ABO and Rh Incompatibility. I. Fetal and Neonatal Mortality with ABO and Rh Incompatibility: Some New Interpretations

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The effects of ABO incompatibility and Rh incompatibility have been of interest to geneticists concerned with their role in maintaining the blood group polymorphisms, and to clinicians concerned with their role in sterility, differential fertility, and risk of fetal and neonatal death. Recently, examination of a large body of data from New York City live-birth and fetal-death records, although indicating a greater risk of pregnancy wastage among mothers of ABO- and Rh-incompatible types, suggested that the action of the two incompatibilities, singly and in combination, are more complex than previously recognized (Newcombe 1963; Cohen and Sayre 1968). Since the New York data were limited to maternal blood types, and many other studies were similarly or otherwise restricted, it became apparent that a study series containing more extensive data grouped in families by parental mating type was required. With detailed information not only on the mothers, fetal deaths, and live births, but also on the fathers and neonatal deaths, the Child Health and Development Studies (CDS), described in previous reports (Yerushalmy 1964; Reed 1967*b*), provides just such a series.

While certain aspects of incompatibility examined in the CDS series by Peritz (1967) and Reed (1968*b*) failed to yield evidence of significant ABO- or Rh-associated differences in the parameters studied, their findings did not exclude other possible manifestations. Peritz (1967), limiting his analysis to live births, tested a hypothesis which assumed a specific mechanism of ABO selection—that the effects are directed specifically against ABO-incompatible progeny, and can be detected from the ABO distribution of liveborn offspring of different mating types, without any consideration of fetal or neonatal mortality. Despite negative results, Peritz stated: "The absence of a discernible A-O incompatibility effect in our data should not be taken as proof of non-existence of such an effect in our population. Actually, our data on reproductive history provide some hints pointing toward such an effect, as will be shown in a later paper. All one can say is that A-O incompatibility cannot be as important in

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our population as some authors seem to believe: at most it may reach the lower regions of the confidence interval proposed by Levene and Rosenfield (1961), somewhere around 0.1."

Reed (1967*b*, 1968*a*, 1968*b*) sought to evaluate the role of blood group selection by a regression analysis of infant and gravida measurements and couple reproductive performance involving seven different blood systems. Like Peritz, he too concluded that "it is important not to assume that selective effects of these blood group systems on reproduction are absent or negligible. A mating type effect on number of pregnancies of as much as 5–10% of the mean might not have been recognized as a real effect . . . . Studies to date have not tested adequately for the existence of weak effects (less than 5% of the mean)."

Facets of manifestation not studied by Peritz and Reed are explored in the present investigation. The specific objectives are (1) to examine prenatally manifest ABO and Rh effects (singly and in combination) in the CDS series, and (2) to study the influence of ABO and Rh incompatibilities (singly and in combination) on the ABO and Rh distribution of liveborn offspring and on neonatal survivorship. This report deals primarily with simple ABO and Rh effects, respectively, rather than with their interaction, which is examined in terms of postulated models in another report (Cohen 1970).

METHOD

The study group, members of a prepaid medical insurance plan who for the most part are of middle and upper socioeconomic status, is under detailed investigation by the CDS (Yerushalmy 1964; Reed 1967*b*). Included in this report are all CDS families who met the preestablished criteria regarding date of registration, date and place of delivery, typing of a paternal blood sample at the study pregnancy in question, and lack of inconsistency of blood type of parents and child with recognized modes of inheritance.

Standard blood grouping techniques of the Blood Grouping Laboratory, Boston, were utilized. Only four ABO phenotypes are used here—O, A, B, and AB—for gravidae, husbands, and offspring. No attempt is made to subclassify A individuals into A_1 or other A subtypes. Cord blood specimens were obtained at delivery for most infants (Reed 1967*b*). If cord bloods were, for any reason, not available, capillary bloods were taken in the hospital during the first week of life. If neither was available, efforts were made to get a sample after the infant left the hospital. For this analysis, however, only those samples obtained and typed during the first three months of life were used.

Blood groups of family members from each study pregnancy were carefully checked for consistency with recognized modes of inheritance. Wherever a discrepancy suggesting nonpaternity, nonmaternity, or other aberrancy was noted, its resolution by typing additional specimens was attempted. If that was not possible, the family member or total family group (father, mother, and infant) was excluded from this analysis by a systematic procedure indicated as exclusion TT (see Appendix A). For comparison purposes, distributions without any exclusions are also presented.

Accordingly, data are tabulated in three ways:

1. Total matings, after removal of TT exclusions, irrespective of length of interval between last menstrual period (LMP) and initial date of contact with clinic (ICD) are termed "all ICD."

2. Those matings, after removal of TT exclusions, where gravida reported for obstetrical care prior to, or within, the seventeenth week following date of LMP are termed "ICD < 17 weeks." This was done so that only those at risk of being observed for early fetal loss, that is, at less than 20 weeks of gestational age, would be considered.

3. Total matings with no omissions because of initial date of contact or blood type discrepancies are termed "no exclusions."

Tabulations of pregnancy outcome comprise all infants, including cotwin members of twin pairs. Analyses based on mating types are limited to one pregnancy per gravida and to only those pregnancies in which the husband's blood was typed. If the gravida had more than one study pregnancy and/or more than one husband while in the study, the gravida's first study pregnancy where the husband reported for typing was selected.

Matings are specified—gravida first, then husband. Racial classification is based on race of the gravida. Reciprocal matings are those containing the same combination of blood groups, but reversed for gravida and husband. In accordance with conventional terminology, an incompatible mating is one where the gravida lacks an antigen her husband possesses. Compatibility classification of matings, based on spouse ABO types and Rh_o (D) types, respectively, is presented in Appendix B.

For convenience, the letters "c" and "i" are used to specify mating compatibility and incompatibility status. When designated together, Rh status of mating is first, ABO second. Thus cc = Rh-compatible, ABO-compatible matings; ic = Rh-incompatible, ABO-compatible matings; ci = Rh-compatible, ABO-incompatible matings; and ii = Rh-incompatible, ABO-incompatible matings.

To estimate the effects of incompatibility, various ratios are used such as death indices, indicator ratios, and blood group ratios.

Death indices:

$$\text{Total fetal death index (total f.d.i.)} = \frac{\text{fetal deaths (all gestational ages)} \times 100}{\text{live births}}$$

$$\text{Early f.d.i.} = \frac{\text{early fetal deaths (}<\text{20 weeks gestational age)} \times 100}{\text{live births}}$$

$$\text{Late f.d.i.} = \frac{\text{late fetal deaths (28 weeks or more gestational age)} \times 100}{\text{live births}}$$

$$\text{Neonatal d.i. (n.d.i.)} = \frac{\text{neonatal deaths (28 days or less after birth)} \times 100}{\text{live births}}$$

The index for total loss from time of recognition of pregnancy through neonatal life is estimated by combining fetal and neonatal deaths, thus:

$$\text{Fetal-neonatal index (FNI)} \text{ or } \text{Viability loss index (VLI)} = \frac{\text{total fetal and neonatal deaths} \times 100}{\text{live births}}$$

Indicator ratios:

Indicator ratios or i/c ratios based on death indices are used to estimate the impact of incompatibility-compatibility status:

$$\text{Indicator ratio (IR)} = \frac{\text{specific death index for a given incompatible ABO and/or Rh mating class}}{\text{specific death index for corresponding compatible ABO and/or Rh mating class}}$$

Thus an indicator ratio exceeding unity suggests greater risk of loss for the i matings than for the corresponding c matings. Indicator ratios using total or late fetal deaths are actually equivalent to relative risk statistics.

Blood group ratios:

Ratios designating the proportionate blood group distribution of offspring are compared for reciprocal incompatible and compatible matings.

The influence of race, maternal age, parity, number of previous fetal deaths, and similar characteristics are also examined to evaluate their possible interrelationship with incompatibility effects.

The statistical methods used are similar to those previously described (Newcombe 1963; Cohen and Sayre 1968), including the χ^2 test of significance and various modifications thereof, as well as relative risk statistics (Cochran 1954; Woolf 1954–1955; Haldane 1955–1956).

RESULTS

Fetal, Neonatal, and Total Viability Risk with ABO Incompatibility

Table 1 contains indices and indicator ratios for ABO-incompatibility effects. Over 7,700 matings of Caucasian gravidae are classified by ABO status and tabulated separately for all Rh types and for Rh-compatible types only.

The indicator ratios (IR) for ABO-incompatibility effect based on total fetal deaths to Caucasian gravidae exceed unity consistently, though not significantly statistically, for all CDS groups (all ICD, ICD $<$ 17, or no exclusions). As in the New York series (Cohen and Sayre 1968), the elevation with ABO incompatibility is limited to early fetal loss (fig. 1; table 1), and is most marked when Rh compatibles only are considered. Although statistical significance is attained only for Rh-compatible pooled ABO i/c ratios, every IR based on early f.d.i.'s is above unity and the IR's for reciprocal mating combinations (O $\times$ A/A $\times$ O) exceed unity by over 50% (1.59, 1.57, and 1.62 for the three CDS groups, respectively, table 1). Late f.d.i.'s (28 + weeks) show no elevation, and in some combinations show the suggestion of a decrease with ABO incompatibility (fig. 1).

