2]Based on allele frequencies: O = .685, A = .181, B = .134 (Glass and Li, 1953); Rh-negative = .272, Rh-positive = .728 (Sinnott, Dunn and Dobzhansky, 1958).

except the high-risk AB Rh-negative mothers. As applied to the two extreme opposite classes of mothers, AB Rh-positive and AB Rh-negative, predictions based on the above view do not necessarily differ from those which would be inferred from a protective effect of ABO incompatibility against Rh sensitization of the mother. Only for the medium-risk mothers of the remaining blood types would predictions based on the two alternative views differ. And, for these mothers, the observed risks of fetal deaths are precisely predictable only on the former view.

The present data do not necessarily conflict with previous findings although they might perhaps appear to do so. For example, Cohen (1960) has shown, by means of an exceedingly thorough statistical analysis, that the frequencies of the different ABO phenotypes deviate significantly from random expectation among sensitized Rh-negative mothers married to Rh-positive husbands, among the husbands of the sensitized women, and among living offspring. In each case, the deviation is in the direction that would be expected if ABO incompatibility of the fetus tends to protect against Rh-sensitization of the mother. There are at least two possible kinds of effect, however, that cannot be excluded by this prior work.

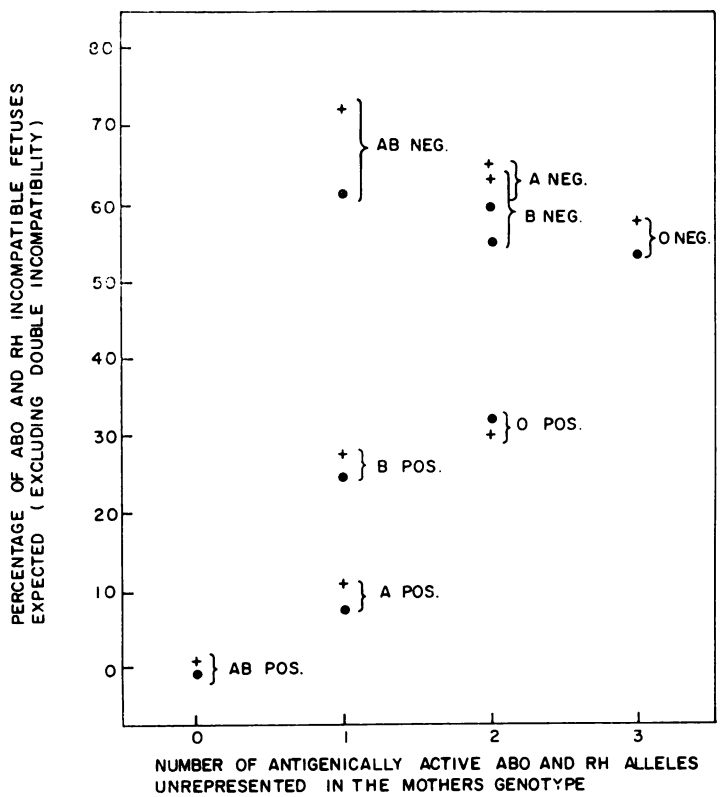

FIG. 4. Frequency of incompatible fetuses expected of white and Negro mothers. Circle = white; Cross = Negro.

First, the analysis carried out by Cohen was not designed to account quantitatively for the relative magnitudes of the various deviations from random expectation, in terms of partial or complete protection of this sort alone, and thus does not wholly exclude a possible disproportionate risk of sensitization among mothers of certain ABO constitutions as compared with others, even where fetal incompatibilities, if any, are of similar kinds.

Second, it is at least a formal possibility that the various ABO and Rh maternal phenotypes might be associated with differences in risk of fetal loss other than those arising out of the known antigenic responses, and perhaps uncorrelated with fetal ABO or Rh constitution. If so, these additional risks would remain undetected with the kinds of information analyzed by Cohen, and could only be satisfactorily studied using ascertainments of actual fetal deaths.

