# ABO and Rh Incompatibility. II. Is There a Dual Interaction in Combined ABO and Rh Incompatibility?

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The ameliorating influence of ABO incompatibility on Rh incompatibility* manifestation has long been recognized, but the reported suggestion that Rh status may also influence ABO selection has not yet been adequately examined.

Ever since Levine (1943) first pointed out the deficiency of ABO incompatibles among mothers of infants with Rh erythroblastosis fetalis, a number of studies have confirmed the improved prognosis for pregnancies of Rh-incompatible women if they are also ABO-incompatibly mated (Reepmaker et al. 1954, 1962; Reepmaker 1955; Levine 1958, 1959; Cohen 1960. However, little attention has been given to the possible impact of Rh incompatibility on ABO selection until recently (Cohen and Sayre 1968), even though Grubb and Sjöstedt (1954–1955), on the basis of a study of intrauterine death, and Bresler (1964), on the basis of an investigation of postnatal mortality of offspring, had suggested that the coexistence of ABO and Rh incompatibility is less deleterious than either ABO or Rh incompatibility alone.

The purpose of this report is (1) to consider the action of combined ABO and Rh incompatibility in data from the Child Health and Development Studies (CDS) with regard to the two aspects of ABO-Rh interaction—the well-documented influence of ABO incompatibility status on Rh selection, referred to as interaction 1, and the influence of Rh compatibility status on ABO selection, referred to as interaction 2—and (2) to test the fit of these observations to models of ABO-Rh interaction previously used in a study of New York City vital records (Cohen and Sayre 1968).

Since the CDS data included paternal as well as maternal blood types and other detailed information not available in the New York series, more definitive classification

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* The term "incompatibility" is used as previously (Cohen 1970) to refer to mating (i.e., maternal-paternal) blood type incompatibility. ABO incompatibility (ABOi) is defined as the absence in the female spouse of an A and/or B antigen when present in the male spouse. Similarly, Rh incompatibility (Rhi) is defined as the absence of $Rh_0$ (D) antigen in the female spouse when present in the male spouse. The term "spouses" is used to indicate members of a mating pair irrespective of legal marriage status. ABOc designates ABO compatibility and Rhc, Rh compatibility.

of compatibility status and more detailed examination of other pertinent factors—for example, parity—can be carried out. The background of the CDS families, members of a prepaid medical insurance plan and for the most part of middle and upper-middle socioeconomic status, has been described elsewhere (Yerushalmy 1964; Reed 1967). More than 7,450 Caucasian families met the preestablished criteria for inclusion in this investigation in terms of registration, delivery date and place, typing of paternal blood sample at the study pregnancy, and lack of inconsistency of blood type of parents and child with recognized modes of inheritance.