On the other hand, n.d.i.'s for CDS ABO-incompatible matings are about 50% above those for ABO-compatible matings, ranging from 1.44 to 1.80. However, as levels of statistical significance are not attained, the possible association between neonatal mortality and ABO incompatibility thus suggested requires further confirmation (table 1).

When total fetal and neonatal mortality in the CDS series are combined (FNI or VLI), the markedly greater loss for ABO-incompatible matings compared to ABO-compatible matings is striking. Confined to Rh-compatible matings only, the VLI ranges from 26% to 47% higher for the various ABO-incompatible mating combinations, attaining statistical significance in "all ICD" and "no exclusions" tabulations.

Fetal, Neonatal, and Total Viability Risk with Rh Incompatibility

The indices and indicator ratios in table 2 pertain to the effect of Rh-incompatibility selection in matings of Caucasian gravidae and are presented for both pooled ABO

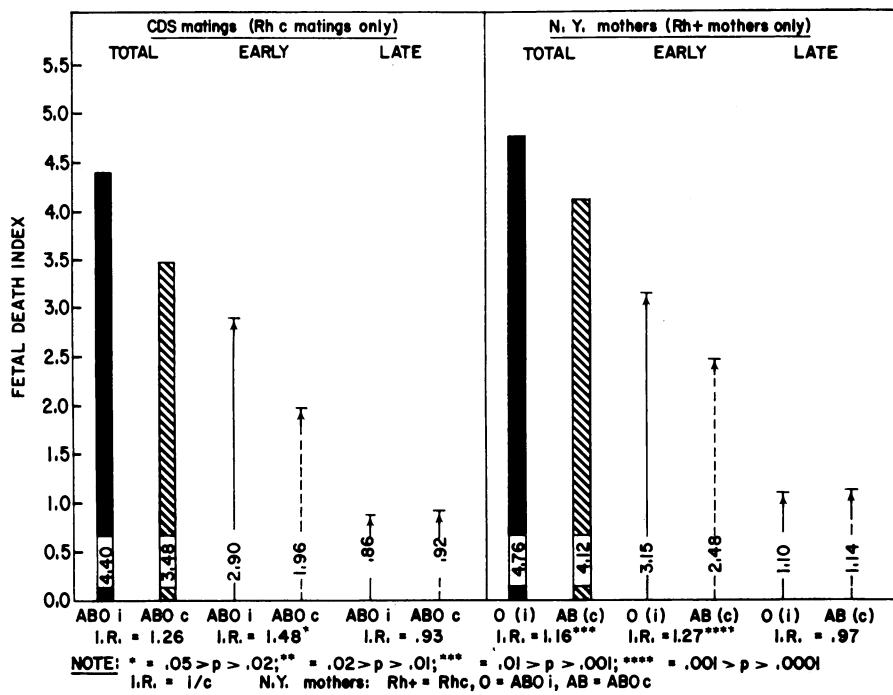

FIG. 1.—Effects of ABO incompatibility on total, early, and late fetal loss (Rh compatible only) ("all ICD" tabulation).

types (including ABO incompatibles) as well as for ABO-compatible types only. All Rh indicator ratios based on total fetal deaths consistently, though not always significantly, exceed unity, with the most apparent effect occurring where ABO-incompatible types have been eliminated. Accordingly, with ABO-compatible matings only considered, the total f.d.i.'s in Rh-incompatible matings are over 50% higher than in the pooled Rh-compatible matings in the "all ICD" and "no exclusions" tabulations ($P < .02$, table 2; fig. 2). It is of interest that these differences derive from significantly increased early as well as late fetal wastage, and though the indicator ratios in late fetal loss are above unity (ranging from 1.36 to 1.72), they do not attain statistical significance in the CDS series. This observation is in contrast to the New York

TABLE 1

EFFECT OF ABO INCOMPATIBILITY ON PREGNANCY OUTCOME AND NEONATAL SURVIVORSHIP IN MATINGS CLASSIFIED BY ABO-Rh STATUS (CAUCASIAN)

MATING CATEGORIES	NO. OF PREGNANCIES	NO. OF LIVE BIRTHS	f.d.i.			n.d.i.	VLI
			Total	Early	Late		
	All ICD (after TT Exclusions)						
All Rh types:							
ABO (i)...	2,649	2,559	4.26	2.77	0.90	1.33	5.59
ABO (c)..	4,793	4,656	3.74	2.13	0.97	0.88	4.62
IR.....	.....	.....	1.14	1.30	0.93	1.51	1.21
Rh (c) only:							
ABO (i)...	2,289	2,207	4.40	2.90	0.86	1.36	5.75
ABO (c)..	4,138	4,027	3.48	1.96	0.92	0.92	4.40
IR.....	.....	.....	1.26	1.48*	0.93	1.48	1.31*
O×A (i)..	1,161	1,111	5.04	3.15	0.99	1.17	6.21
A×O (c)..	1,195	1,160	3.45	1.98	0.86	0.78	4.22
IR.....	.....	.....	1.46	1.59	1.15	1.50	1.47*
Recip. (i).	1,729	1,662	4.69	3.01	1.02	1.32	6.02
Recip. (c).	1,752	1,698	3.65	2.06	0.88	0.77	4.42
IR.....	.....	.....	1.28	1.46	1.16	1.71	1.36*
	ICD <17 Weeks (after TT Exclusions)						
All Rh types:							
ABO (i)...	2,142	2,055	4.91	3.45	0.83	1.36	6.28
ABO (c)..	3,821	3,690	4.39	2.68	1.06	0.92	5.31
IR.....	.....	.....	1.12	1.29	0.78	1.48	1.18
Rh (c) only:							
ABO (i)...	1,847	1,769	5.03	3.62	0.73	1.41	6.44
ABO(c)...	3,284	3,178	4.12	2.49	1.01	0.98	5.10
IR.....	.....	.....	1.22	1.45*	0.72	1.44	1.26
O×A (i)..	930	884	5.66	3.96	0.79	1.36	7.01
A×O (c)..	947	911	4.28	2.52	0.99	0.88	5.16
IR.....	.....	.....	1.32	1.57	0.80	1.55	1.36
Recip. (i).	1,391	1,329	5.27	3.76	0.83	1.35	6.62
Recip. (c).	1,388	1,334	4.50	2.62	1.05	0.75	5.25
IR.....	.....	.....	1.17	1.44	0.79	1.80	1.26
	No Exclusions						
All Rh types:							
ABO (i)...	2,746	2,655	4.18	2.71	0.90	1.28	5.46
ABO (c)..	4,958	4,817	3.72	2.06	1.04	0.87	4.59
IR.....	.....	.....	1.12	1.32	0.87	1.47	1.19
Rh (c) only:							
ABO (i)...	2,373	2,290	4.32	2.84	0.87	1.31	5.63
ABO (c)..	4,285	4,171	3.45	1.89	0.98	0.91	4.36
IR.....	.....	.....	1.25	1.50**	0.89	1.44	1.29*
O×A (i)..	1,207	1,155	5.02	3.12	1.04	1.13	6.15
A×O (c)..	1,229	1,194	3.43	1.93	0.92	0.75	4.19
IR.....	.....	.....	1.46	1.62	1.13	1.51	1.47*
Recip. (i).	1,793	1,724	4.64	2.96	1.04	1.28	5.92
Recip. (c).	1,803	1,749	3.60	2.00	0.91	0.74	4.35
IR.....	.....	.....	1.29	1.48	1.14	1.73	1.36*

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viability loss index; ABO (c) = O × O, A × A, B × B, AB × AB, A × O, B × O, AB × O, AB × A, AB × B; ABO (i) = O × A, O × B, O × AB, A × B, A × AB, B × A, B × AB; Recip. (i) = O × A, O × B, O × AB, A × AB, B × AB; Recip. (c) = A × O, B × O, AB × O, AB × A, AB × B; IR = indicator ratio = specific death index of given ABO incompatible group over the corresponding death index of the ABO compatible group; Caucasian includes six subcategories of Caucasians of varied European-Eurasian ancestry but excluding Mexicans.

* = $.05 > P > .02$.

