Spontaneous Abortion Risks in Man: Data from Reproductive Histories Collected in a Medical Genetics Unit

DOROTHY WARBURTON AND F. CLARKE FRASER

Department of Medical Genetics, The Montreal Children's Hospital, and Department of Genetics, McGill University

SPONTANEOUS ABORTION is one of the most common and least understood pathological processes. Because it is so difficult to obtain reliable information about abortion, even the basic facts about its frequency, familial distribution, and relation to parity and parental age are largely unknown or disputable. Such information is needed to provide a basis for advising women with several abortions about their chances of successfully completing another pregnancy, to evaluate measures for the prevention of abortion, as well as to provide clues to the etiology of the condition.

Reproductive histories taken by personal interview with a random series of women would probably be the best available data for estimating spontaneous abortion statistics. These would include very early terminations of pregnancy, recognized as spontaneous abortions by the women concerned but not receiving medical attention, which are under-represented in series of consecutive hospital admissions or in consecutive cases from private obstetrical practice. They would allow estimation of abortion risks in women with given numbers of previous abortions and at given ages. Some reservations must be held about the validity of self-diagnosis of early abortion, but this source of error should not affect comparisons within the sample.

The data presented here were derived from family histories taken in the Department of Medical Genetics at The Montreal Children's Hospital during the years 1952 to 1962, inclusive. For some parts of the analysis, only histories from a part of the period were used. Each history routinely includes details about all recognized pregnancies of the woman being interviewed; she is specifically asked about "miscarriages" and about attempts to induce abortion. Because of the leisurely nature of the interview and the excellent rapport usually existing between interviewer and mother, the data are considerably more reliable than those found in routinely taken hospital histories. Losses of unrecognized pregnancies are not taken into account. A woman was interviewed because she had a child who was of research interest to some member of the department, or because she was referred by the hospital staff or a private physician for counseling or possible genetic interest. The proband child either had a clear-cut genetic defect (*e.g.*, amaurotic idiocy), a defect of unknown etiology but with a familial tendency (*e.g.*, cleft palate), an undiagnosed defect or series of multiple mal-

Received January 9, 1963; revised version received September 7, 1963.

formations, or was a twin with no defect. A control series of random admissions to the hospital also was included.

The method of collecting families requires that every woman interviewed have had at least one non-aborted pregnancy (the proband child) and thereby excludes women who have had only abortions.

Possible biases resulting from the special nature of the families and the method of ascertainment had to be taken into account. If not eliminated by the method of analysis, their nature and extent have been investigated within the data themselves, where possible.

The length of gestation of pregnancies is known by the mother with limited accuracy, and she usually expresses gestation time in months and halves of months. For this study, all uterine pregnancies stated by the mother to have terminated at less than 6½ months gestation were considered abortions. An abortion is defined as the termination of an intrauterine pregnancy before the fetus is viable outside the uterus. Difficulties in classification arise from disagreement about when such viability is achieved; 6½ months proved to be a satisfactory dividing line in these data, since no child reported to be born at less than 6½ months gestation survived more than a few hours, while several reported to be born at 6½ months did survive through infancy. Children born living at 6½ to 8 months gestation were considered premature, and children born dead at 6½ months or later were considered stillbirths. Twin pregnancies were counted as single pregnancies.

All families where there was an admitted abortion attempt, a successful induced abortion, or an illegitimacy were omitted, since it seemed likely that there was an increased probability of induced abortion in such families.

RESULTS

Frequency of Abortion in the Population

Table 1 summarizes the distribution of abortion frequencies by family size. Since all families were ascertained through a liveborn pregnancy, and very few families were ascertained more than once, the situation is very close to single ascertainment as defined by Morton (1959). In such situations, the chance of ascertaining a family is proportional to the number of liveborn pregnancies it contains, and the resulting excess of liveborn children is exactly corrected for by omitting the liveborn proband in each family and then counting the number of aborted and non-aborted pregnancies. The resulting frequency of recognized abortion is 14.7 per cent ± 0.4 per cent of all pregnancies (table 2). If the frequency in the population of women who have had only abortions is no greater than that expected if each woman has a 15 per cent risk for each pregnancy, this method of analysis will correct for the omission of these women from our sample, and 14.7 per cent is an unbiased estimate of the over-all abortion frequency in the population. If there are more such "habitual aborters" than expected by chance, 14.7 per cent is an underestimate but the bias is not likely to be large, a point to which we will return.

TABLE 1. NUMBER OF ABORTIONS PER FAMILY FOR VARIOUS FAMILY SIZES

Family size	No. of families with no. of abortions							Total no. of families
	0	1	2	3	4	5	6	
2	522	36						558
3	403	102	13					518
4	248	126	24	6				404
5	122	72	33	9	1			237
6	73	39	22	9	2	0		145
7	37	26	17	6	0	2	0	88
8	29	17	10	8	3	2	0	69
9	12	14	7	4	1	2	0	40
10	5	7	8	2	1	0	1	24
11	2	3	3	3	0	0	0	11
12	7	2	3	0	1	0	1	14
13	2	1	1	0	1	1	0	6
14	0	1	2	1	1	0	0	5
15	1	1	1	0	0	1	0	4
16	0	1	1	0	1	0	1	4
17	1	0	1	1	0	0	1	4
18	0	0	0	0	0	0	0	0
19	0	0	2	0	0	0	0	2

Relation of Abortion Frequency to Family Size

Table 2 presents numbers of abortions in our series of families classified by size of family (including aborted pregnancies). The frequency of abortion varies significantly from one family size to another. Most of the heterogeneity arises because of the much lower frequency of abortion in families of size 2 and 3 than in larger families. This suggests that prolific families are disproportionately more likely to have abortions than small families, but the possibility that the difference was secondary to some other difference between the groups has to be considered.

Attempts to explain the effect of family size by differences between large and small families in the degree of completeness of the family, the maternal age distribution, pregnancy spacing and socio-economic status all were unsuccessful. Large and small families did differ in all these factors, but when they were held constant the effect of family size remained. Another explanation might be that women who have aborted undertake more pregnancies than they otherwise would, in an attempt to make up for the children lost through abortion. There is a little evidence from our data that this may be so. In families of comparable size, the second pregnancy began on the average 12 months after the first, if the first ended in abortion, but 21 months after the first if the first ended in a livebirth. Some of this difference could be due to the longer infertile period after a full-term birth, but this would not explain an average difference of 9 months.