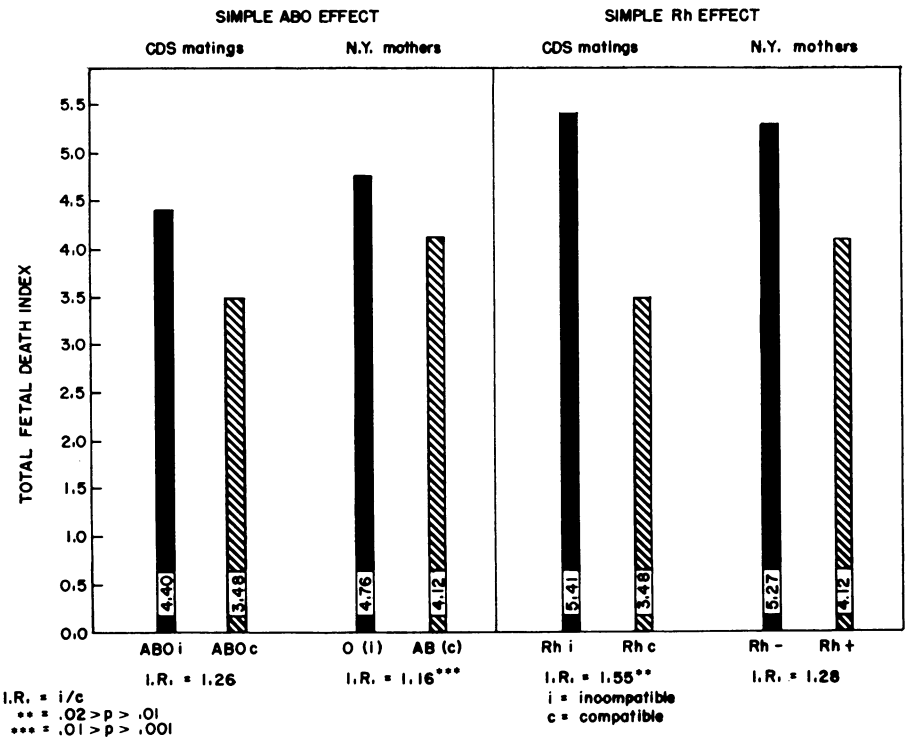


FIG. 1.—Effects of simple incompatibility: ABO and Rh

The CDS findings on single incompatibility already presented in detail (Cohen 1970) are briefly summarized in figure 1 and table 1. They show very consistent patterns. With simple ABO incompatibility (i.e., ABO incompatibility in the absence of Rh incompatibility), fetal loss is increased. The total fetal death index* for ABOi matings is 26% higher than for ABOc matings (4.40 vs. 3.48), just as in the previously studied New York series, O mothers—the type most often ABO-incompatibly mated—had an f.d.i. 16% ($P < .01$) higher than the always ABO-compatibly

* Fetal death index = f.d.i. = 100 × fetal deaths of given mating class or maternal group/live births of same mating class or maternal group. The f.d.i. may be specified as *total f.d.i.*, based on fetal deaths of all gestational ages; *early f.d.i.*, based on fetal deaths less than 20 weeks of gestational age; or *late f.d.i.*, based on fetal deaths at 28 weeks or more.

mated type AB mothers (4.76 vs. 4.12) (Cohen and Sayre 1968). Similarly, with simple Rh incompatibility (i.e., Rh incompatibility in the absence of ABO incompatibility), fetal wastage is significantly increased. In the CDS series, Rh-incompatible matings have a total f.d.i. 55% ($P < .02$) higher than that of Rhc matings (5.41 vs. 3.48); again in the New York series the total f.d.i. for Rh negative mothers was 28% higher than for Rh positive mothers (5.27 vs. 4.12), though the latter difference was not statistically significant. Thus, the effects of simple ABO and Rh incompatibility, respectively, are as marked in the CDS series as in the New York series, and possibly more so.

## METHOD

The CDS method of sample selection and criteria for exclusion of discrepancies in maternal, paternal, or infant blood types have been described (Cohen 1970). The

TABLE 1

A. EFFECTS OF SINGLE ABO INCOMPATIBILITY ON FETAL LOSS (Rhc TYPES ONLY) BY GESTATIONAL AGE OF MANIFESTATION

| | EARLY | | LATE | |
|---|---|---|---|---|
| | f.d.i. | i/c Ratio | f.d.i. | i/c Ratio |
| CDS matings[a]— | | | | |
| Rhc only: | | | | |
| ABOi | 2.90 | 1.48 | 0.86 | 0.93 |
| ABOc | 1.96 | | 0.92 | |
| N.Y. mothers— | | | | |
| Rh+ (c) only: | | | | |
| O (i) | 3.15 | 1.27**** | 1.10 | 0.97 |
| AB (c) | 2.48 | | 1.14 | |

B. EFFECTS OF SINGLE Rh INCOMPATIBILITY ON FETAL LOSS (ABOc TYPES ONLY) BY GESTATIONAL AGE OF MANIFESTATION

| | EARLY | | LATE | |
|---|---|---|---|---|
| | f.d.i. | i/c Ratio | f.d.i. | i/c Ratio |
| CDS matings[a]— | | | | |
| ABOc only: | | | | |
| Rhi | 3.18 | 1.62* | 1.27 | 1.38 |
| Rhc | 1.96 | | 0.92 | |
| N.Y. mothers— | | | | |
| ABOc only: | | | | |
| Rh− | 2.58 | 1.04 | 2.31 | 2.03**** |
| Rh+ | 2.48 | | 1.14 | |

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index.