** = $.02 > P > .01$.

TABLE 2

EFFECT OF Rh INCOMPATIBILITY ON PREGNANCY OUTCOME AND NEONATAL SURVIVORSHIP IN MATINGS CLASSIFIED BY ABO-Rh STATUS (CAUCASIAN)

MATING CATEGORIES	NO. OF PREGNANCIES	NO. OF LIVE BIRTHS	f.d.i.			n.d.i.	VLI
			Total	Early	Late		
	All ICD (after TT Exclusions)						
All ABO types:							
Rh (i)	1,015	981	4.69	2.75	1.22	0.82	5.50
Rh (c) pooled	6,427	6,234	3.80	2.29	0.90	1.07	4.88
IR			1.23	1.20	1.36	0.77	1.13
ABO (c) only:							
Rh (i)	655	629	5.41	3.18	1.27	0.64	6.04
Rh (c) pooled	4,138	4,027	3.48	1.96	0.92	0.92	4.40
IR			1.55**	1.62*	1.38	0.70	1.37
Rh−×+ (i)	655	629	5.41	3.18	1.27	0.64	6.04
Rh+×− (c)	612	591	4.23	2.37	0.85	1.02	5.25
IR			1.28	1.34	1.49	0.63	1.15
	ICD<17 Weeks (after TT Exclusions)						
All ABO types:							
Rh (i)	832	798	5.39	3.38	1.38	0.75	6.14
Rh (c) pooled	5,131	4,947	4.45	2.89	0.91	1.13	5.58
IR			1.21	1.17	1.52	0.66	1.10
ABO (c) only:							
Rh (i)	537	512	6.05	3.91	1.37	0.59	6.64
Rh (c) pooled	3,284	3,178	4.12	2.49	1.01	0.98	5.10
IR			1.47	1.57	1.36	0.60	1.30
Rh−×+ (i)	537	512	6.05	3.91	1.37	0.59	6.64
Rh+×− (c)	493	473	4.86	2.96	0.85	1.06	5.92
IR			1.24	1.32	1.61	0.56	1.12
	No Exclusions						
All ABO types:							
Rh(i)	1,046	1,011	4.65	2.67	1.29	0.79	5.44
Rh (c) pooled	6,658	6,461	3.76	2.23	0.94	1.05	4.81
IR			1.24	1.20	1.37	0.75	1.13
ABO (c) only:							
Rh (i)	673	646	5.42	3.10	1.39	0.62	6.04
Rh (c) pooled	4,285	4,171	3.45	1.89	0.98	0.91	4.36
IR			1.57**	1.64*	1.42	0.68	1.39
Rh−×+ (i)	673	646	5.42	3.10	1.39	0.62	6.04
Rh+×− (c)	635	614	4.07	2.28	0.81	1.14	5.21
IR			1.33	1.36	1.72	0.54	1.16

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viability loss index; IR = indicator ratio for Rh effect = (specific death index for Rh incompatible types of ABO status designated)/(specific death index for corresponding Rh compatible types); Rh (i) = Rh− × Rh+; pooled Rh (c) = Rh+ × Rh+, Rh+ × Rh−, Rh− × Rh−.

* = $.05 > P > .02$.

** = $.02 > P > .01$.

series, where the Rh deviations were entirely dependent on significant differences in late fetal deaths and not at all on early fetal loss (fig. 2).

Neonatal loss in the CDS series shows no increase with Rh incompatibility (table 2).

In view of the observed difference in effect of Rh incompatibility on fetal and neonatal survivorship, the VLI is not very meaningful in terms of biological causation. Nevertheless, because it remains a useful single reference statistic for indicating a total effect, it is presented in table 2.

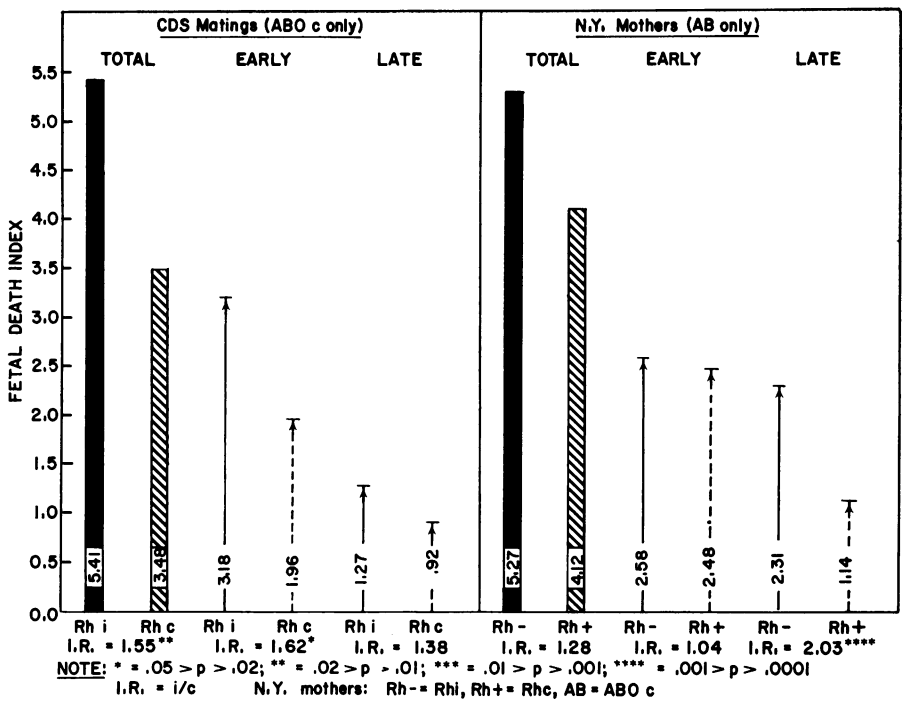

FIG. 2.—Effects of Rh incompatibility on early, late, and total fetal loss (ABO compatible only) ("all ICD" tabulation).

Non-Blood Group Factors and the Effects of ABO and Rh Incompatibility

Race-ethnic groups. In the CDS series, racial-ethnic classification comprises six subcategories of Caucasians, as well as Mexican, Negro, Oriental, and two categories of "mixtures." Other than pooled Caucasians (excluding Mexicans), which constitute the Caucasian category tabulated here, only Negroes provide a racial-ethnic group large enough for examination of mortality risk. This group is of particular interest since, in the New York series, Negroes showed neither the clear pattern of ABO incompatibility found in Caucasians, nor any evidence of negative selection with Rh incompatibility.

In the 2,183 matings of CDS Negroes, none of the incompatible-compatible differences, either ABO or Rh, reach levels of statistical significance (tables 3, 4). There is,

possibly, a suggestion of a higher risk of early fetal death among Negro gravida with ABO-incompatible husbands, than among those with ABO-compatible husbands for pooled Rh types and Rh-compatible matings (the latter involving only 11 fetal deaths), but this is not observed in the reciprocal mating categories (table 3). The findings pertaining to selection effect with Rh incompatibility are similarly equivocal (table 4).

TABLE 3

EFFECT OF ABO INCOMPATIBILITY ON PREGNANCY OUTCOME OF MATINGS CLASSIFIED BY ABO-Rh STATUS (NEGRO)

MATING CATEGORIES	NO. OF PREGNANCIES	NO. OF LIVE BIRTHS	f.d.i.			n.d.i.	VLI
			Total	Early	Late		
	All ICD (after TT Exclusions)						
All Rh types:							
ABO (i) pooled...	807	788	4.19	1.65	1.52	1.52	5.71
ABO (c) pooled...	1,376	1,333	4.43	1.35	1.80	2.18	6.60
IR.....	.....	.....	0.95	1.22	0.84	0.70	0.87
Rh (c) only:							
ABO (i) pooled...	749	731	4.24	1.50	1.64	1.64	5.88
ABO (c) pooled...	1,274	1,236	4.37	1.29	1.78	2.27	6.63
IR.....	.....	.....	0.97	1.16	0.92	0.72	0.89
O×A (i)...	281	272	4.41	0.74	1.84	2.94	7.35
A×O (c)...	288	274	6.20	1.09	2.92	2.92	9.12
IR.....	.....	.....	0.71	0.68	0.63	1.01	0.81
Recip. (i)..	535	520	3.85	1.15	1.54	1.73	5.58
Recip. (c)..	563	536	5.97	1.87	2.24	2.61	8.58
IR.....	.....	.....	0.64	0.61	0.69	0.66	0.65
	ICD <17 Weeks (after TT Exclusions)						
All Rh types:							
ABO (i) pooled...	569	550	4.91	2.18	1.82	1.82	6.73
ABO (c) pooled...	921	885	5.31	1.92	1.69	2.26	7.57
IR.....	.....	.....	0.92	1.14	1.08	0.81	0.89
Rh (c) only:							
ABO (i) pooled...	532	514	4.86	1.95	1.95	1.95	6.81
ABO (c) pooled...	848	816	5.27	1.84	1.72	2.45	7.72
IR.....	.....	.....	0.92	1.06	1.13	0.80	0.88
O×A (i)...	200	191	5.24	1.05	2.62	3.14	8.38
A×O (c)...	189	176	7.95	1.70	3.98	2.27	10.23
IR.....	.....	.....	0.66	0.62	0.66	1.38	0.82
Recip. (i)..	379	362	4.97	1.66	2.21	1.93	6.91
Recip. (c)..	368	346	7.23	2.60	2.31	2.31	9.54
IR.....	.....	.....	0.69	0.64	0.96	0.84	0.72

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viable loss index; ABO (c) pooled = O × O, A × A, B × B, AB × AB, A × O, B × O, AB × O, AB × A, AB × B; ABO (i) pooled = O × A, O × B, O × AB, A × B, A × AB, B × A, B × AB; Recip. (i) = O × A, O × B, O × AB, A × AB, B × AB; Recip. (c) = A × O, B × O, AB × O, AB × A, AB × B; IR = indicator ratio = specific death index of given ABO incompatible group over the corresponding death index of the ABO compatible group.