Risk of Abortion Frequency after a Previous Abortion

Average risk: There is general agreement in the literature that a pregnant woman is more likely to abort if she has already had an abortion. The extent of the increase in risk is disputed, however, and good data for its esti-

TABLE 2. ABORTION FREQUENCY BY FAMILY SIZE

Family size	No. of families	No. of conceptions (minus proband)	No. of abortions	% abortions
2	558	558	36	6.5
3	518	1036	128	12.4
4	404	1212	192	15.8
5	237	948	169	17.8
6	145	725	118	16.3
7	88	528	88	16.7
8	69	675	83	12.3
9	40	320	54	16.9
10	24	216	39	18.1
over 10	51	617	96	15.5
	2134	6835	1003	14.7 ± 0.4

mation are hard to obtain. The commonly quoted figures given by Malpas (1938) and Eastman (1956) are not valid estimates of the recurrence risk of spontaneous abortion, for reasons discussed in detail elsewhere (Warburton and Fraser, 1961).

To answer the question, "What is the risk that a given pregnancy will abort if there has been one previous abortion (or two, or three)?", those families with at least one abortion were analyzed. If the proband livebirth is omitted from each family, this subsample represents "complete ascertainment" with respect to abortions, since the chance of ascertaining the family is independent of the number of abortions it contains.

Once the proband is eliminated, unbiased methods for calculating the risk of abortion after one abortion are Finney's iteration solution of the truncated binomial maximum likelihood equations, Fisher's "sib" method where each family is counted once for every affected (in this case aborted) member (see Steinberg, 1959), and the method of counting only sibs after the first abortion (Hogben, 1931). The recurrence risks for abortion given by these methods are, respectively, .245, .237 and .237.

The risk of aborting in a pregnancy where there is no history of abortion in previous pregnancies can be calculated by subtracting those pregnancies (abortions and livebirths) which occurred after a spontaneous abortion (tabulated in table 3) from the total number of pregnancies shown in table 2. This gives $(1003 - 333)/(6835 - 1403) = 12.3$ per cent, which is significantly different ($P < .001$) from the risk in pregnancies in women with a history of a previous abortion. There are thus at least two groups of women in the population, one with a higher risk of aborting than the other. James (1961) has reached a similar conclusion, using a different method and the data of Whitehouse (1929).

The calculated probability of aborting after at least one previous abortion is only an average risk figure for all women and does not indicate whether this risk is constant throughout a woman's succeeding pregnancies (*i.e.*, within families) or for all women who have had an abortion (*i.e.*, between families).

TABLE 3. ESTIMATE OF ABORTION RISK IN PREGNANCIES FOLLOWING A GIVEN NUMBER OF ABORTIONS

No. of previous abortions	No. of succeeding pregnancies	No. of abortions	% abortions
0	5432	670	12.3
1	1403	333	23.7
2	385	101	26.2
3	121	39	32.2
4	58	15	25.9

Heterogeneity of risk between families: If there is heterogeneity between families the risk of abortion should increase with the number of previous abortions, since the women with large numbers of previous abortions will tend to be those with the highest risk of aborting again. To estimate the risk in women with two or three previous abortions, only pregnancies after the given number of abortions were counted. The results are shown in table 3. The apparent increase in risk with the number of previous abortions (23.7 per cent after one, 26.2 per cent after two, and 32.2 per cent after three) cannot be tested for statistical significance since the classes are not independent.

Another way to approach the question of heterogeneity of risk among women who abort is to calculate for each family size the number of families expected to have a given number of abortions, on the assumption that this follows a truncated binomial distribution with a constant risk. Table 4 shows the observed and expected values for families of size 3 to 9, calculated using 0.25, the average recurrence risk for families of this size range as estimated by the sib method, as the risk of aborting any pregnancy. The χ^2 based on the totals for all family sizes, with two degrees of freedom, is significant at the 2 per cent level, and the χ^2 which measures heterogeneity between family sizes, with ten degrees of freedom, is not significant ($.30 < P < .40$). If recurrence risks are estimated separately for each family size (and the appropriate changes made in degrees of freedom), the significance of the deviations is unchanged. Differences in recurrence risks among family sizes are thus not an important source of the deviations.

Although the data show poor agreement with a binomial distribution with constant risk, examination of table 4 reveals that the type of variability in risk cannot be easily interpreted. For every family size, there is an excess of families with one abortion and a deficiency of families with two abortions. However, there is no excess of families with three or more abortions, as would be expected if there were some women with a very high risk of aborting any pregnancy.

Clustering tendency: If the risk of abortion varies from time to time in the same woman, it is possible that it might be greater in the pregnancies immediately succeeding an abortion than in later pregnancies. Such a "clustering" effect was investigated as follows: For all women who had at least one abortion, all succeeding pregnancies were ranked according to their order after the first abortion. The proband livebirth was omitted wher-

TABLE 4. COMPARISON OF THE DISTRIBUTION OF ABORTIONS IN VARIOUS FAMILY SIZES

Family size (excluding proband)	Recurrence risk (sib method)	d.f.	χ^2	No. of families with no. of abortions					
				1		2		3 or more	
				obs.	exp.	obs.	exp.	obs.	exp.
2	.203	1	0.822	102	98.6	13	16.4		
3	.219	2	7.237	126	113.8	24	38.0	6	4.2
4	.260	2	0.455	72	71.0	33	35.5	10	8.5
5	.258	2	0.562	39	37.3	22	24.9	11	9.8
6	.250	2	1.872	26	22.1	17	18.4	8	10.5
7	.289	2	2.103	17	14.4	10	14.4	13	11.2
8	.238	2	5.566	14	8.3	7	9.7	7	10.0
Total	.252	13 − 1 = 12	18.617	396	365.5	126	157.3	55	54.2
						$\chi^2_{(2)} = 8.785$			

χ^2 for heterogeneity = 18.617 − 8.785 = 7.438
d.f. = 12 − 2 = 10.

ever it occurred. The abortion frequency was then determined for each birth order following the first abortion.

The results (table 5) contain deviations in the direction expected if clustering occurred. The probability of the signs of the deviations being distributed as expected (*i.e.* ++−−, omitting the middle class) is .0625. The χ^2 value for the significance of the sizes of the deviations is 3.297, giving a P value of .51. Combining the P value for the signs and sizes of the deviations by Fisher's test gives a total probability of between .10 and .20 of the observed deviations occurring by chance. Thus the clustering tendency is not large enough to be statistically significant, and even if it is really present, its effect on the abortion risk must be very small.

Parental age and birth order: Parental ages were divided into five year classes for analysis: These range from 15–19 to 40–44, for maternal age, and from 15–19 to 44–47, for paternal age. Since aborted pregnancies are shorter than non-aborted pregnancies, parental ages were considered at the estimated time of conception rather than at the end of the pregnancy. The frequency of abortion in all pregnancies in the sample at a given parental age-birth order category was calculated. It is not practical to display the data as subdivided by all three variables, but tables 6 and 7 show abortion frequencies for given maternal ages and birth orders, and for given maternal and paternal ages.