[a] All ICD.

* $.05 > P > .02$.

**** $.001 > P > .0001$.

analysis is carried out for three subgroups as follows: (1) pregnancies irrespective of initial date of contact for prenatal care relative to date of last menstrual period, but excluding pregnancies with discrepant blood types in mother-father-infant combinations (*all ICD*); (2) those pregnancies where initial contact date was within 17 weeks of last menstrual period and where there were no discrepant blood types in the mother-father-infant combinations (*ICD < 17*); and (3) pregnancies irrespective of date of initial visit or blood type discrepancies in family combinations (*no exclusions*).

Where only one tabulation is to be presented or subclassification (such as for maternal age or parity) leads to small numbers in individual cells, "all ICD" tabulation is used, since that procedure excludes only on the basis of discrepant blood types and thus provides maximum utilization of the data.

For simplicity of reference, symbol abbreviations are used throughout: c = compatible; i = incompatible. In matings, Rh status is specified first and ABO status second; thus ii matings are doubly incompatible, cc matings are doubly compatible, ic matings are singly Rh incompatible, and ci matings are singly ABO incompatible.

The procedure for the investigation of the impact of combined incompatibility is as follows:

First, the fetal death indices for pooled gestational ages are compared for four mating groups classified by combined compatibility status: the doubly incompatible matings (ii); the two types of singly incompatible matings (ic, ci); and the doubly compatible (cc).

Second, the CDS observations are examined in terms of the interaction models where the relative fetal loss of pertinent mating groups is expressed in (1) a simple $2 \times 2$ cross-classification of matings and (2) interaction ratios hypothesized for the New York series (Cohen and Sayre 1968) but using the parameters that are appropriate for the CDS series (for example, mating combinations rather than maternal types, and fetal death indices based on pooled gestational ages rather than specific age of occurrence). It is necessary to use total instead of early and/or late fetal deaths for the interaction evaluation in the CDS series, since early as well as late fetal loss was observed to be elevated with Rh incompatibility and thus no specific gestational age can be delineated for the manifestation of Rh incompatibility (table 1), as discussed in another report (Cohen 1970).

The details of each set of models are presented in the next section directly preceding the findings in order to clarify the comparisons between expectancies and observations.

## RESULTS

Table 2 compares the effects of double incompatibility with the fetal wastage observed in single ABO and Rh incompatibility. Clearly, the f.d.i.'s of the doubly incompatible matings are lower than those of either of the singly incompatible matings in the CDS series. Not only does *simple Rh incompatibility* show greater fetal loss than combined ABO and Rh incompatibility in all subgroups in the CDS series (5.41 vs. 3.41, 6.05 vs. 4.20, 5.42 vs. 3.29), but, similarly, *simple ABO incompatibility* yields higher f.d.i.'s than doubly incompatible types (4.40 vs. 3.41, 5.03 vs. 4.20, 4.32 vs. 3.29), a result which suggests that combined ABO-Rh incompatibility is less detri-

mental than either ABO or Rh incompatibility *alone*. Thus, in the CDS series both aspects of ABO-Rh interaction are quite apparent from the comparison of total fetal loss among double incompatibles and single incompatibles, whereas in the New York series the comparisons of total fetal wastage provide evidence for only one aspect of interaction: interaction 1 (ABO → Rh selection). Interaction 2 (Rhi → ABO selection) was suggested on the basis of further examination of the New York data by gestational age of occurrence of fetal loss (Cohen and Sayre 1968).