Despite the inconclusive nature of these results, they do not rule out the possibility of ABO or Rh selection in Negro families, nor is there the distinct contrast in pattern between Negroes and Caucasians in the CDS series that was noted in the New York series, where Negro mothers showed significantly lower fetal loss rates for Rh incompatibles than for Rh compatibles and there was no suggestion of any ABO-incompatibility manifestation. This raises the question of whether a real difference exists between the New York series Negroes and the CDS Negroes, and, if so, why. There is the possibility of increased Caucasian intermixture in California, or at least

TABLE 4

EFFECT OF Rh INCOMPATIBILITY ON PREGNANCY OUTCOME OF MATINGS CLASSIFIED BY ABO-Rh STATUS (NEGRO)

MATING CATEGORIES	NO. OF PREGNANCIES	NO. OF LIVE BIRTHS	f.d.i.			n.d.i.	VLI
			Total	Early	Late		
	All ICD (after TT Exclusions)						
All ABO types:							
Rh (i).....	160	154	4.55	2.60	1.30	0.65	5.19
Rh (c) pooled...	2,023	1,967	4.32	1.37	1.73	2.03	6.35
IR.....	.....	.....	1.05	1.90	0.75	0.32	0.82
ABO (c) only:							
Rh (i).....	102	97	5.15	2.06	2.06	1.03	6.19
Rh (c) pooled...	1,274	1,236	4.37	1.29	1.78	2.27	6.63
IR.....	.....	.....	1.18	1.60	1.16	0.45	0.93
Rh−×+ (i).....	102	97	5.15	2.06	2.06	1.03	6.19
Rh+×− (c).....	100	96	4.17	2.08	2.08	0.00	4.17
IR.....	.....	.....	1.24	0.99	0.99	0.00	1.48
	ICD <17 Weeks (after TT Exclusions)						
All ABO types:							
Rh (i).....	110	105	5.71	3.81	0.95	0.00	5.71
Rh (c) pooled...	1,380	1,330	5.11	1.88	1.80	2.26	7.37
IR.....	.....	.....	1.12	2.03	0.53	0.00	0.77
ABO (c) only:							
Rh (i).....	73	69	5.80	2.90	1.45	0.00	5.80
Rh (c) pooled...	848	816	5.27	1.84	1.72	2.45	7.72
IR.....	.....	.....	1.10	1.58	0.84	0.00	0.75
Rh−×+ (i).....	73	69	5.80	2.90	1.45	0.00	5.80
Rh+×− (c).....	69	65	6.15	3.08	3.08	0.00	6.15
IR.....	.....	.....	0.94	0.94	0.47	0.00	0.94

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viability loss index; IR = indicator ratio for Rh effect = (specific death index for Rh incompatible types of ABO status designated)/(specific death index for corresponding Rh compatible types); Rh (i) = Rh− × Rh+; pooled Rh (c) = Rh+ × Rh+, Rh+ × Rh−, Rh− × Rh−.

in the CDS Negroes, where recent migration or possibly better integration into the total community might be reflected in a trend toward the Caucasian incompatibility pattern. Or, possibly socioeconomic factors might provide the primary basis for the different findings. The CDS series, derived from a voluntarily health-insured group, is more heavily weighted in the middle class, with the lowest socioeconomic groups omitted. That is certainly not the situation in the total population of Negroes tabulated in the New York vital statistics records during the second half of the 1950s. Underreporting of early fetal deaths and masking of blood group effects by factors having a greater influence on fetal loss than blood groups could contribute heavily to the New York results, whereas these factors could be relatively less important in the CDS series.

Previous pregnancy history of gravidae. The impact of multiple pregnancies is examined in the CDS Caucasian matings. Mothers are classified as multiparous if any pregnancy prior to the study pregnancy is reported. Indicator ratios for early fetal loss to pooled ABO-incompatible versus pooled ABO-compatible matings appear somewhat higher for multiparae than for primiparae, when either all Rh or Rh-compatible matings only are considered (table 5). Since this pattern is not only absent in tabulations for late fetal deaths, as would be expected from table 1 and the New York data, but also does not hold for early fetal deaths to ABO-reciprocal matings or for neonatal deaths of any specific ABOi/ABOc mating combination, no relationship between parity and ABO effects can be postulated. There are, however, reasonable hypotheses that might explain differences between the ABO-associated effects of previous pregnancies on early wastage and their impact on neonatal mortality. Neonatal mortality in firstborn may be directly or indirectly related to immune antibodies which high-risk mothers produce during the first pregnancy, and which may not only increase the likelihood of neonatal stress for that pregnancy, but may interfere subsequently with conception and/or cause early fetal wastage in subsequent pregnancies. Thus deleterious effects may be shifting toward earlier manifestation, causing greater early fetal loss to be observed in multiparae, whereas there is greater neonatal loss in primiparae. Jakobowicz and Graydon (1968) have recently reported an association of heterospecific pregnancies and the presence of saliva antibodies. They note a significantly higher frequency of saliva antibodies in a group of O women with heterospecific (ABO incompatible) pregnancies than in a group composed of O women with O husbands, primiparae with an O child, nonparous women, and O males. This difference remained significant whether or not the O males were included. Of particular interest was their observation that in the compatible group, the number of pregnancies had no influence on the presence or absence of antibodies; whereas in the incompatible group, there was a statistically significant decrease of saliva antibodies with the increase in the number of pregnancies, suggesting that "immunized" women became infertile. Consequently, multiparity tended to be associated with lack of antibodies. It is difficult to reconcile these findings with those of Solish (1969) and Solish and Gershowitz (1969), who found no association of infertility with cervical agglutinins or ABO-incompatible blood types. While the Solish and Gershowitz findings are based on a selected sample attending an infertility clinic, and it is not possible to attempt an estimation of fetal loss since sterility is a criterion for clinic attendance, nevertheless, the results are quite puzzling.

With Rh incompatibility, on the other hand, indicator ratios appear higher for multiparae than for primiparae in all comparisons, suggesting a simple relationship between parity and unfavorable pregnancy outcome (table 6). While the size of the sample precludes any definitive statements, these findings are consistent with the recognized pattern of maternal Rh isoimmunization by previous pregnancies.

Maternal age. To determine the relationship of maternal age to incompatibility manifestation (table 7), two broad maternal age classifications are used, as in the New York series: (1) under and over 25 years, and (2) under and over 30 years.

Since ABO incompatibility tends to manifest primarily before 20 weeks of pregnancy, maternal age effects are examined for early fetal deaths. Table 7 shows ABO-effect indicator ratios for all older mothers to be consistently higher than for younger mothers, regardless of which age boundary is used. This is unlike the New York

TABLE 5

INDICATOR RATIOS FOR ABO-INCOMPATIBILITY MANIFESTATION IN (CAUCASIAN) MOTHERS WITH AND WITHOUT PREVIOUS PREGNANCIES

MATING CATEGORIES	PREVIOUS PREGNANCIES	TOTAL LB[a]	INDICATOR RATIOS BASED ON:				
			Early f.d.i.	Late f.d.i.	Total f.d.i.	n.d.i.	VLI
All Rh types:							
ABO (i)	0	819					
ABO (c)	0	1,626					
i/c			1.14	1.84	1.31	2.69**	1.55**
ABO (i)	1+	1,570					
ABO (c)	1+	2,735					
i/c			1.29	0.66	1.09	1.13	1.10
Rh (c) only:							
ABO (i)	0	711					
ABO (c)	0	1,401					
i/c			1.13	1.48	1.20	2.77**	1.48
ABO (i)	1+	1,355					
ABO (c)	1+	2,359					
i/c			1.53*	0.80	1.32	1.05	1.25
O×A (i)	0	352					
A×O (c)	0	403					
i/c			3.46	3.98	4.35***	1.54	3.28***
O×A (i)	1+	690					
A×O (c)	1+	687					
i/c			1.20	0.57	1.09	1.33	1.13
Sum of:							
Recip. (i)	0	530					
Recip. (c)	0	582					
i/c			2.19	2.46	2.20*	2.74	2.33***
Sum of:							
Recip. (i)	1+	1,020					
Recip. (c)	1+	1,009					
i/c			1.23	0.79	1.10	1.21	1.12

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viability loss index; LB = live births.

[a] Total live births for pregnancies (one per mating) upon which f.d.i., n.d.i., and VLI are based.

* = $.05 > P > .02$.

** = $.02 > P > .01$.

*** = $.01 > P > .001$.

series, where no discernible increase in ABO effect was observed and the peak of incompatibility seemed to appear between 25 and 30 years of age.

Since Rh-incompatibility manifestation does not appear to be limited to a specific gestational period in the CDS series, maternal age and Rh incompatibility were examined for total fetal deaths. Older mothers clearly appear to have elevated indicator ratios, with one exception: that occurs where ABO-compatibility status is not controlled.