A computer program prepared by Dr. A. F. Naylor was used to calculate maximum likelihood regression constants, after transformation of the data to logits. (For a discussion of the choice of transformations, see Finney, 1952). A χ^2 value for the goodness of fit of the observed number of abortions in each class with that expected from the calculated regression equations was included in the analysis.

The regression constants for abortion frequency on maternal age, paternal age, and birth order were estimated separately and in various combinations, as shown in table 8. When only one variable at a time was considered, the regression constant was in each case positive and more than three times its standard error. For maternal age and birth order, the χ^2 for goodness of

TABLE 5. TEST FOR CLUSTERING EFFECT

	Pregnancy order after first abortion					
	1	2	3	4	5 and over	Total
No. of pregnancies	420	352	220	144	267	1403
No. of abortions (observed)	112	87	44	31	59	333
% abortion	26.7	24.7	20.0	21.5	22.1	23.7
Expected no. of abortions	100	84	52	34	63	333
Differences (obs. – exp.)	+12	+3	−8	−3	−4	0

fit was not significant, while for paternal age it was significant at the 2 per cent level. One can conclude that there is a significant tendency for abortion frequency to increase with some factor which is almost equally well estimated by maternal age, paternal age, or birth order, although the lack of a good fit for the paternal age makes it a less valuable predictor of abortion frequency. The total frequencies for paternal age classes, shown in table 7, indicate that there is no simple explanation for the lack of fit to a linear model. No obvious curvilinearity is present, and the largest contributions to χ^2 arise from classes 25–29 and 30–34, where the relative frequencies are the reverse of those expected from a linear model.

By considering the factors in various combinations, an attempt was made to determine which of the three highly correlated variables was most important in increasing the abortion frequency.

When the maternal age and birth order constants were estimated simultaneously, each was about twice its standard error. The same was true when the paternal age and birth order constants were estimated together. The goodness of fit was again reasonably good when maternal age was involved and poor when paternal age was involved. When the interaction between birth order and either parental age was also estimated, the values of the other constants did not change appreciably, nor did the fit improve: In each case the interaction constant was very much smaller than its standard error, and the only effect of including it in the analysis was to inflate the standard errors of the other constants.

When the maternal age and paternal age regression constants were estimated simultaneously, the paternal age constant was reduced only slightly from previous estimates and remained about twice its standard error, while the maternal age constant was reduced in size and almost equal to its standard error. The χ^2 for goodness of fit was not reduced by the addition of the interaction constant, which did, however, have the effect of reversing the sign and relative size of the previously estimated constants.

When all three constants were estimated simultaneously, none was more than twice its standard error, and the χ^2 for goodness of fit was significant at the 5 per cent level.

Interpretation of these results is difficult. It appears that our sample is not large enough, particularly in the crucial extreme classes, to partition successfully what is in total a rather small effect of parental age and/or birth order on abortion frequency. The more constants estimated, the larger

TABLE 6. RELATION OF ABORTION FREQUENCY TO BIRTH ORDER AND MATERNAL AGE AT CONCEPTION

Maternal age		Birth order 1	2	3	4	5	6	7	8	9	10+	Total
< 20	No. Preg.	339	132	42	12							525
	No. Abort.	36	20	6	2							64
	%	10.6	15.2	14.3	16.7							12.2
20–24	No. Preg.	549	581	345	169	83	25	8				1760
	No. Abort.	78	86	46	24	11	5	1				251
	%	14.2	14.8	13.3	14.2	13.3	20.0	12.5				14.3
25–29	No. Preg.	372	466	451	298	175	117	66	33	16	9	2003
	No. Abort.	38	53	53	43	29	21	15	3	1	2	275
	%	10.2	11.4	11.8	14.4	16.6	17.9	22.7	9.1	6.3	22.2	13.7
30–34	No. Preg.	104	195	207	204	141	115	79	62	35	54	1196
	No. Abort.	18	29	28	30	17	22	10	9	7	15	185
	%	17.3	14.9	13.5	14.7	12.1	19.1	12.7	14.5	20.0	27.8	15.5
35–39	No. Preg.	17	45	69	67	82	44	43	36	29	71	503
	No. Abort.	8	9	12	13	8	9	10	10	5	10	94
	%	47.1	20.0	17.4	19.4	9.8	20.5	23.3	27.8	17.2	14.1	18.7
40–44	No. Preg.		3	6	11	12	12	9	10	11	36	110
	No. Abort.		0	1	4	4	2	2	4	2	9	28
	%		0.0	16.7	36.4	33.3	16.7	22.2	40.0	18.2	25.0	25.5
Total	No. Preg.	1381	1422	1120	761	493	313	205	141	91	170	6097
	No. Abort.	178	197	146	116	69	59	38	26	15	36	897
	%	12.9	13.9	13.0	15.2	14.0	18.8	18.5	18.4	16.5	21.2	14.7

TABLE 7. RELATION OF ABORTION FREQUENCY TO MATERNAL AND PATERNAL AGE AT CONCEPTION

Maternal age		Paternal age							
		< 20	20–24	25–29	30–34	35–39	40–44	44+	Total
< 20	No. Preg.	90	272	113	31	9	9	1	525
	No. Abort.	11	27	16	7	1	1	1	64
	%	12.2	9.9	14.2	22.6	11.1	11.1	100.0	12.2
20–24	No. Preg.	24	653	726	265	69	13	10	1760
	No. Abort.	3	79	114	34	19	1	1	251
	%	12.5	12.1	15.7	12.8	27.5	7.7	10.0	14.3
25–29	No. Preg.	3	104	887	734	208	53	14	2003
	No. Abort.	0	15	139	88	25	7	1	275
	%	0.0	14.4	15.7	12.0	12.0	13.2	7.1	13.7
30–34	No. Preg.	—	9	144	519	388	107	29	1196
	No. Abort.	—	2	26	68	63	20	6	185
	%		22.2	18.1	13.1	16.2	18.7	20.7	15.5
35–39	No. Preg.	—	1	6	66	226	148	56	503
	No. Abort.	—	0	0	14	33	32	15	94
	%		0.0	0.0	21.2	14.6	21.6	26.8	18.7
40–44	No. Preg.	—	—	—	5	13	59	33	110
	No. Abort.	—	—	—	1	3	15	9	28
	%				20.0	23.1	25.4	27.3	25.5
Total	No. Preg.	117	1039	1876	1620	913	389	143	6097
	No. Abort.	14	123	295	212	144	76	33	897
	%	12.0	11.8	15.7	13.1	15.8	19.5	23.1	14.7

the standard errors, even when their actual size does not change appreciably (*e.g.*, when a non-significant interaction constant is estimated). Also, the goodness of fit to a linear model is only adequate at best. Some tentative conclusions can be drawn, however. None of the three factors involved can be eliminated as a contributor to the rise in abortion frequency. In particular, the birth order constant remains significant when the effect of its correlation with age of either parent is removed (lines 4 and 6, table 8). No interaction between parental age and birth order was demonstrable, although this type of interaction has been indicated for stillbirths (Neel and Schull, 1956) and birthweight (Millis, 1958) and has been suggested by data on abortions (Stevenson, Dudgeon and McClure, 1959). The relative effects of paternal and maternal age remain undecided by this analysis, although there is a rather strong suggestion that paternal age may be the more important of the two (line 8, table 8). The lack of a good fit whenever paternal age is involved complicates the picture, however, and there is also the possibility of some real interaction between the parental ages. For predictive purposes, linear regression of abortion frequency on maternal age seems the most informative procedure, and throughout the rest of this paper maternal age will be used as the index of the parental age–birth order factors.