Further discussion of interpretations would not be profitable at this point, especially as the primary purpose of the paper is to emphasize the extent of the present failure to integrate, and to make systematic use of, the large quantities of information on blood groupings, family reproductive events, and social characteristics that are already being recorded routinely.

AGE ANALYSIS — RATIOS OF BLOOD TYPES AMONG MOTHERS OF LIVEBORN INFANTS AND OF DEAD FETUSES, FOR DIFFERENT AGE GROUPS OF MOTHER

The special predisposition of AB Rh-negative mothers to lose their fetuses should operate to increase the proportion of Rh-positive blood types among AB mothers who are successful in producing live offspring. This effect is observed and, as would be expected, is all the more striking when mothers below age 25 are excluded (table 8).

Substantially lower proportions of Rh-positives are found among types A, B, and O mothers of liveborn offspring, and the proportion is lowest for type A

TABLE 8. PROPORTIONS OF Rh BLOOD TYPES AMONG MOTHERS OF DIFFERENT ABO CONSTITUTIONS AND OF DIFFERENT AGE GROUPS

ABO Blood Type of Mother	Rh-Positive Mothers of Liveborn	Rh-Negative Mothers of Liveborn	Ratio pos./neg. (for mothers of liveborn)	Ratio pos./neg. (for mothers of dead fetuses)
All ages of mother[1]				
AB	1,829	320	5.71	
O	21,189	4,152	5.27	
B	6,064	1,152	5.26	
A	15,232	3,162	4.82	
Mothers 25 and over[2]				
AB	1,247	200	6.23	3.77
O	13,615	2,647	5.15	4.70
B	3,860	756	5.10	5.07
A	9,969	2,020	4.94	4.69

[1]Data from table 3.

[2]Data from table 4. The over all ratio of positive/negative is 5.05 as based on combined data for all mothers of liveborn infants and dead fetuses, and allowing for the fact that the data for livebirths represent only a 10 per cent sample.

mothers in whom the risk of fetal death is known to be least affected by presence or absence of the Rh-positive allele (see table 4). This large difference between AB and A mothers is statistically significant and is consistent for all age groups from 25 years up (table 9). The relationships are approximately of the kinds predictable from known ABO-Rh interactions, except that type O mothers would be expected to be more extreme in relation to types A and B.

In view of such observed deficiencies of the Rh-negative allele among mothers of liveborn infants we might expect to find increased numbers among mothers of dead fetuses as compared with the overall ratio. This, however, is only partially true and there is an apparent failure of the two groups of mothers to complement one another. At least three interpretations are possible: (a) Fetal deaths to Rh-negative mothers may tend to be selectively lost to the present study through some substantial fraction of them occurring prior to the usual time at which a mother is blood typed, thus leading to a higher-than-expected ratio of positive/negative mothers of dead fetuses. (b) A substantial under-reporting of all kinds of fetal deaths, irrespective of cause or maternal blood group, might prevent some part of the deficiency of Rh-negative phenotypes which are deficient among mothers of liveborn infants from being represented as an excess among mothers of dead fetuses. (c) Mothers of Rh-negative constitution might tend, where they have experienced prior difficulties from Rh incompatibility, to refrain from further reproduction. The present data provide no rigorous discrimination between these alternatives, although at first sight the second and third will seem more in keeping with previous findings.