TABLE 6

INDICATOR RATIOS FOR Rh-INCOMPATIBILITY MANIFESTATION IN (CAUCASIAN) MOTHERS WITH AND WITHOUT PREVIOUS PREGNANCIES

MATING CATEGORIES	PREVIOUS PREGNANCIES	TOTAL LB[a]	INDICATOR RATIOS BASED ON:				
			Early f.d.i.	Late f.d.i.	Total f.d.i.	n.d.i.	VLI
All ABO types:							
Rh (i)	0	333					
Rh (c)	0	2,112					
i/c			1.15	1.21	1.20	0.53	1.03
Rh (i)	1+	591					
Rh (c)	1+	3,714					
i/c			1.27	1.57	1.29	0.94	1.22
ABO (c) only:							
Rh (i)	0	225					
Rh (c)	0	1,401					
i/c			1.11	0.51	0.95	0.62	0.89
Rh (i)	1+	376					
Rh (c)	1+	2,359					
i/c			1.88*	2.00	1.89***	0.75	1.64**
Rh−×+(i)	0	225					
Rh+×−(c)	0	199					
i/c			1.10	0.00	1.03	0.00	1.18
Rh−×+(i)	1+	376					
Rh+×−(c)	1+	368					
i/c			1.47	1.37	1.50	0.49	1.23

NOTE.—i = incompatible, c = compatible; f.d.i. = fetal death index, n.d.i. = neonatal death index, VLI = viability loss index; LB = live births.

[a] Total live births for pregnancies (one per mating) upon which f.d.i., n.d.i., and VLI are based.

* = $.05 > P > .02$.

** = $.02 > P > .01$.

*** = $.01 > P > .001$.

The consistent maternal age effect agrees with the parity effect noted above and as far as is discernible, is probably derived from it. Unfortunately, subclassification by both maternal age and number of pregnancies is not possible in the New York series because of lack of documentation, and is not feasible in this series because of the small sample.

Previous fetal deaths and incompatibility risk. Although the opposite pattern might be expected, ABO-indicator ratios based on fetal deaths are lower for gravidae reporting previous pregnancy loss than for those without a history of wastage. There is, however, a suggestion that indicator ratios based on neonatal mortality may be increased with prior pregnancy loss. No explanation is immediately apparent for these

TABLE 7

MATERNAL AGE AND INDICATOR RATIOS

	INDICATOR RATIOS FOR ABO EFFECT AND Rh EFFECT											
	Maternal Age <25			Maternal Age 25+			Maternal Age <30			Maternal Age 30+		
	LB		IR[a]	LB		IR[a]	LB		IR[a]	LB		IR[a]
	i	c		i	c		i	c		i	c	
	ABO Effect (Based on Early f.d.i.'s)											
All Rh types:												
ABO i/c	1,159	2,042	1.21	1,360	2,538	1.36	1,852	3,348	1.20	667	1,232	1.45
Rh (c):												
ABO i/c	1,004	1,783	1.27	1,165	2,174	1.57*	1,594	2,897	1.36	575	1,060	1.61
O×A/A×O (i/c)	524	519	1.28	565	621	1.78	807	841	1.17	282	299	2.42
Sum recip. i/c	771	746	1.04	858	923	1.74*	1,208	1,213	1.36	421	456	1.59
	Rh Effect (Based on Total f.d.i.'s)											
All ABO types:												
Rh i/c	414	2,787	1.26	559	3,339	1.17	709	4,491	1.04	264	1,635	1.46
ABO (c):												
Rh i/c	259	1,783	1.26	364	2,174	1.63*	451	2,897	1.29	172	1,060	1.89*
Rh−×+/Rh+×−(i/c)	259	261	1.13	364	321	1.32	451	421	1.13	172	161	1.50

NOTE.—i = incompatible, c = compatible; LB = live births; IR = indicator ratio; f.d.i. = fetal death index.

[a] = i/c based on early f.d.i. (ABO effect) or total f.d.i. (Rh effect) as indicated.

* = $.05 > P > .02$.

findings, which could be the result of random deviations with the small numbers of deaths involved (table 8).

The pattern in Rh incompatibility is simpler. Indicator ratios for Rh-incompatibility effects appear higher after previous fetal loss, but here, too, caution is required regarding inferences because of sample size.

*Blood Groups of Offspring of Incompatible and Compatible Matings**

To determine whether ABO- and Rh-incompatibility effects are mediated through specific selection against ABO- or Rh-incompatible gametes, zygotes, or fetuses, and in favor of corresponding compatible types, the blood groups of the offspring of reciprocal incompatible and compatible mating categories have been examined for relative proportions of incompatible and compatible offspring. The compatibility-incom-

* Matings are indicated mother × father.

TABLE 8

PREVIOUS FETAL LOSS[a] OF CAUCASIAN MOTHERS AND INDICATOR RATIOS OF CORRESPONDING ABOi AND ABOc MATINGS

	Previous Fetal Deaths	No. LB		Indicator Ratios Based on:			
		i	c	Early FD	Late FD	Total FD	Neonatal Deaths
	ABO Indicator Ratios						
All Rh types:							
ABO i/c	0	1,025	1,866	1.58	0.65	1.33	0.91
	1+	547	877	0.92	0.64	0.80	1.26
Rh (c):							
ABO i/c	0	891	1,610	1.87**	0.82	1.61*	0.77
	1+	466	756	1.08	0.73	0.96	1.32
O×A/A×O (i/c)	0	445	464	1.67	0.00	1.43	1.56
	1+	245	227	0.72	1.23	0.74	1.16
Sum recip. i/c	0	674	672	1.56	0.66	1.44	0.98
	1+	347	340	0.82	0.97	0.70	1.37
	Rh Indicator Ratios						
All ABO:							
Rh i/c	0	390	2,501	1.08	1.20	1.08	0.33
	1+	202	1,222	1.56	1.89	1.56	1.51
Rh i/c	0	256	1,610	1.74	1.72	1.74	0.00
	1+	121	756	2.08	2.27	2.08*	1.70
Rh−×+/Rh+×−(i/c)	0	256	241	0.94	1.41	1.11	0.00
	1+	121	128	3.71	1.41	2.29	0.79

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

[a] Primiparae omitted.

* = $.05 > P > .02$.

** = $.02 > P > .01$.

patibility designation of the offspring is based on their status in the incompatible matings; these same designations are used in the reciprocal compatible matings, even though all offspring of compatible matings would be compatible. For example, in O × A matings, A offspring are the ABO incompatibles and O offspring the ABO compatibles; and they are so designated in A × O matings although in this case both A and O types would actually be ABO compatible. Similarly, Rh-positive offspring are designated incompatible and Rh-negative offspring compatible in both the reciprocal matings Rh− × Rh+ and Rh+ × Rh−.

On the null hypothesis, the ratio of incompatible to compatible offspring would be the same for reciprocal mating types—for example, the ratio of proportion of A offspring to proportion of O offspring would be the same in O × A matings as in A × O, and the Rh−/Rh+ offspring ratio would be the same in Rh− × Rh+ matings as in Rh+ × Rh−. Thus a lower A/O ratio in O × A than A × O matings would suggest selection against ABO-incompatible offspring relative to ABO-compatible types; similarly, a lower Rh+/Rh− offspring ratio in Rh− × Rh+ matings than in Rh+ × Rh− matings would suggest selection against Rh-incompatible types. It is thus possible to determine whether the blood group distribution of liveborn offspring is altered by either ABO or Rh incompatibility.

While there seem to be fewer total live births in ABO-incompatible matings than in corresponding ABO-compatible types, the difference does not appear to be at the expense of the offspring of ABO-incompatible types. As shown in table 9, reciprocal ABO-incompatible matings of pooled Rh types yield an offspring i/c ratio of 1.20 with a very similar corresponding ratio of 1.19 in ABO-compatible matings.* When ABO effect is examined in Rh-compatible matings only, the corresponding ratios are 1.21 and 1.20, respectively. When both Rh and ABO groups are considered, there is a similar, if not greater, proportion of A offspring in O × A than in A × O matings among Rh− as well as among Rh+ offspring (table 10). Clearly, therefore, there is no evidence that the "selection" in ABO-incompatible matings shown in elevated fetal and neonatal loss is associated with altered ABO distribution of liveborn progeny.

In contrast, Rh incompatibility appears to exhibit a somewhat different tendency, with consistent, although not statistically significant, deviations in blood type of offspring (table 11). The proportion of Rh-incompatible offspring (Rh+) of Rh-negative mothers with Rh-positive spouses is slightly lower than from Rh-negative fathers with Rh-positive spouses, regardless of ABO-compatibility status of matings or exclusions. It seems, therefore, that Rh selection is directed, at least in part, against Rh-incompatible progeny in favor of the Rh-compatible progeny at some period from gamete formation to parturition.

Thus, in the CDS series, the two incompatibilities appear to differ as to whether there is specific selection against reproductive products on the basis of the genes they bear, or whether selection is directed against all the reproductive products of incompatible matings irrespective of the genetic composition of those products.

* Since all offspring in O × AB matings would be incompatible, that mating type and its reciprocal are excluded from this comparison.

DISCUSSION

The data on mating classifications and detailed family information available in the CDS series have made it possible to examine ABO and Rh incompatibility as etiological factors in differential pregnancy outcome and neonatal survivorship more definitively than in other series. As a result, not only has the CDS series confirmed the previous findings that ABO and Rh incompatibility have clear and distinct effects on fetal loss, but it has also provided further insight into incompatibility effects by extending the observations to neonatal risk and blood group distribution of liveborn offspring.