Relation between maternal age and recurrence risk: The fact that older mothers are more likely to abort suggests the possibility that the increased risk of abortion after having an abortion may merely reflect the increasing maternal age at succeeding pregnancies. The following facts indicate that this

TABLE 8. REGRESSION ANALYSIS FOR ABORTION FREQUENCY (TRANSFORMED TO LOGITS) ON MATERNAL AGE, PATERNAL AGE, AND BIRTH ORDER

Constants estimated	G = general constant	MA = Maternal age constant	PA = Paternal age constant	BO = Birth order constant	Degrees of freedom	χ^2 for goodness of fit	P value for χ^2
1. G, MA	−1.1053 ± .05091	+.05805 ± .01553†			4	6.02	.10–.20
2. G, PA	−1.1070 ± .05515		+.05194 ± .01384†		5	13.59	.01–.02
3. G, BO	−0.9829 ± .03097			+.02690 ± .007002†	9	9.43	.30–.50
4. G, MA, BO	−1.0630 ± .05121	+.03755 ± .01877*		+.01747 ± .008458*	51	64.06	.10–.20
5. G, MA, BO, MA × BO	−1.0630 ± .08447	+.03753 ± .02549		+.01745 ± .02501	50	64.06	.05–.10
		(MA × BO) = .000005322 ± .005875					
6. G, PA, BO	−1.0980 ± .05506		+.04103 ± .01611*	+.01643 ± .008145*	66	86.32	.02–.05
7. G, PA, BO, PA × BO	−1.1060 ± .09209		+.04273 ± .02362	+.01884 ± .02575	65	86.21	.02–.05
		(PA × BO) = −.0005145 ± .005214					
8. G, MA, PA	−1.1200 ± .05793	+.02719 ± .02176	+.04017 ± .01944*		34	45.17	.05–.10
9. G, MA, PA, MA × PA	−0.9217 ± .1335	−.04388 ± .04848	−.01246 ± .03758		33	44.21	.05–.10
		(MA × PA) = +.01717 ± .01045					
10. G, MA, PA, BO	−1.1090 ± .05819	+.01459 ± .02309	+.03373 ± .01987	+.01462 ± .008634	255	301.19	.02–.05

*Regression constant more than two times its standard error.
†Regression constant more than three times its standard error.

is not so. If the maternal age effect alone were responsible for the increased recurrence risk after an abortion, the frequency of abortion at a particular maternal age should be the same whether or not there has been a previous abortion. Table 9 shows that women of a particular age who have had an abortion are more likely to abort again than women of the same age who have not previously aborted. Furthermore, while there appears to be an increase in abortion frequency with maternal age in mothers who have not aborted previously (χ^2 for heterogeneity of risk among maternal age groups gives $P < .05$), the recurrence risk seems merely to fluctuate randomly about 24 per cent for all maternal ages (χ^2 for heterogeneity gives $P > .60$) in mothers who have previously aborted.

It seems clear that the increased risk of aborting in women who have had an abortion cannot be explained by the increased maternal age at subsequent pregnancies. The increase in risk with maternal age which appears when all families are considered together is the result of (1) the increasing risk of having a *first* abortion at the late maternal ages (table 9) and (2) the increasing proportion of women pregnant at late maternal ages who have previously aborted. (In our data about 7 per cent of pregnancies at ages less than 20 occur in women who have previously aborted, while 43 per cent of pregnancies at ages greater than 40 occur in women who have aborted.)

Association of Abortion Risk with Other Parental Factors

Ethnic background: No significant differences between abortion frequency were found among families classified by "racial" origin of the father into four main ethnic groups: English-speaking with ancestry in the British Isles (chiefly Protestant), French-speaking (chiefly Roman Catholic), Jewish, and "Other" (chiefly continental European immigrant groups, with a very few Negroes and Orientals).

Presence of defective offspring: A possible source of bias in our data was the fact that many families were ascertained through a defective child. It might be that the same factors which caused the defect would cause abortion in other pregnancies of the same mother, particularly when the risk of recurrence of the defect does not correspond to a Mendelian ratio. This possibility was investigated by comparing the frequency of abortion in families ascertained through various types of abnormal children with the frequency in families ascertained through a normal child. The latter group consisted of families ascertained for another purpose (Metrakos and Metrakos, 1961) by random selection of admissions to The Montreal Children's Hospital. Children with congenital defects were removed from the group, leaving children who were admitted for fractures, tonsillectomies, appendectomies, pneumonias, *etc.*, conditions for which we are unable to see any possible association with a history of abortion in their mothers.

The families with abnormal children were separated into several categories, as shown in table 10. Families interviewed from 1952–1957 only were used, except for family histories taken after 1957 added to the original series to

TABLE 9. RISKS OF ABORTION AT A GIVEN AGE, WITH AND WITHOUT A HISTORY OF ABORTION

Maternal age	% of pregnancies aborting				Total
	No history of abortion		History of abortion		
< 20	(566)	11.7	(43)	20.9	12.3
20–24	(1842)	11.9	(76)	26.6	13.9
25–29	(1639)	12.0	(422)	24.2	14.5
30–34	(899)	13.6	(342)	22.5	16.0
35–39	(308)	17.9	(236)	20.8	19.1
40–44	(50)	18.0	(65)	29.2	24.3
Total	(5304)	12.6	(1394)	23.8	14.9

The number in brackets is the number of pregnancies used in calculating the risk.

give more data on rare conditions, or those which seemed to show interesting trends. The categories of families are not mutually exclusive, since some children with cleft palate also have epilepsy, some children with clear-cut genetic diseases are twins, *etc.* There is no overlap between the control group and the other families, however, so that χ^2 tests can be performed.

There are only two significant deviations from the abortion frequency in the families of random admissions. The high frequency in families containing a pair of monozygotic twins is significant only at the 5 per cent level; the low abortion frequency in families with cleft lip or palate is significantly different from the control families at the 2 per cent level. Of course, with such a large number of comparisons, a statistically significant difference may be expected occasionally on the basis of chance alone.

There is therefore no evidence that the abortion frequency in these families is seriously biased by ascertainment through an abnormal child. The frequency of abortion in the control families where there was no abnormal child is almost equal to the frequency calculated from the entire sample (14.2 per cent *vs.* 14.7 per cent).