TABLE 2

TOTAL FETAL DEATH INDICES (f.d.i.) AND ABO-Rh COMPATIBILITY STATUS

| CDS MATINGS | DOUBLY INCOMPATIBLE | SINGLY INCOMPATIBLE | | DOUBLY COMPATIBLE |
|---|---|---|---|---|
| | Rhi-ABOi (ii) | Rhi-ABOc (ic) | Rhc-ABOi (ci) | Rhc-ABOc (cc) |
| All ICD: | | | | |
| FD | 12 | 34 | 97 | 140 |
| LB | 352 | 629 | 2,207 | 4,027 |
| f.d.i. | 3.41 | 5.41 | 4.40 | 3.48 |
| ICD <17 weeks | | | | |
| FD | 12 | 31 | 89 | 131 |
| LB | 286 | 512 | 1,769 | 3,178 |
| f.d.i. | 4.20 | 6.05 | 5.03 | 4.12 |
| No exclusions: | | | | |
| FD | 12 | 35 | 99 | 144 |
| LB | 365 | 646 | 2,290 | 4,171 |
| f.d.i. | 3.29 | 5.42 | 4.32 | 3.45 |
| NEW YORK MOTHERS | (O−) | (AB−) | (O+) | (AB+) |
| FD | 1,108 | 98 | 7,581 | 572 |
| LB | 2,129 | 186 | 15,912 | 1,389 |
| f.d.i. | 5.20 | 5.27 | 4.76 | 4.12 |

NOTE.—i = incompatible, c = compatible; FD = fetal deaths, LB = live births.

It is also interesting to note that the f.d.i.'s of the doubly incompatible CDS matings (ii) are no higher than those of the doubly compatible matings (cc). It is not clear at this time whether this derives entirely from the buffering of one incompatibility effect by the other, or from a combination of buffering and heterozygote advantage (Grubb and Sjöstedt 1955; Chung and Morton 1961; Matsunaga 1962), the latter becoming discernible when the deleterious potential of each incompatibility is partially counteracted by the interaction of simultaneous incompatibility in both systems.

The impact of combined incompatibility is most graphically demonstrated by the interaction models. In figure 2 the interaction pattern is presented in a 2 × 2 cross-

classification of matings where the effects are indicated in terms of matings for the CDS series and mothers for the New York series: Rh status is given on the horizontal axis and ABO status on the vertical axis, with greater-than and less-than symbols used to specify relative fetal death indices. Thus, if ci matings have higher f.d.i.'s than cc matings, that is consistent with ABOi selection, a simple ABO incompatibility effect; if ic matings have higher f.d.i.'s than cc matings, that is consistent with Rhi selection, a simple Rh incompatibility effect. Given both a simple ABOi effect and a simple Rhi effect, then, if doubly incompatible (ii) matings have lower f.d.i.'s than singly Rhi (ic) matings (ii < ic), an interaction has occurred whereby ABO incompatibility has a favorable or protective influence against Rh selection (called interaction 1). If ii matings have lower f.d.i.'s than singly ABOi (ci) matings (ii < ci),

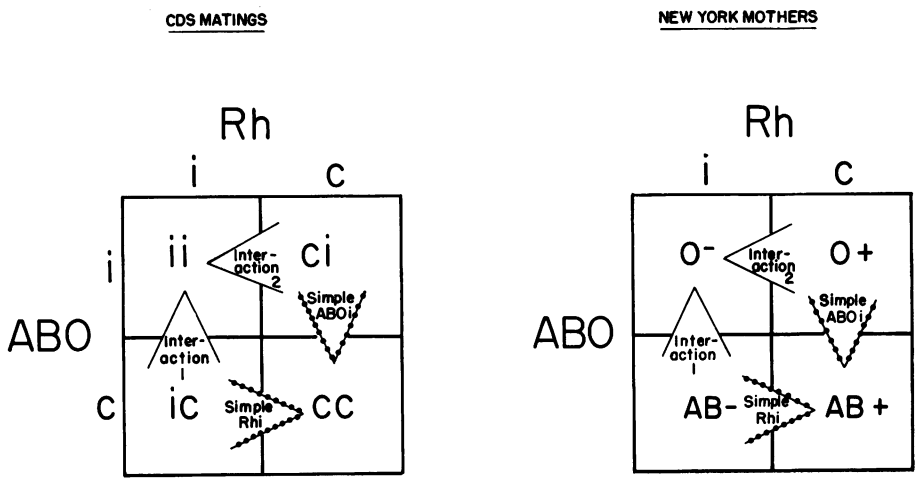


FIG. 2.—Summary of interaction models as applied to fetal death indices for CDS matings and New York mothers. Interaction 1 and interaction 2 are not mutually exclusive.

an interaction has occurred whereby Rhi has a favorable or protective influence against ABO selection (called interaction 2).