Granted that levels of statistical significance are not always attained in the incompatibility/compatibility ratios of death indices in the CDS series, nevertheless the

TABLE 9

RELATIVE FREQUENCY OF ABO-INCOMPATIBLE AND COMPATIBLE OFFSPRING OF ABO-INCOMPATIBLE AND ABO-COMPATIBLE MATINGS[a] (CAUCASIAN)

MATINGS +	ALL Rh TYPE MATINGS						Rh COMPATIBLE MATINGS ONLY					
	TLB	c Offspring		i Offspring		Offspring Ratio (i/c)	TLB	c Offspring		i Offspring		Offspring Ratio (i/c)
		No.	%	No.	%			No.	%	No.	%	
O×A (i)	1,305	496	43.74	638	56.26	1.29	1,111	414	42.86	552	57.14	1.33
A×O (c)	1,330	537	44.97	657	55.03	1.22	1,160	464	44.36	582	55.64	1.25
O×B (i)	348	154	48.73	162	51.27	1.05	303	139	49.82	140	50.18	1.01
B×O (c)	368	156	47.27	174	52.73	1.12	314	141	48.96	147	51.04	1.04
A×AB (i)	114	50	48.54	53	51.46	1.06	98	44	48.89	46	51.11	1.05
AB×A (c)	95	38	46.91	43	53.09	1.13	79	33	48.53	35	51.47	1.06
B×AB (i)	36	20	64.52	11	35.48	0.55	33	20	71.43	8	28.57	0.40
AB×B (c)	27	13	52.00	12	48.00	0.92	23	10	47.62	11	52.38	1.10
Total:†												
i	1,803	720	.....	864	.....	1.20	1,545	617	.....	746	.....	1.21
c	1,820	744	.....	886	.....	1.19	1,576	648	.....	775	.....	1.20
Sum of recip.:												
i	1,941	.....	.....	.....	.....	.....	1,662	.....	.....	.....	.....	.....
c	1,954	.....	.....	.....	.....	.....	1,698	.....	.....	.....	.....	.....

NOTE.—i = incompatible, c = compatible; offspring having questionable reaction with anti-A_1 but negative with anti-A are excluded from phenotype classification but are included in number of total live births (TLB); "i" offspring refers to those types which would be ABO incompatible in the "i" mating of the reciprocal pair ("A" in O × A, "B" in O × B, "B" and "AB" in A × B and "A" and "AB" in B × A, respectively) with the same designation (i) for those offspring types respectively in the corresponding compatible matings; "c" offspring refers to those types which would be ABO compatible in the "i" mating of the reciprocal pair ("O" in O × A, O × B, etc., as well as "A" in A × B and "B" in B × A matings) with similar designation (c) in the corresponding compatible matings.

[a] Excluding O × AB matings (along with reciprocal AB × O), since only "i" offspring are possible from this "i" mating type.

† Total = Sum of reciprocal omitting O × AB versus AB × O, where no compatible offspring are possible in the "i" type.

differences are consistent with one another and with other reports. The similarity of pattern in the various subclassifications and the fact that the more inclusive tabulations ("all ICD" and "no exclusions") tend to reach statistical significance suggest that the numbers in the sample, rather than the degree of deviation, are probably responsible for the nondefinitive outcome of the statistical tests in the smaller groupings.

While the suggested elevation in neonatal mortality with ABO incompatibility in the CDS series requires corroboration in another study, the increased risk of early fetal loss with ABO incompatibility and of total fetal wastage with Rh incompatibility

TABLE 10

ABO-Rh DISTRIBUTION OF OFFSPRING OF RECIPROCAL MATINGS O×A AND A×O (CAUCASIAN)

OFFSPRING	ALL ICD (AFTER TT EXCLUSIONS)				NO EXCLUSION			
	O×A		A×O		O×A		A×O	
	No.	%	No.	%	No.	%	No.	%
	All Rh Matings							
O−	78	6.88	83	6.96	81	6.85	85	6.90
O+	418	36.89	454	38.09	438	37.06	468	38.02
O	496	43.78	537	45.05	519	43.91	553	44.92
A−	99	8.74	101	8.47	100	8.46	103	8.37
A+	538	47.48	554	46.48	561	47.46	573	46.55
A	637	56.22	655	54.95	661	55.92	676	54.91
Rh−	177	15.62	184	15.44	181	15.31	190	15.43
Rh+	956	84.38	1,008	84.56	1,001	84.69	1,041	84.57
Total	1,133	100.00	1,192	100.00	1,182	100.00	1,231	100.00
A/O	1.28		1.22		1.27		1.22	
	Rh Compatible (c) Matings							
O−	49	5.08	61	5.84	51	5.06	62	5.75
O+	365	37.82	403	38.60	383	38.00	416	38.59
O	414	42.90	464	44.44	434	43.06	478	44.34
A−	74	7.67	77	7.38	75	7.44	79	7.33
A+	477	49.43	503	48.18	497	49.31	520	48.24
A	551	57.10	580	55.56	572	56.75	599	55.57
Rh−	123	12.75	138	13.22	126	12.50	142	13.17
Rh+	842	87.25	906	86.78	882	87.50	936	86.83
Total	965	100.00	1,044	100.00	1,008	100.00	1,078	100.00
A/O	1.33		1.25		1.32		1.25	

are themselves a confirmation of the significant differences reported in the New York and other series, and consequently justify more definite conclusions. Moreover, the composite findings of the CDS series and of other reports suggest further interpretations of incompatibility effects. Differences in the biological mediation of the two incompatibilities have long been indicated. It now appears that the mechanisms are more complex than was previously recognized, and that more than one mechanism may be involved in each incompatibility, especially in ABO incompatibility.

Let us review the evidence with the hypotheses. In the absence of selection, it would be expected that equal numbers of progeny of equal viability would be produced by reciprocal mating types and that the blood group distribution of those

TABLE 11

Rh DISTRIBUTION OF OFFSPRING OF RECIPROCAL Rh (i) AND Rh (c) MATINGS (CAUCASIAN)

OFFSPRING	ALL ICD (AFTER TT EXCLUSIONS)				NO EXCLUSION			
	Rh− ×Rh+		Rh+ ×Rh−		Rh− ×Rh+		Rh+ ×Rh−	
	No.	%	No.	%	No.	%	No.	%
All ABO matings:								
Rh+ (i)	591	69.86	618	71.86	614	70.01	650	72.46
Rh− (c)	255	30.14	242	28.14	263	29.99	247	27.54
Total	846	100.00	860	100.00	877	100.00	897	100.00
ABO (c) Matings only:								
Rh+ (i)	388	70.80	401	73.31	400	70.67	423	74.21
Rh− (c)	160	29.20	146	26.69	166	29.33	147	25.79
Total	548	100.00	547	100.00	566	100.00	570	100.00

NOTE.—i = incompatible, c = compatible.

progeny would be similar in the reciprocal matings. Failure to satisfy either of the above conditions would suggest that selection is operating. However, the two conditions are not necessarily interdependent—failure of the first does not necessarily imply the second, although this assumption has been made.

Some studies have demonstrated ABO-incompatibility effects on the basis of number of liveborn offspring of different parental ABO types without any data on the distribution of the offspring types (Kirk et al. 1953); others have indicated distorted ABO frequencies of liveborn offspring without data on fetal or neonatal survivorship (Bryce et al. 1950–1951; Kirk et al. 1955). Yet deficiency of offspring or fetal wastage in ABO-incompatible matings does not necessarily imply distorted ABO distributions among liveborn progeny. Peritz's (1967) study of a smaller sample of CDS families and the larger CDS sample here presented show no relative deficiency of offspring of ABO-incompatible blood groups, although the present study does clearly indicate an elevation of fetal wastage associated with parental ABO-incompatibility. Thus, rather

than selection directed specifically against ABO incompatible fetuses, embryos, zygotes, or gametes and in favor of compatibles, there appears to be selection directed against the overall "biological fitness" of the matings—possibly against the gametes of the fathers whose ABO type is incompatible with their spouses, or possibly against the products of conception of these incompatible fathers and their spouses, but, in any case, independent of the genotype of the concepti. It follows, therefore, that the term "ABO incompatibility" should be given a broader connotation—"maternal-paternal incompatibility" or "parental incompatibility," rather than "maternal-fetal" incompatibility. It must be noted, however, that even though such ABO selection may very well be acting as early as the gametic stage, the essential process differs from the "meiotic drive" postulated by Hiraizumi (1964). For meiotic drive infers preferential selection against gametes of one genotype in favor of another (e.g., against incompatibles), whereas the CDS evidence suggests negative selection against all the gametic products of an incompatible potential father.