This line of reasoning may be pursued quantitatively in the case of AB mothers and some consequences of the various interpretations may be examined. Among mothers of age 25 and over who have had dead fetuses the ratio of Rh-positive/Rh-negative is only 3.77 (*i.e.*, 618/164; see tables 4 and 8) as compared with 6.23 for those who have had live births. The directions of the two deviations from an over all ratio of approximately 5.0 for all mothers irrespective of ABO blood type are as expected, but their magnitudes are not. The shift to a ratio of 6.2 for AB mothers of liveborn infants implies a deficiency of about 33 Rh-negative mothers per thousand among those of AB blood type who have

TABLE 9. PROPORTION OF Rh-POSITIVE MOTHERS OF LIVEBORN INFANTS, AMONG THOSE WHO ARE AB AS COMPARED WITH A, BY AGE GROUP OF MOTHER

Age Group of Mother	AB Mothers of Liveborn		A Mothers of Liveborn		Relative Frequency	χ^2
	Rh-pos	Rh-neg	Rh-pos	Rh-neg		
0-19	106	20	839	208	1.31	
20-24	476	100	4,424	934	1.01	
25-29	637	98	5,042	1,019	1.34	
30-34	432	70	3,216	624	1.20	
35-39	149	27	1,391	309	1.23	
40-49	29	5	320	68	1.23	
Weighted mean (all ages)					1.19	7.2
Weighted mean (ages 25 and up)					1.27	8.9

succeeded in having live offspring. Only a small fraction of this deficiency is accounted for by the excess of Rh-negatives found among AB mothers of dead fetuses which, when calculated, is found to be only about 3 per 1,000 live births to AB mothers. Thus, for each thousand live births to AB mothers there is an apparent deficiency of about 33 AB Rh-negative mothers of which only about 3 appear as an excess of Rh-negative constitution among mothers of dead fetuses. If only one of the suggested interpretations were correct we would have to suppose that the thirty who are not accounted for, either (a) lost their fetuses before being blood-typed, (b) represented a failure to report as much as 90 per cent of all fetal deaths, or (c) refrained from reproducing because of previous Rh difficulties. In view of the magnitude of the effect it is altogether possible that more than one of these causes may be operating.

A similar line of argument might be followed using data from other ABO blood types of mothers, but would be less profitable because the differences are small and of limited statistical significance. That A, B and O mothers differ so little from one another, and so much from AB mothers, has been noted earlier in another connection.

Such deficiencies of Rh-negative individuals among mothers of liveborn infants are particularly noticeable in the middle reproductive years (table 10) as is strikingly shown for AB mothers (Fig. 5). Presumably, younger Rh-negative mothers tend not to have been sensitized and so are better represented in the early part of the reproductive period than in the middle. Just why they should again become well represented towards the end of the period is not immediately apparent, although the trend occurs consistently within all ABO blood types. Conceivably, sensitized women may choose to continue reproducing longer in order to achieve desired family sizes, or perhaps there are biological reasons that are still unknown.

Blood types of mothers of dead fetuses do seem to provide a clue (Fig. 6). For those of type AB, in whom such effects are most easily studied, there is a complementary rise in the proportion of Rh-positives in the latter part of the reproductive period. This would argue that the additional Rh-negative mothers who attempt to reproduce at this time in their lives are successful at it and are

TABLE 10. EFFECT OF MATERNAL AGE ON THE PROPORTIONS OF Rh BLOOD TYPES AMONG ALL MOTHERS OF LIVEBORN INFANTS

Age Group of Mother	All Mothers of Liveborn		Ratio	Relative Incidence	χ^2
	Rh-pos	Rh-neg	pos/neg		
0-19	2,932	587	5.00		
20-24	12,691	2,556	4.94		
25-29	14,541	2,716	5.36		
30-34	9.009	1,736	5.24		
35-39	4,158	880	4.73		
40-49	893	191	4.67		
Comparison					
25-34	23,640	4,452	5.31		
not in this range	20,674	4,224	4.88	1.09	13.4