Similarly, models can be indicated in terms of ratios of f.d.i.'s as presented for the original New York models, but for the CDS series, based on f.d.i.'s of mating combinations rather than just maternal blood groups (table 3). Simply stated: given a ratio of ci/cc in excess of unity (i.e., a simple ABO effect) and a ratio of ic/cc in excess of unity (i.e., a simple Rh effect), then, if the ratio ii/ic is less than 1.0, interaction 1 has occurred (ABOi has had a beneficial effect against Rh selection); if the ratio of ii/ci is less than 1.0, interaction 2 has occurred (Rhi has buffered ABO selection).

It should be noted, and can be deduced from both the 2 × 2 illustration (fig. 2) and the interaction models of table 3, that the two interactions are not mutually exclusive: both may occur, one may occur without the other, or neither may occur.

When the CDS results are examined in terms of the specifications of figure 2 and/or table 3, the observations fit the hypothesized pattern with regard to *both* aspects of ABO-Rh interaction. Substitution of the CDS-series fetal death indices from table 2

into the appropriate cells of the 2 × 2 model of figure 2 yields clear consistency with the hypothesized pattern irrespective of which of the three tabulation schemata is utilized (table 4). In terms of the models presented in table 3, the observed CDS ratios for all three tabulation schemata fit the requisites (fig. 3). The CDS ratios for simple ABOi (ci/cc) and for simple Rhi (ic/cc) clearly exceed 1.00 (1.26, 1.22, and 1.25 for ABOi, and 1.55 [$P < .02$], 1.47, and 1.57 [$P < .02$] for Rhi), fulfilling the prior specifications of the models. In agreement with the requirements for interaction 1, the ratio of ii/ic f.d.i.'s is less than 1.00 (0.63, 0.69, and 0.61), which confirms a favorable effect of ABOi on Rh selection shown in other series. Likewise, in agreement with requirements for interaction 2, the ratio of f.d.i.'s of ii/ci is less than 1.0 (0.78, 0.83, and 0.76), which lends support to a favorable effect of Rhi on ABO selection, suggested but not shown so clearly in the New York data.

The effects in mothers over 25 are even more striking than those for pooled ages (fig. 4).* While the simple ABO and Rh effects clearly exceed unity (1.38 for ABOi

TABLE 3

MODELS OF TWO ASPECTS OF ABO-Rh INTERACTION (IN TERMS OF RATIOS OF TOTAL FETAL DEATH INDICES OF DIFFERENT MATING COMBINATIONS)

| | |
|---|---|
| GIVEN— | |
| Simple ABOi effect: | ci/cc = >1.0 |
| and | |
| Simple Rhi effect: | ic/cc = >1.0 |
| THEN— | |
| If, | |
| ii/ic = <1.0 | Interaction 1 occurs. (ABO incompatibility protects against Rh selection) |
| If, | |
| ii/ci = <1.0 | Interaction 2 occurs. (Rh incompatibility protects against ABO selection) |

NOTE.—i = incompatible, c = compatible; interaction 1 and interaction 2 are not mutually exclusive.

TABLE 4

SUBSTITUTION OF FETAL DEATH INDEX VALUES FOR CDS MATINGS INTO 2 × 2 (FIG. 2) MODEL

| All ICD | | | ICD<17 | | | No Exclusions | | |
|---|---|---|---|---|---|---|---|---|
| | | Rh | | | Rh | | | Rh |
| | | i c | | | i c | | | i c |
| ABO | i | 3.41<4.40 | ABO | i | 4.20<5.03 | ABO | i | 3.29<4.32 |
| | | ∧ ∨ | | | ∧ ∨ | | | ∧ ∨ |
| | c | 5.41>3.48 | | c | 6.05>4.12 | | c | 5.42>3.45 |

NOTE.—i = incompatible, c = compatible.