Clearly, the determination of the mechanism of ABO selection requires further investigation. It is hoped that future studies will supplement the statistical observations with laboratory analysis of reproductive physiology. Thus far, statistical evidence indicates that ABO-incompatible loss occurs early—sometimes possibly so early that pregnancy has not been recognized or has not even occurred. An association of ABO incompatibility with sterility, discussed by Reed (1967*a*) although not confirmed in his own studies (Reed et al. 1964) or those of Solish and Gershowitz (1969), has been reported by Matsunaga and Itoh (1957–1958), Haga (1959), and Behrman et al. (1960). The last group of investigators has shown, moreover, that among carefully evaluated physiologically and anatomically normal couples, infertile for five years or more, over 87% were ABO incompatible, compared to 38.6% ABO incompatible among the fertile couples. In addition, many of the husbands were reported to be aberrant ABH secretors. Behrman and coworkers thus concluded that fertilization was prevented or inhibited at the level of contact of sperm and cervical secretion. The observation of higher frequency of saliva antibodies in women who have had heterospecific pregnancies, together with an inverse relationship in the frequency of antibodies and parity in incompatible women, further supports a possible association between ABO incompatibility and infertility (Jakobowicz and Graydon 1968). It seems quite possible that incompatible A or B antigens in the seminal fluid of secretors, or perhaps even in the cell envelope of sperm of both nonsecretors and secretors, may react with maternal anti-A or B in the female reproductive tract, causing either inactivation and/or dysfunction of the sperm. As a consequence, perhaps, ability to fertilize the ovum is altered or some biochemical change is induced so that even if syngamy occurs, the resultant zygote is inviable or has decreased viability. Residual deleterious effects so incurred could thus be responsible for the increased loss in early gestation associated with ABO incompatibility, and may possibly provide the basis for elevated neonatal mortality. On the other hand, Solish's (1969) observation of a larger proportion of fertile than infertile women with cervical agglutinins raises questions concerning such a mechanism, unless the crucial antibodies involved in infertility are not saline agglutinins and/or show a reciprocal relationship with those saline antibodies.

In regard to postzygotic mechanisms, Szulman (1966*a*, 1966*b*) has studied ABH

antigens in embryos, and indicated that they are present in early embryonic stages and then disappear. His observations suggest that ABH antigens may have some role in development, respiration, or biochemical activities during one or more critical periods of the embryo and neonate. Such possibilities are certainly not inconsistent with the findings in the CDS, New York, and other series, which seem to indicate that ABO-incompatibility damage may act prenatally only during limited critical periods (gametic, embryonic, and early fetal) with overt manifestation, sometimes immediate and sometimes possibly postponed to postnatal life.

Whatever the biological mechanism of the early pregnancy ABO-incompatibility effect may be, its mediation must be different from that of erythroblastosis, recognized as a hemolytic disease of late pregnancy. Levene and Rosenfield (1961) have already pointed out that ABO-incompatible erythroblastosis, while potentially an important clinical problem, is doubtless very rare and, as such, does not make a substantial contribution to ABO selection—a view supported by the lack of any detectable increase in late fetal wastage with ABO incompatibility in either the CDS or the New York series.

Because neonatal mortality seems to be elevated with ABO incompatibility, this period is possibly another critical time for ABO effects. Several explanations can be postulated for neonatal manifestation. Possibly a subclinical type of erythroblastosis causes an "ABO-incompatible disease" with low-grade jaundice which is not sufficiently severe to manifest any loss in late fetal life, but leads to greater susceptibility to the usual stresses of the neonate. An extremely mild ABO-incompatibility disorder in newborns has often been referred to (Chung and Morton 1961; Levene and Rosenfield 1961). Icterus praecox was first described by Halbrecht in 1944 as a very early icterus, different from physiological icterus in that it appears within 24 hours of birth and is associated with ABO incompatibility. It was suggested that the condition may be more severe in nonsecretor infants, and "perhaps even erythroblastosis fetalis." It therefore seems reasonable that this ABO-incompatibility-induced condition, even if not fatal per se, may have any of a number of deleterious complications. By impairing adjustment to extrauterine life or increasing susceptibility to neonatal stresses, icterus praecox may indirectly predispose infants to a higher mortality risk. Another possibility is that residual tissue damage or faulty organogenesis from early ABO-incompatibility effects, such as Szulman (1966*a*, 1966*b*) postulated, while not fatal in intrauterine life, may become crucial when the neonate's cardiovascular and respiratory systems must act independently of maternal support. Whether classified as ABO hemolytic disease, icterus praecox, neonatal hyperbilirubinemia or even some less specific condition, there is further recent evidence that ABO-incompatibility effects can be quite deleterious in the neonate (Sever 1969).

Thus, although the nature of the mechanism operating in ABO incompatibility is still quite speculative, the early presence, disappearance, and reappearance of ABH antigens in various tissues of the fetus suggest a variable type and degree of involvement of these antigens at different developmental stages. There may be multiple modes of mediation in ABO-incompatibility selection, the mechanism varying with the developmental stage of the reproductive product. Extrinsic and intrinsic factors may also influence the competence of the different mechanisms, so that not all are

operating in every population, and more than one may operate in any population. The different findings in several Japanese series (Matsunaga 1955, 1956; Matsunaga and Itoh 1957–1958; Haga 1959), separated in space and time, may result from a situation of this kind.

As for Rh selection, the overall increase in total fetal wastage with Rh incompatibility among CDS families agrees with clinical and epidemiological observations reported in other series. However, two of the observations of the CDS series—elevated fetal wastage early in pregnancy and lack of an increase in neonatal mortality with Rh incompatibility—are somewhat difficult to explain.

Earlier studies have pointed out the absence of any increase in early spontaneous abortions in Rh-negative women (Overstreet et al. 1947; Glass 1949; Cohen and Sayre 1968), while the association of late pregnancy erythroblastosis fetalis with Rh incompatibility is well known (reviewed by Race and Sanger 1962; Cohen 1960). If Rh selection operates primarily through maternal isoimmunization resulting in this condition, then not only the observed increment in late pregnancy wastage but also a continuum of high risk into neonatal life might be expected, with early fetal loss not indicated. Why then the high early fetal wastage and no neonatal mortality increment? Although these findings on early fetal and neonatal loss may be spurious or peculiar to the CDS series, nevertheless, if they are real, various explanations must be considered.

The blood group distribution of CDS live births is consistent with the view that Rh selection seems to be directed in part, if not entirely, against Rh-incompatible concepti. Previous clinical and epidemiological studies have shown that the increase in fetal risk with Rh incompatibility is a direct consequence of maternal-fetal genotype combinations and subsequent maternal Rh sensitization. Having been influenced by both the Rh and ABO incompatibility of the prior concepti, the mother responds with specific antibodies that act upon the incompatible erythrocytes of the fetus. Nevertheless, a continuum of late fetal loss into the neonatal period is not requisite to an Rh effect mediated through erythroblastosis, for those fetuses with severe disease may tend to succumb prenatally, while those who survive through birth have a prognosis no longer subject to the stress of a hostile intrauterine environment. Moreover, the high negative prenatal selection pressure may also eliminate the Rh-incompatible fetuses of lesser biological fitness due to characteristics other than Rh. Therefore, it is not unrealistic that the Rh incompatibles surviving into neonatal life are less likely to die during the neonatal period from non-Rh-associated causes than those not subjected to such stringent prenatal selection. This selective process and the very judicious medical attention afforded these infants of Rh-sensitized mothers during their first weeks of life may prove advantageous. That would be in contrast to ABO-incompatibility effects, discussed above, where full-blown erythroblastosis is very rare, and does not impose a hazard in late pregnancy. There, the neonate with a clinically undiagnosed mild ABO disease, whose mother's incompatibility is also unrecognized, is without the benefit of the extra medical surveillance provided the Rh incompatibles, and may fall victim to a combination of various extrinsic stresses complicated by problems of residual ABO-incompatibility effects.

The early fetal loss with Rh incompatibility observed in the CDS series is some-

what more difficult to explain. There is no reported evidence that Rh sensitization leads to some form of Rh disease manifested in early pregnancy. It may be that repeated Rh fetal deaths late in pregnancy may modify the obstetrical prognosis of subsequent pregnancies, thus increasing the risk of early wastage from nonspecific complications that are only indirectly Rh-related.

To summarize, while the evidence for elevated total fetal wastage with ABO incompatibility and Rh incompatibility, respectively, is unequivocal, and the evidence for increased neonatal mortality with ABO incompatibility is suggestive, the biological mechanisms require further study. Certainly, the time of manifestation for both incompatibilities is an important problem, and its resolution undoubtedly holds clues to the ultimate answers. Meanwhile, given the observations, one may speculate concerning their biological bases.

One ought not to speculate concerning the impact of reproductive wastage on gene frequencies, however. As indicated by the ABO pattern shown here, greater fetal loss in incompatible matings cannot be assumed to indicate selection against offspring of incompatible types. If there is selection against the reproductive performance of ABO-incompatible males, irrespective of the genes carried by the reproductive product, this would certainly cause less deviation from equilibrium, especially if there were compensation through higher fertility of females of corresponding types, than if gametes or progeny of a specific genotype only were affected. The fact remains that some studies have reported deviation of ABO frequencies of offspring of ABO-incompatible matings, while other studies report no deviation, leaving open the question of whether populations vary—or only investigations.