Böök and Rayner (1950) and Coffey and Jessop (1958) have reported an increased frequency of abortion among the pregnancies of women who have had anencephalic children. Our original sample did not contain enough families with anencephalic children to investigate this question, and a group of obstetrical histories from Montreal maternity hospitals were obtained for the purpose. For every anencephalic born in the years when records were available, the next two hospital livebirths were used as a control, and the recorded frequency of spontaneous abortion in previous pregnancies was compared in the two groups of mothers. The results, shown at the bottom of table 10, confirm the results of other workers. The recorded abortion frequency in other pregnancies of women who have borne an anencephalic child is significantly higher than that of women who have never borne an anencephalic child.

Relation to menstrual irregularities in the mother: No significant difference was found between the abortion frequency of mothers with irregular and mothers with regular menstrual cycles. Cycles were considered irregular if

TABLE 10. ABORTION FREQUENCY IN FAMILIES CLASSIFIED BY DEFECT IN PROBAND

Condition for which proband was ascertained	No. of families	No. of pregnancies (minus proband)	Abortions No.	Abortions %
Random admissions	178	528	75	14.2
Cleft lip and/or cleft palate	248	812	79	9.7*
Clubfoot	75	225	40	15.3
Condition with clear pattern of inheritance[2]	101	298	35	11.7
Congenital heart disease	202	580	81	14.0
Epilepsy	290	870	137	15.7
Hemiplegia (± epilepsy)	98	308	59	19.2
Miscellaneous malformations[1]	86	232	41	17.7
Mental retardation (± epilepsy, excl. mongols)	24	83	12	14.5
Mongolism	79	238	41	17.2
Spina bifida and meningocele	92	278	41	14.7
Twinning (no congenital defect)	116	339	55	16.2
All families with at least one twin pair	293	947	158	16.7
Known MZ	43	124	28	22.5*
Known DZ	115	333	50	15.2
Over-all frequency	2134	6835	1003	14.7
Anencephaly (hospital data)	289	462	102	22.1
Control for anencephaly (hospital data)	477	625	87	13.0

[1]Malformations other than those listed individually, for which no clear-cut genetic basis is known, e.g., pyloric stenosis, hypospadias.

[2]Known to result from single gene difference, e.g., hemophilia, infantile amaurotic idiocy.

*Significantly different from control series ($P < .05$).

they varied in length by at least 14 days or if menstruation had ceased for more than one month during the child bearing period (without pregnancy).

Relation to a history of stillbirth: The over-all frequency of stillbirth in our 1952–57 sample is 54/3936 = 1.4 per cent of pregnancies (excluding the proband). Since this is comparable with many other estimates of stillbirth frequency (McDonald, 1958), it appears that the ascertainment of many families through a defective child has not increased the estimate of the frequency of stillbirth in siblings. In families with at least one abortion, the stillbirth frequency was 1.6 per cent, compared to 1.7 per cent in families with no abortions. Aborted pregnancies were omitted from these calculations, to make the two groups comparable. There is thus no evidence that stillbirths and abortions tend to be associated in families.

Consanguinity: In 75 families where the parents were first or second cousins, the abortion frequency of 43/290 = 14.8 per cent was not different from the over-all frequency of 14.7 per cent. In 45 families where it was recorded that the mother's parents were first or second cousins, 19/131 = 14.5 per cent of her pregnancies ended in abortion. In 33 families where it was recorded that her husband's parents were first or second cousins, 11/83 = 13.3 per cent of her pregnancies ended in abortion. Neither of these frequencies differs from the over-all abortion frequency.

Classification of Abortions by Period of Gestation

It is of interest to know whether women aborting several times tend to abort at about the same stage of gestation in each pregnancy. To investigate this question, women who had aborted were subdivided according to the month of pregnancy when their first abortion occurred, and for each group the average month of succeeding abortions was calculated (table 11). These data include histories collected from 1957 to 1960. There is a significant increase in the average month of subsequent abortions as the month of the first abortion increases. This suggests that the most probable stage for abortion varies from woman to woman, so that classifying them by the month of their first abortion will achieve some degree of etiological separation.

Further evidence for such a separation is presented in table 11. The frequency of premature births was much higher in women whose first abortion occurred in the sixth month than in women who aborted earlier (19.5 per cent *vs.* 5.0 per cent; χ^2 for heterogeneity among women classified by gestation time of abortion gives $P < .001$).

Recurrence risks were also calculated separately for women whose first abortion occurred at particular gestation times. The results, shown in table 12, are based on all histories from 1952 to 1962. For women whose first abortion is said to occur in the first month, the recurrence risk is not higher than the over-all risk of abortion in the population. This is interpreted to mean that the mother's report of an abortion in the first month is of such doubtful validity that a group of women who claim to have experienced such an abortion are equivalent to a random sample of women whose abortion history is not known at all. It is also possible that pregnancies which abort very early in gestation do so for non-recurrent reasons.

There does not appear to be any real difference in recurrence risks after one abortion among women aborting in different months. There is a suggestion of a greater elevation in risk after two abortions in women whose first abortion occurred in months 5 or 6, but the numbers involved are small and the differences are not statistically significant.

Comparisons of the maternal age distributions of abortions occurring at different gestation times did not reveal any striking differences.

DISCUSSION

Recurrence risks for abortion are useful for predicting the outcome of a given pregnancy; they and their associations with factors such as parental age may also provide clues to the etiology of abortion. While no attempt will be made here to discuss all the suggested causes of spontaneous abortion, some of the genetic implications will be examined.

Caution should be used in interpreting statistical trends in data dealing with a condition as heterogeneous as spontaneous abortion probably is. For example, a moderate relation of maternal age to risk may mean that (1) most causes of abortion are influenced by maternal age, (2) some very common causes of abortion are somewhat influenced by maternal age, or

TABLE 11. RELATION OF GESTATION PERIOD FOR SUBSEQUENT ABORTIONS, AND PREMATURITY RISK, TO MONTH OF FIRST ABORTION

Month of first abortion	No. of succeeding abortions	Avg. month of succeeding abortions	No. of other pregnancies (excl. abortions, incl. probands)	% of prematurity
1	8	2.5	105	1.9
2	85	2.7	640	5.9
3	98	3.0	900	3.9
4	23	3.2	252	8.7
5	10	3.7	107	3.7
6	21	3.9	149	19.5

TABLE 12. RECURRENCE RISKS RELATED TO MONTH OF FIRST ABORTION

	Risk after one abortion		Risk after two abortions	
Month of first abortion	No. of preg. after first abortion	% abortion	No. of preg. after second abortion	% abortion
1	67	10.4	12	0.0
2	384	26.0	132	29.5
3	504	20.8	121	27.3
4	124	21.0	20	15.0
5	82	23.2	21	47.6
6	140	25.7	47	34.0
Total	1301	22.5	353	28.6

(3) in some uncommon causes of abortion, maternal age is very important. Also, trends which are present in only a small proportion of cases may be obscured by the bulk of the data.