* The total fetal deaths and live births upon which f.d.i.'s of figs. 1, 3, and 4 are based are presented in Appendix tables. A tabulation of f.d.i.'s for mothers over 30 was also carried out.

and 1.63 [$P < .05$] for Rhi), a result which fulfills the necessary prior criteria, the interaction 1 ratio is only 0.47 and the interaction 2 ratio, only 0.55, well below unity, even though not statistically significant. That this apparently more marked effect in mothers over 25 may be a function of parity rather than maternal age is suggested by the ratios for multiparous mothers, which are less than half of unity: the interaction 1 ratio is 0.34, and interaction 2 is 0.49.

Thus not only are the data from the CDS matings clearly consistent with the terms of the models for both aspects of ABO-Rh interaction (interaction 2 as well as interaction 1), but the CDS ratios based on total fetal death indices deviate from unity in accordance with the terms of the models, even more clearly than do the corresponding New York ratios—simple incompatibility ratios exceeding unity to a greater extent and the interaction ratios falling farther below unity. For example, in figure 4, for

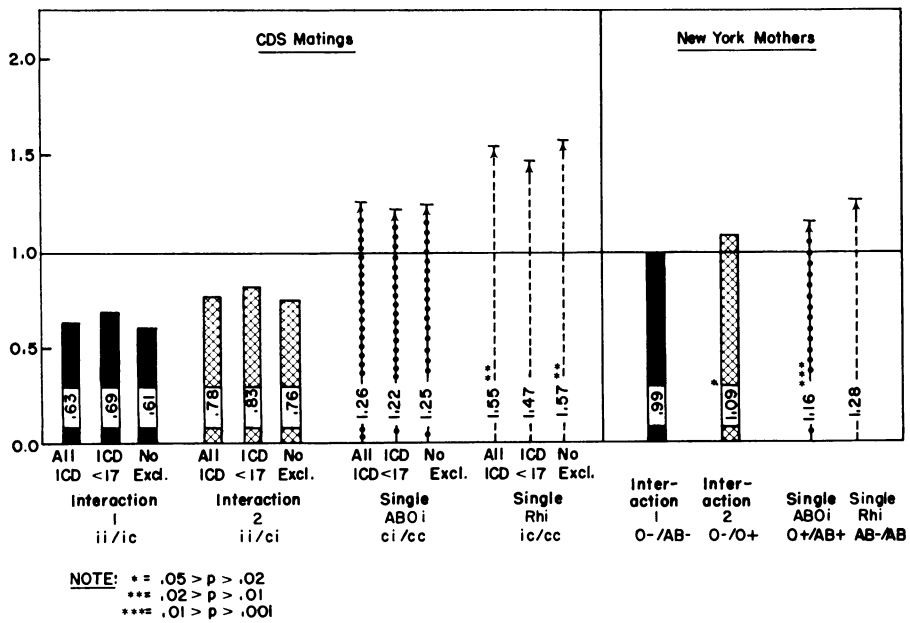


FIG. 3.—ABO-Rh interaction ratios based on total fetal death indices (all maternal ages)

mothers over 25, the CDS simple ABOi effect and Rhi effect ratios are 1.38 and 1.63, as compared with 1.19 and 1.53 for New York. Moreover, the CDS interaction 1 and 2 ratios are 0.47 and 0.55, as compared with 0.87 and 1.13 for New York—the latter not even below unity.

## DISCUSSION AND CONCLUSIONS

The models for interactions 1 and 2 presented here and those previously presented (Cohen and Sayre 1968) are rather rigorous in specifications. They actually infer a positive protective effect of one incompatibility against the other by requiring ratios to be below unity. Since a prior specification of the models is that single incompatibility ratios be above unity, and many are significantly so, a buffering effect of one incompatibility against another may be occurring even where the interaction ratios

are not below unity but are less in excess of unity than would be expected if ABO-incompatibility and Rh-incompatibility effects were additive. However, it is difficult to delineate the requisites for such a model beyond the same prior specifications of simple effects indicated for the more rigorous model; in particular situations where the magnitudes of the simple single incompatibility effects are known, hypothetical boundaries for interaction ratios could be postulated, but generally the range for interaction ratios cannot be established a priori. Consequently, a buffering effect or partial counteraction of one incompatibility against the other may go unrecognized where it fails to meet the specifications of the rigorous model and no alternative, less rigorous models are available. For example, this may be the case with interaction 2