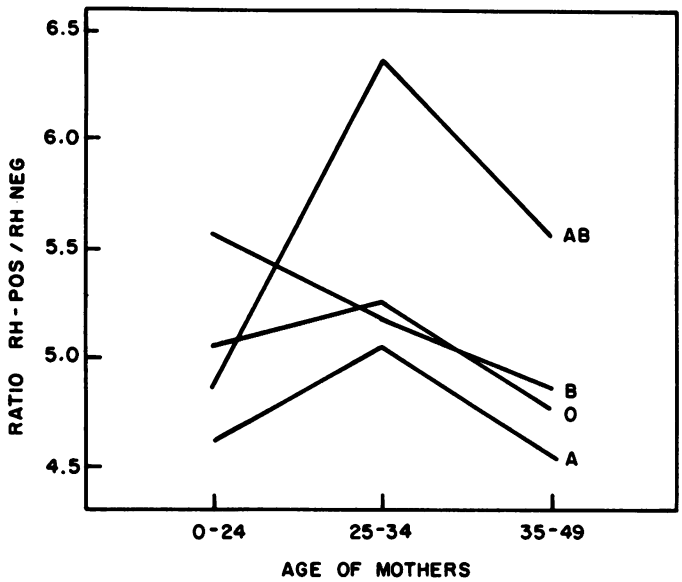

FIG. 5. Age analysis, mothers of liveborn infants.

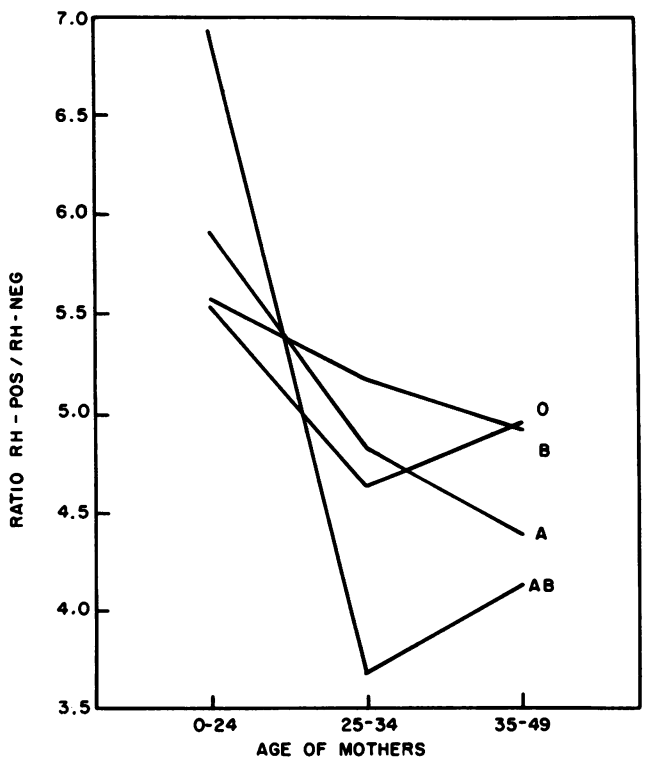

FIG. 6. Age analysis, mothers of dead fetuses.

not contributing unduly to the fetal deaths. Thus, it would be wrong to suppose that they are sensitized women, who because of earlier difficulties, are completing their families late.

DISCUSSION

Studies of mortality are not usually designed to throw light on that component of selection associated with fertility differences as such. However, an inference may perhaps be drawn from the present data regarding the theory that mothers tend to "compensate" for fetal deaths due to Rh incompatibility, and to perpetuate the negative allele by attempting to replace the lost child with a live one. While one report of a higher parity among Rh-negative mothers attending a blood clinic suggests that they may be more fertile than average (Glass, 1950), only a study of child spacing can show that the mother of a dead fetus or child becomes pregnant again sooner than would normally be expected.

Such child spacing studies are now technically feasible on a fairly large scale using the vital records systems, but limited findings have not so far tended to support the "compensation theory" of selection for the Rh-negative allele, at least as applied to current births (Newcombe and Rhynas, 1962, and unpublished data for British Columbia).

If, as has been suggested by this study, some substantial proportion of fetal losses to Rh-negative mothers occur early in pregnancy it may be that, instead of consciously compensating for loss of a dead infant, the mother is merely trying, or perhaps permitting herself, to have a baby. The genetic consequences would be much the same whatever the stage at which the loss occurred.