In our data, attempts to demonstrate heterogeneity of risk among women who abort were largely unsuccessful. There was no large increase in risk as the number of previous abortions increased (from 23.7 per cent after one previous abortion to 32.2 per cent after three previous abortions). Among women with at least one abortion the distribution of families with given numbers of abortions differed significantly from that expected from a binomial distribution with a constant risk of abortion, but there was an excess of families with only one abortion, rather than the excess of families with large numbers of abortions expected if there were a group of women with a much higher risk than the rest. Parental age or birth order (as measured by maternal age) did not appear to affect the risk after one abortion had occurred, although it seemed to affect the risk of having the *first* abortion. The lack of a demonstrable clustering tendency within sibships indicated that the abortion risk did not change with time or further pregnancies.

The possible exceptions to the lack of heterogeneity among women who have aborted at least once were women who aborted late in the second trimester, where it appeared that there might be a substantial increase in risk with the number of previous abortions. The incompetent internal os, which is believed by some obstetricians (Lash and Lash, 1950) to be an important cause of late abortions, might be one factor which produced a high recurrence risk.

In view of the *a priori* expectation that there are many causes of early abortions, the apparent lack of heterogeneity of risk is puzzling. However, it must be stated that these analyses would reveal only quite extreme kinds of heterogeneity.

Parental Age and Birth Order

The trends apparent in these data suggest that some circumstances which become more likely with increasing parental age and/or birth order can predispose a woman to abort and that once she has become so predisposed her risk of aborting a further pregnancy changes very little with time, further pregnancies, or further abortions. There would thus be two main risks to be taken into account, the risk of having a *first* abortion (which probably changes with parity) and the risk of aborting again, which is higher and almost constant. Given these risks, the expected distribution of families with given numbers of abortions within any family size can be calculated. Table 13 shows the expected numbers calculated using risks derived from the data. This new distribution tends to give higher expected numbers of families with one abortion than the simple binomial distribution and agrees very well with the observed distribution.

Such a scheme also provides at least a partial explanation for the low abortion rates in small families. Since the smaller the family the less likelihood that an abortion has occurred, there will be fewer mothers with a high abortion risk in small families, and the over-all risk will therefore be associated with family size.

A peculiar feature of the data, however, is that, although they do not fit a simple binomial distribution, the sib method, which utilizes pregnancies both before and after the first abortion, gives an estimate of the recurrence risk almost identical to that given by the method which utilizes only pregnancies *after* the first abortion. On the proposed scheme, one would expect that the sib method would give a somewhat lower estimate of the recurrence risk, as should Finney's method, which also assumes the binomial distribution.

Although it does appear from table 9 that there is an increased risk of having a first abortion at late maternal ages, it is clear that the effect of maternal age is not as great as might appear from examination of the over-all data. Even if maternal age had *no* effect on the abortion risk either with or without a previous abortion, there would still appear to be an association when all pregnancies were considered together, because the older a woman is at a given pregnancy, the more likely she is to have had at least one abortion and thus to have a higher risk of aborting. This makes the significance of the birth order–parental age effects previously analyzed on the over-all data rather questionable from a causal point of view. However, there does seem to be an association of maternal age (and probably paternal age and birth order) on the frequency of first abortions, which remains to be explained.

Penrose (1956) has suggested that a paternal age effect without a maternal age effect suggests copy-error mutations accumulated in the male germ cells, while the existence of both a maternal and a paternal age effect re-

TABLE 13. COMPARISON OF DISTRIBUTIONS

Family size excl. proband	No. of abortions per family	No. of families		
		$p_1 \times p_2$*	Binomial, constant risk $p = 0.25$	Observed
2	1	99.7	98.6	102
	2	15.3	16.4	13
3	1	118.2	113.8	126
	2	34.1	38.0	24
	3	3.6	4.2	6
4	1	75.9	71.0	72
	2	32.1	35.5	33
	3+	7.0	8.5	10
5	1	41.7	37.3	39
	2	22.5	24.9	22
	3+	7.9	9.8	11
6	1	25.7	22.1	26
	2	16.9	18.4	17
	3+	8.4	10.5	8
7	1	17.5	14.4	17
	2	13.5	14.4	10
	3+	8.9	11.2	13
8	1	10.7	8.3	14
	2	8.8	9.7	7
	3+	8.5	10.0	7

*p_1 (risk of first abortion) = 0.12 for parity 1 and 2; 0.13 for parity 3 and 4; 0.14 for parity 5, 6, and 7; 0.15 for parity 8 and 9.

p_2 (risk of subsequent abortion) = 0.25.

quires mutations due to "hits" by something such as radiation, where the time of exposure is the only important factor. However, if mutation in the gonads were an important cause of abortion, then a high recurrence risk would not be expected. A true birth order effect is most probably due to changes in maternal physiology due to pregnancy. Maternal age might have a similar direct effect upon the reproductive organs, but a true paternal age effect is extremely difficult to explain.

It is possible that the effect of parental age is due to an increase in chromosomal aberrations, rather than in genic mutations, with increasing age. Slizynski (1960) has suggested that in female germ cells, which remain in meiotic prophase from the birth of the female to ovulation, terminalization of chiasmata might increase with maternal age. This would not be true of male germ cells where prophase is of much shorter duration. Bodmer (1961) has evidence to support this view from studies in mice demonstrating a decrease in crossing-over with maternal age, presumably due to an increase in terminalization of chiasmata. Terminalization of chiasmata leads to reduced efficiency in pairing of the chromosomes, with subsequent increase in the frequency of nondisjunction. Thus older mothers might have an increased prob-

ability of producing gametes with abnormal chromosome complements and therefore of producing abnormal fetuses. To relate this idea to our data one could asume that terminalization occurs at different ages in different women, but that after it has been completed the probability of lethal chromosomal aberrations might be as high as 25 per cent. Chiasmata terminalization cannot, of course, provide an explanation for an increased production of chromosomal abnormalities with paternal age.

Maternal Fetal Immunization

Another possible explanation for the type of predisposition to abortion found in our data is an immunization of the mother to fetuses of certain genotypes. Birth order might act to increase the predisposition by increasing the possibility of sensitization by an incompatible fetus, and an independent effect of maternal age could similarly be interpreted as the result of physiological changes such as a less effective placental barrier. A paternal age effect would not be explicable on this basis. Once immunization had proceeded to the point where fetal death occurred, any subsequent pregnancy would have an abortion risk dependent upon the genotype of the fetus and the efficacy of the immune reaction in causing fetal death.