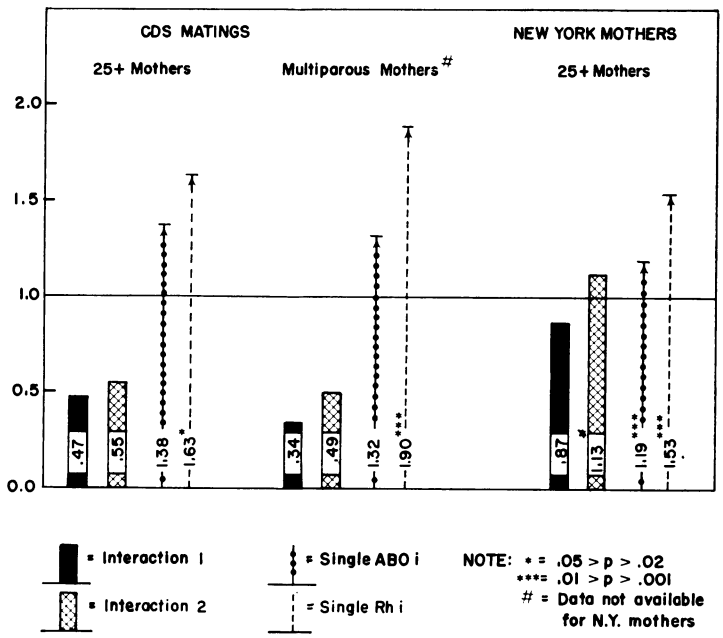


FIG. 4.—ABO-Rh interaction ratios for older and multiparous mothers

in the New York series, where the interaction ratio ii/ci based on fetal deaths of pooled gestational ages is not below unity but the ratio based on early fetal loss is, which suggests that the requisites of a less rigorous model based on total fetal wastage might have been met by the New York data. Whether a less binding version of the interaction models than presented here could be generally applicable remains to be demonstrated, however. What is quite clear is that the version of interaction requisites presented in figure 2 and table 3 is quite rigorous and that data having satisfied these rigorous models unequivocally indicates the interactions hypothesized. Such is the situation with the CDS series where the findings without exception follow the specified pattern of the rigorous version of the models, though levels of statistical significance are not always attained.

In conclusion, therefore, despite the limitations of sample size, the pattern of fetal deaths in the CDS series not only fits the proposed interaction models but agrees with

them even more convincingly than does that of the New York series. The greater precision of compatibility classification provided by the addition of paternal as well as maternal ABO-Rh types and the availability of adequate information on parity status in the CDS series have doubtless contributed to the stability of these findings. This confirmation of the dual nature of ABO-Rh interaction indicates the need for reexamination of previously proposed theories of the biological bases, as well as exploration of new facets of that interaction. Postulated biological mechanisms for the two aspects of interaction have already been discussed (Cohen and Sayre 1968), but certainly specific evidence is required before any mode of action can be accepted.

Of interest also is the possible unmasking of heterotic effects. Whether there is a basic heterozygote advantage that is overbalanced in singly ABO-incompatible and/or singly Rh-incompatible offspring by the damaging effects of the incompatibility is not yet clear. However, since the fetal death indices of ii matings are as low as, or possibly lower than, those of cc matings, it appears that there may be an underlying heterosis which becomes detectable when in combined incompatibility the deleterious manifestation of each incompatibility is buffered through ABO-Rh interaction.