It is to be hoped that extensive records of fetal deaths at all stages, such as those now kept by the City of New York, will one day also be linked into family groupings to permit the two aspects of selection, namely fertility and child spacing on the one hand and fetal and child mortality on the other, to be studied simultaneously.

SUMMARY

Risk of fetal death in relation to maternal ABO and Rh blood type has been studied using the New York City birth records for the period 1954-59 in which both blood groups had been recorded. In all, 27,260 records of fetal deaths together with 53,100 records of live births, the latter representing a 10 per cent sample, were used in the study.

Considering the two loci separately, differences in ABO type are associated with substantially more fetal deaths than are differences in Rh type. A non-additivity is shown in the protection afforded by presence in the maternal genotype of A and of B, singly and in combination.

An observed high risk of fetal loss to AB Rh-negative as compared with AB Rh-positive mothers is as would be expected on the current view that ABO incompatibility protects against the consequences of Rh incompatibility.

Alleles at the two loci were observed to interact in an unexpectedly simple manner, however, when AB Rh-negative mothers were excluded from the com-

parisons. The risk of fetal death to mothers above age 24 increased uniformly with the number of antigenically active alleles missing from the maternal genotype. This relationship differs substantially from that expected on current theory, and is too precise and uniform to be easily interpretable as a chance consequence of minor modifying factors. The possibility that the number of antigenically active alleles missing from the maternal genotype may be the important underlying variable, for mothers other than those of AB Rh-negative constitution, will be difficult to exclude unless alternative assumptions of a more conventional nature can be found which will provide equally good quantitative agreement between observed and expected relative risks. Only the AB Rh-negative mothers fail to fit this scheme, they being nearly twice as vulnerable as would be expected.

A deficiency of Rh-negative mothers of liveborn children above age 24 cannot be wholly accounted for by the observed excess among mothers of dead fetuses, the discrepancy being particularaly striking for AB mothers. Possible contributing factors are discussed.

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REFERENCES

CHUNG, C. S., AND MORTON, N. E., 1961. Selection at the ABO locus. *Amer. J. Hum. Genet.* 13: 9-27.

COHEN, B. H. 1960. ABO-Rh interaction in an Rh-incompatibly mated population. *Amer. J. Hum. Genet.* 12: 180-209.

GLASS, B. 1950. The action of selection on the principle Rh alleles. *Amer. J. Hum. Genet.* 2: 269-278.

GLASS, B., AND LI, C. C. 1953. The dynamics of racial intermixture; an analysis based on the American Negro. *Amer. J. Hum. Genet.* 5: 1-20

LEVINE, P. 1958. The influence of the ABO system on Rh hemolytic disease. In: *Natural Selection in Man*, J. N. Spuhler, ed. Detroit: Wayne State Press.

NEWCOMBE, H. B., AND RHYNAS, P. O. W. 1962. Child spacing following stillbirth and infant death. *Eugen. Quar.* 9: 25-35.

REED, T E., AND AHRONHEIM, J. H. 1959. An association between ABO blood groups and fertility in a normal American population. *Nature* (Lond.) 184: 611-612.

REED, T. E., AND KELLY, E. L. 1958. The complete reproductive performance of 161 couples selected before marriage and classified by ABO blood group. *Ann. Hum. Genet.* 22: 165-208.

ROBERTS, J. A. F. 1957. Blood groups and susceptibility to disease. *Brit. J. Prev. Soc. Med.* 11: 107-125

SINNOTT, E. W., DUNN, L. C., AND DOBZHANSKY, T. 1958. *Principles of Genetics*, 5th ed., New York: McGraw-Hill.

SONNEBORN, T. M. 1956. Paternal age and stillbirth rate in man. *Rec. Genet. Soc. Amer.* No. 25: 661.

WOOLF, B. 1955. On estimating the relationship between blood group and disease. *Ann. Hum. Genet.* 19: 251-253.