Thus, although fetal, neonatal, and other pregnancy outcome data can provide information on relative risk to progeny of various classes of compatible and incompatible matings under the specific conditions of that population, they cannot form the basis for any reasonable estimates of the magnitude of resultant gene frequency trends. Moreover, to make quantitative estimates, or to provide even gross evaluations of direction of influence, data on total reproductive performance (including sterile individuals) are required, preferably for two or more generations. Only a few studies of total reproductive performance including zero offspring families (Reed and Kelly 1957–1958; Reed and Ahronheim 1959) have been carried out—and these for the most part retrospectively, with incomplete follow-up and lacking any assurance of representativeness of the sampling or exclusion of biases of reporting. The mode of ascertainment of most other study samples—through obstetrical services and vital records over less than 10 years—selectively eliminates the sterile group and probably does not represent in true proportion those of low fertility and/or with very early pregnancy loss. Since it seems likely that much ABO selection occurs in such situations, a quantitative evaluation of ABO-incompatibility effects is not attainable from the data available. Even within the circumscribed sample ascertained through recognized pregnancy, it is debatable how representative of true proportions the ABO reciprocal matings are with regard to their own relative number or the relative number of pregnancies and liveborn offspring, although it does not appear that voluntary inclusion would be more likely for one ABO type than for another, as seems to be the case with Rh incompatibility. With Rh, where tabulations depend on obtaining blood typing of both gravida and husband in the Rh system, an excess of Rh− × Rh+

class matings relative to the Rh+ × Rh− class may very well be a function of the fact that there is more medical pressure for husbands of Rh-negative gravidae to be blood typed than for husbands of Rh-positive gravidae. Even in the CDS study where a high proportion of husbands were typed, there still appears to be more incentive for husbands of Rh-negative gravidae than those of Rh-positive to participate; only 9% of Rh-negative gravidae, but over 13% of Rh-positive gravidae do not have husbands blood typed. While this difference should not distort the Rh distribution of offspring from Rh− × Rh+ versus Rh+ × Rh− matings, the total number of recorded pregnancies and offspring of these reciprocal matings could be altered. Moreover, extreme care is required in the design of ingenious statistical or mathematical procedures to circumvent the deficiency of data. In human populations, the impact of extraneous factors is sufficiently formidable without compounding random and artifactual discrepancies by further extrapolations.

In conclusion, although it seems appropriate to postulate possible mechanisms and to speculate concerning the overall impact of incompatibility effects, it is important to recognize the limitations of the data and to evaluate realistically those inferences which can be derived, as well as those which cannot. Blood group effects are, unfortunately, small. Therefore, even where consistent patterns are noted, the differences do not reach levels of statistical significance. The investigator is caught between using vital statistics data, where the numbers are large enough but inadequate detail precludes definitive classification and insight into specific aspects (e.g., the New York series with only maternal types), and privately collected data, where the detail and classification are more precise but the sample size is inadequate and the cost of obtaining a truly satisfactory series is prohibitive. An additional complication is the possibility that populations may vary temporally and geographically with regard to the major mechanism operating and the degree to which other factors are acting.

Clarification of these aspects awaits controlled simultaneous and similarly designed studies carried out in different areas and subpopulations. Data banks are needed—cooperative efforts by numerous investigators in different centers to collect essential information on a continuous basis, devise family record linkage programs, and supervise record storage and retrieval facilities; the findings can then be compared to determine the nature and cause of differences between centers, and can be pooled where feasible to realize the maximum potential for population analysis and genetic inference.

This plea has its most apparent application in the need for genetic-demographic data on population samples of adequate size. However, just as urgent are cooperative and collaborative efforts between laboratories, between researchers in basic science, and between clinical investigators to acquire information on underlying biological mechanisms. Clearly, the ultimate resolution of many of the problems of population genetics resides in the concomitant elucidation of the biological basis with the statistical evidence. The problem of ABO- and Rh-incompatibility effects provides a case in point.

SUMMARY

The CDS series, by providing maternal *and* paternal blood types, allows more definitive classification of compatibility status than other previously studied series.

In addition, the detailed information available for this group permits examination of incompatibility effects with regard to neonatal risk, blood group distribution of offspring, and parity effects.

In agreement with the findings in New York City birth and death records, Caucasian CDS families show ABO incompatibility, especially in the absence of Rh incompatibility, to be associated with increased fetal loss derived entirely from a significant increment in early wastage, and not at all in late wastage. Neonatal mortality for ABO-incompatible matings also appears to be elevated, although that difference does not attain levels of statistical significance.

With Rh incompatibility, especially in the absence of ABO incompatibility, there is also a significant increase in fetal mortality in the CDS Caucasians, but, in contrast to the New York series, the elevation is observed in early fetal loss as well as in late fetal loss. There is no discernible increase in neonatal mortality with Rh incompatibility, however.

There is no alteration in ABO distribution of liveborn offspring associated with the elevated fetal wastage in ABO-incompatible matings. On the other hand, there is a consistently (although not significantly) lower proportion of Rh-positive offspring in Rh-incompatible matings than in Rh-compatible matings, suggesting that Rh selection is directed at least in part against Rh-incompatible progeny during the prenatal period. Thus ABO and Rh incompatibility, respectively, appear to differ as to whether there is specific selection against reproductive products on the basis of the genes they bear (e.g., with Rh incompatibility), or whether selection may be directed against all reproductive products of the incompatible matings (e.g., with ABO incompatibility).

Among the CDS Caucasian families, maternal age and multiparity are both associated with increased fetal loss in Rh incompatibility, and possibly also in ABO incompatibility.

The effect of previous pregnancy wastage on ABO manifestation is somewhat puzzling, and even though Rh-associated fetal deaths appear to be increased with a history of previous loss, caution is required regarding inferences.

Among CDS Negro families, no incompatible-compatible differences, either ABO or Rh, reach levels of statistical significance, but the possibility of ABO or Rh selection in Negro families cannot be ruled out. Clearly, there is not the distinct contrast in pattern between Negroes and Caucasians of the CDS series that was observed in the New York series.

Various interpretations of the observed incompatibility effects are discussed. It is suggested that more than one biological mechanism may be involved in each incompatibility, especially ABO incompatibility. The likelihood that the mode of mediation differs according to the critical period of embryonic and neonatal development, the population, and other extrinsic factors is considered.

In conclusion, the increase in fetal wastage with ABO and Rh incompatibility is confirmed in the CDS series, and a possible increase in ABO-associated neonatal mortality suggested. While further study of the biological basis of incompatibility effects is required, one may speculate concerning the mechanisms. However, the currently available evidence for selection does not permit extrapolation to its impact on gene frequencies.

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APPENDIX A

EXCLUSION TT SPECIFICATIONS

Exclusion of families and/or specific family members is based on the occurrence of a genetically "impossible" combination of infant blood type and parents. With the infant type used as the index family member, the causes of exclusion are as follows: (1) maternal: the maternal blood group specified would not be possible, given the infant type (e.g., AB mother with O infant, O mother with AB infant; C negative, c positive mother with C positive, c negative infant; etc.); (2) paternal: the paternal blood type would not be possible, given the infant type as above for maternal; (3) joint: given the infant type, at least one or the other of the parents is impossible; (4) both: given the infant type, neither of the parents is possible.

The general procedure for exclusion TT involves exclusion on the basis of discrepancy in one or more of the following—ABO; $Rh_0(D)$, Cc, or Ee (Rh); MN; Kell; Duffy; or Lutheran types for both Caucasians and Negroes.

In Caucasians, Ss is also included in the series and handled similarly; and a summary exclusion classification is based on the results of all systems for the trio (infant, mother, and father), with "maternal" and "both" classifications in any type taking precedence over "paternal" and "joint" classifications in any other type.

In Negroes, Ss exclusions are classified on a different basis from other systems because of the occurrence of "silent types" (S—s—). The summary classification in Negroes is a dual exclusion classification based on (1) the summary category derived from all other systems (ABO, $Rh_0(D)$, Cc (Rh), Ee (Rh), MN, Kell, Duffy, Lutheran) and (2) the classification based on Ss for Negroes, with the classification decision determined by the maximum exclusion indicated.

Exclusions were therefore carried out for classifications (*a*) in any system for Caucasians, or (*b*) in any system other than Ss for Negroes as follows: (1) "maternal," "both," or "joint" discrepancy: entire trio (infant, gravida, and husband) is excluded from all tabulations* and (2) "paternal" discrepancy: husband only is excluded from all blood group tabulations.

Exclusions based on Ss discrepancies in Negroes are: (1) "maternal" or "both" discrepancy in Ss, no discrepancy in any other system: entire trio (gravida, husband, and infant) is excluded in Ss tabulations only; (2) "paternal" discrepancy in Ss with or without paternal discrepancy in other systems but no other type of discrepancy: husband is excluded from all tabulations, gravida and infant from Ss tabulations only; (3) joint discrepancy in Ss with or without paternal discrepancy in another system: husband is excluded from all tabulations, gravida and infants from Ss tabulations only; and (4) "paternal" discrepancy in Ss with "maternal" or "both" discrepancy in another system: entire trio (husband, gravida, and infant) is excluded in all blood group tabulations.*

* "All tabulations" here refers to tabulations involving blood groups and labeled "TT after exclusions."

APPENDIX B

CLASSIFICATION OF MATINGS ON COMPATIBILITY STATUS

ABO STATUS

ABO-Compatible Matings (Gravida ×Husband)		ABO-Incompatible Matings (Gravida ×Husband)
A×O	←——— ———→	O×A
B×O	←——— ———→	O×B
AB×O	←——— ———→	O×AB
AB×A	←——— ———→	A×AB
AB×B	←——— ———→	B×AB
O×O		A×B
A×A		B×A
B×B		
AB×AB		

Rh STATUS

Rh-Compatible Matings		Rh-Incompatible Matings
Rh+×Rh+		
Rh+×Rh−	←——— ———→	Rh−×Rh+
Rh−×Rh−		

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