The more marked effects of both aspects of ABO-Rh interaction with multiparity and possibly with increased maternal age are noteworthy, and probably related—directly in interaction 1 and indirectly in interaction 2—to the recognized increased risk of maternal Rh isoimmunization with parity. Primiparae would not be Rh sensitized unless from transfusion or nonpregnancy exposure; thus, except for those unusual situations, any ABO-incompatibility effect on Rh selection (interaction 1) would not be expected until those later pregnancies when Rh selection would be capable of being manifested. Does it also follow that, since Rh sensitization usually does not appear in primiparae, the influence of Rh incompatibility on ABO selection (interaction 2) would likewise not be apparent until subsequent pregnancies? That is, at least one or more Rh-incompatible pregnancy challenges are necessary for either of the dual aspects of ABO-Rh interaction to occur. While these questions and the details of the biological mechanisms, especially for interaction 2, are yet to be resolved, they do not alter one clear conclusion: not only the impact of ABO incompatibility on Rh selection but also the impact of Rh incompatibility on ABO selection must be taken into account in any consideration of selection involving either of these blood group systems.

## SUMMARY

This report considers the action of combined ABO and Rh incompatibility in data from the Child Health and Development Studies (CDS) and tests the fit of the observations to models of two aspects of ABO-Rh interaction: (1) an influence of ABO incompatibility on Rh selection and (2) an influence of Rh incompatibility on ABO selection. Doubly incompatible matings (i.e., with combined ABO and Rh incompatibility) have lower fetal loss rates than do singly incompatible matings, either ABO or Rh, a result which suggests dual interaction.

Moreover, there is clear agreement of the CDS findings with the proposed models for each of the two aspects of ABO-Rh interaction. When all mothers are studied, and more markedly when matings of older and/or multiparous mothers are examined, all the CDS interaction ratios based on total fetal death indices deviate from unity in

accordance with the terms of the models. It is suggested that the CDS observations fit the models even more convincingly than a previously reported New York series, possibly because of greater precision of compatibility classification provided by the availability of paternal as well as maternal blood types.

While the underlying biological mechanisms are yet to be completely elucidated, nevertheless, not only the impact of ABO incompatibility on Rh effects but also the impact of Rh incompatibility on ABO effects must not be overlooked in any consideration of selection in either of these blood group systems.

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## APPENDIX A

### APPENDIX FOR FIGURE 1 AND TABLE 1

| | Total FD | LB |
|---|---|---|
| CDS matings: | | |
| Rhc only: | | |
| ABOi | 97 | 2,207 |
| ABOc | 140 | 4,027 |
| ABOc only: | | |
| Rhi | 34 | 629 |
| Rhc | 140 | 4,027 |
| New York mothers: | | |
| Rh+ only: | | |
| O (i) | 7,581 | 15,912 |
| AB (c) | 572 | 1,389 |
| AB only: | | |
| Rh− | 98 | 189 |
| Rh+ | 572 | 1,389 |

NOTE.—i = incompatible, c = compatible; FD = fetal deaths, LB = live births.

## APPENDIX B

### APPENDIX FOR FIGURES 3 AND 4

CDS MATINGS
(FIGURE 4)

| ALL ICD | MOTHERS: 25 YRS AND OLDER | | MULTIPAROUS MOTHERS | |
|---|---|---|---|---|
| | FD | LB | FD | LB |
| ii | 6 | 195 | 5 | 215 |
| ic | 24 | 364 | 26 | 376 |
| ci | 65 | 1,165 | 65 | 1,355 |
| cc | 88 | 2,174 | 86 | 2,359 |

NOTE.—i = incompatible, c = compatible; FD = fetal deaths, LB = live births; data for CDS matings, all maternal ages, are given in table 2.

APPENDIX B—*Continued*

NEW YORK MOTHERS

| | MOTHERS: 25 YRS AND OLDER (FIG. 4) | | ALL AGES (FIG. 3) | |
|---|---|---|---|---|
| | FD | LB | FD | LB |
| O− | 845 | 1,411 | 1,108 | 2,129 |
| O+ | 5,636 | 10,595 | 7,581 | 15,912 |
| AB− | 83 | 121 | 98 | 186 |
| AB+ | 430 | 960 | 572 | 1,389 |

NOTE.—FD = fetal deaths, LB = live births; data are not available for New York multiparous mothers.

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