Chung and Morton (1961) have estimated on the basis of segregation studies that ABO incompatibility kills about 2 per cent of all zygotes in Caucasians. The evidence that any large part of this zygotic death occurs as recognizable abortions is rather inconclusive (see review by Levene and Rosenfield, 1961), at least for Caucasian populations, although Matsunaga and Itoh (1958) collected data in Japan which indicated that about 6 per cent more pregnancies aborted in ABO incompatible matings than in compatible matings.

Studies on recurrence risks and parity and parental age effects for abortions in families subdivided according to ABO mating type might help to clarify the problem. Unfortunately these data cannot be classified in this way. The only data available for this purpose seem to be those of Reed and Kelly (1958). Here the recurrence risk in ABO incompatible matings is 17/41 = 42 per cent after one abortion, and 11/19 = 58 per cent after two abortions; in ABO compatibile matings the risk is 19/61 = 31 per cent after one abortion, and 9/16 = 51 per cent after two abortions. While this suggests that the recurrence risk may be higher in incompatible matings, the numbers are too small to be very meaningful.

There are many other possible types of maternal-fetal incompatibility; there seems to be no reason to restrict such reactions to red cell antigens, since it has been shown that fetal trophoblast cells escape into the maternal blood stream (Douglas *et al.*, 1959), and antibodies to trophoblast cells have been detected (Hulka, Hsu and Beiser, 1961). The report by Gray, Turner, and Rowse (1958) that women who have recently aborted have an unusually high proportion of positive reactions to one of the tests for the RA factor suggests too that some sort of immune reaction may be involved. Immunization of the mother to fetal leukocytes has been demonstrated (Payne and

Rolfs, 1958) and single gene incompatibility systems also are known in mammals (Ashton, 1959; Hollander and Gowen, 1959).

Recessive Lethal Genes

The suggestion that, for early abortions at least, the recurrence risk may be constant and equal to about 25 per cent immediately brings to mind recessive lethal genes. However, there is no evidence that recessive lethals are important causes of spontaneous abortions. No significant increase in abortion frequency in consanguineous marriages has been found (Slatis, Reis and Haene, 1958; Böök and Rayner, 1950, and this paper); such an increase is expected if rare recessive lethals are commonly involved. However, if such genes were maintained in the population at a fairly high frequency because of heterozygote superiority, segregation advantage, *etc.*, then a consanguinity effect would not be expected.

One could not explain the relationship of parental age or birth order to risk of a first abortion if most abortions were due to recessive lethals. While accumulation of mutations could increase the number of matings heterozygous for the same lethal, gonadal mutations do not have a 25 per cent risk of recurring in the next pregnancy.

Spontaneous Abortions and Congenital Defects

In our data, no association was found between a wide variety of defects in her full-term children and a tendency towards abortion on the part of the mother; apparently the two types of mishap are not causally related. The only exceptions were women who had borne an anencephalic baby, where the abortion risk was high, and women who had borne a child with cleft lip or cleft palate, where the risk was low. The fact that women who abort in the sixth month tend also to have prematurely born but otherwise normal children suggests that in these women the failure of gestation timing is not related to any malformation of the fetus. It would be interesting in this connection to compare the frequency of abnormalities in fetuses aborted early with the frequency in those aborted late.

Maternal Genotype

The possibility that the maternal genotype may predispose a woman to abortion is an interesting one, with some analogous situations known in other animals. For example, the amount of prenatal death in mice has been shown to increase with the degree of maternal homozygosity, independently of fetal homozygosity (Falconer, 1960). The few data available suggest a significant but small correlation between the gestation times of viable pregnancies in the same woman (Karn *et al.*, 1950). One approach to the question would be to see whether women who are the product of a consanguineous marriage have more abortions than other women. In 45 families from our files where the maternal grandparents were first or second cousins, 19/131 = 14.5 per cent of pregnancies aborted. This is no different from the all-over frequency of abortion and suggests that homozygosity of the mother for rare recessives

is not an important cause of abortion. Another possible approach would be studies on the reproductive performance of sisters of women who have aborted, compared to a control population. This is currently being carried out in our laboratory.

Other Estimates of Recurrence Risks for Abortion

Our data do not include those women who have had *only* abortions, and our calculations are based on the assumption that such women are not more frequent than would be expected on the basis of the calculated recurrence risks. Many authorities classify women as "habitual aborters" if they have had three or more consecutive spontaneous abortions (regardless of gestation length), and it is assumed that they have a very high risk of aborting any subsequent pregnancies if not treated. If such a group of women whose chances of carrying a pregnancy to term are very small really does exist, then their omission from our data will cause an underestimate of the recurrence risks, which will be negligible for the over-all risk but may be of some importance for risks after several previous abortions.

To determine whether habitual aborters exist, one needs an estimate of the frequency of abortion in untreated pregnancies of women who have previously had three consecutive abortions. This is very difficult to obtain, and only one estimate, based on 19 habitual aborters who were used as a control for a study of the effectiveness of psychotherapy, is known to the authors (Tupper and Weil, 1962). In this group 13 out of 19 pregnancies aborted, giving a risk of 68 per cent with 1 per cent confidence limits, as calculated by James (1962), from 35 to 92 per cent. These women included some "secondary" habitual aborters, *i.e.*, women who had had at least one livebirth before their group of abortions. There are many estimates of the recurrence risks in women who have had at least three abortions but where it was unspecified whether these were consecutive or not. These will be discussed below.

The only other information on risks in habitual aborters comes from series which have been treated in a wide variety of ways, ranging from hormone and vitamin administration to psychotherapy. In almost all of these, the expected high frequency of abortions in subsequent pregnancies was "reduced" to between 20 and 40 per cent (King, 1953; Warburton and Fraser, 1961). This is exactly what one would expect if the treatments were in fact having little or no effect, but the risk of abortion in "habitual aborters" was the same as that calculated from our sample. The success of almost all therapies also has been used as evidence that it is personal contact with the doctor, *i.e.*, a form of psychotherapy, which is beneficial (Mann, 1956).

Another approach to the problem would be to compare the frequency of habitual aborters in the present sample with that expected on the basis of risks calculated from all women who abort. For example, according to our estimates, the probability of a first abortion is about .120 and the risk of aborting in subsequent pregnancies is about .250; of women with three pregnan-

cies .120 × .250 × .250 = .0075 or 0.75 per cent of women with three pregnancies should be classifiable as habitual aborters. Unfortunately, there is no good estimate available for the frequency of habitual aborters in the population, although the figure calculated above does agree with the general opinion of obstetricians that the condition is rare and with the few published estimates, such as that of Bishop (1937), 0.4 per cent, and Javert, Finn, and Stander (1949), 0.5 per cent.

The reports available for the empirical risk of abortion after three or more not necessarily consecutive abortions agree rather well with the estimate derived from our series, *e.g.*, 22 per cent (Tietze, Guttmacher and Rubin, 1950), 16 per cent (Rucker, 1952), 21 per cent (Erhardt and Jacobziner, 1956), and 19 per cent (Speert, 1954). James (1963) suggested that these estimates may be too low because they are based on pregnancies derived from hospital records or records of private obstetrical practice, and thus all received at least the psychotherapy of being under a doctor's care. Erhardt and Jacobziner's data were based on official notifications of births in New York City so that, although all abortions concerned were attended by a doctor, by no means would all pregnancies have received medical attention before they actually terminated. The women in our sample are no more likely to have been under a doctor's care before their pregnancy terminated than were the women in James's sample which is discussed below, since both were ascertained outside of obstetrical hospitals or practices. We do have information concerning prenatal care among the women in our sample; in general it is rather poor.

In our sample, one can divide the women with three previous abortions into those in whom abortions were consecutive and those in whom they were not; no significant difference in risk is found, and the non-consecutive cases actually have a slightly higher risk in subsequent pregnancies than do the consecutive cases. This is not conclusive evidence that the consecutiveness of the abortions makes no difference to the risk, however, since all the women in our sample must have been capable of having at least one liveborn child.

James (1963) has calculated, from data collected at the Kinsey Institute for Sex Research, the risk of abortion in the next pregnancy succeeding two consecutive abortions and has obtained a risk of 16/29 or 55 per cent. These data include women who have had only abortions. James concluded that the risk of abortion after *three* consecutive abortions must be at least as high as this.

Although the numbers in James's series are small, his risk does seem to be quite different from that calculated from our data. Several explanations for this are possible. The over-all abortion frequency in the group of women interviewed by the Kinsey group was high (21.5 per cent as reported by Tietze and Martin, 1957), compared to 14.7 per cent in our sample. In both samples, the risk approximately doubled after two abortions, although the absolute values are different. It is possible that the Kinsey workers were more successful in eliciting information about miscarriages, or used less

stringent criteria of abortion, or that the two populations studied really differ in abortion frequency. It seems unlikely that such a large difference in over-all risks or in risk after only two previous abortions could be due to the omission of primary habitual aborters from our sample, since they would represent only a very small proportion of the women involved. It would be interesting to know the risk after only *one* abortion in the Kinsey data, to see whether the general pattern of increase was the same as in ours.

In summary, the question of whether habitual aborters exist is still not settled, and until it is, conclusions from our data must be drawn with the understanding that they may not apply to women who have never had a full-term pregnancy.

SUMMARY

From data on the previous reproductive histories of women interviewed in a medical genetics unit the following conclusions can be drawn.

The over-all frequency of recognizable abortion in these women is about 15 per cent of all pregnancies.

A woman who has aborted several times tends to abort each time at about the same period of gestation. Those women who abort for the first time in the sixth month also have a high frequency of premature delivery.

A woman who has had only two or three pregnancies has a lower risk of aborting in a given pregnancy than a woman with a large number of pregnancies. This is not due to association with the degree of completeness of the family, maternal age, or the interval between successive pregnancies.

A woman who has had one abortion has a 25 to 30 per cent risk of aborting in each successive pregnancy. For women who abort early in gestation this risk increases only slightly, if at all, after she has had two, three, or four abortions. There is some indication that the risk may increase with the number of previous abortions for women who abort in the fifth or sixth month.

A woman who has never aborted has an increasing risk of aborting for the first time as she grows older. Once she has aborted there is no further increase in her risk with increasing age. It is not clear whether the increase in risk of the first abortion is dependent upon maternal age, paternal age, or birth order, or on all three.

The risk of abortion is not influenced by the proximity of a given pregnancy to a previous abortion.

There was no association between a woman's abortion risk and the presence of a wide variety of defects in her liveborn children, with the exception of mothers of anencephalic babies, where there is an increase in the frequency of abortion, and mothers of babies with a cleft lip or palate, where there is a decrease in the frequency of abortion.

Consanguinity in parents or grandparents, racial origin, and menstrual irregularities in the mother all had no effect upon abortion risk.

Thus the risk that a given pregnancy will abort may vary from woman to woman and from year to year in the same woman. No simple genetic hypothesis could be constructed to account for the relationships observed.

REFERENCES

ASHTON, G. C. 1959. β-Globulin polymorphism and early foetal mortality in cattle. *Nature* (Lond.) 183: 404-405.

BISHOP, P. M. F. 1937. Studies on clinical endocrinology. II. "Habitual abortion," its incidence and treatment with progesterone or vitamin E. *Guy's Hosp. Rep.* 87: 362-371.

BODMER, W. F. 1961. Effects of maternal age on the incidence of congenital abnormalities in mouse and man. *Nature* (Lond.) 190: 1134-1135.

BÖÖK, J. A. 1957. Genetical investigations in a North Swedish population: The offspring of first-cousin marriages. *Ann. Hum. Genet.* 21: 191-221.

BÖÖK, J. A., AND RAYNER, S. 1950. A clinical and genetical study of anencephaly. *Amer. J. Hum. Genet.* 2: 61-84.

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

COFFEY, V. P., AND JESSOP, W. J. E. 1958. A three year study of anencephaly in Dublin. *Irish J. Med. Sci.* 393: 391-413.

DOUGLAS, G. W., THOMAS, L., CARR, M., CULLEN, N. M., AND MORRIS, R. 1959. Trophoblast in the circulating blood during pregnancy. *Amer. J. Obstet. Gynec.* 78: 960-973.

EASTMAN, N. J. 1956. *Williams' Obstetrics,* 11th ed., Chapter 21. New York: Appleton-Century-Crofts.

ERHARDT, C. L., AND JACOBZINER, H. 1956. Ectopic pregnancies and spontaneous abortions in New York City. Incidence and characteristics. *Amer. J. Public Health* 46: 828-835.

FALCONER, D. S. 1960. The genetics of litter size in mice. *J. Cell. Comp. Physiol.* 56: 153–167.

FINNEY, D. J. 1952. *Statistical Method in Biological Assay.* New York: Hafner, pp. 458-467.

GRAY, J. D., TURNER, C., AND ROWSE, J. A. 1958. The problem of spontaneous abortion. II. The genesis of spontaneous abortion. *Amer. J. Obstet. Gynec.* 75: 43-52.

HOGBEN, L. 1931. *Genetic Principles in Medicine and Social Sciences* London: Williams and Norgate.

HOLLANDER, W. F., AND GOWEN, J. W. 1959. A single-gene antagonism between mother and fetus in the mouse. *Proc. Soc. Exp. Biol. Med.* 101: 425-428.

HULKA, J. F., HSU, K. C., AND BEISER, S. M. 1961. Antibodies to trophoblasts during the post-partum period. *Nature* (Lond.) 191: 510-511.

JAMES, W. H. 1961. On the possibility of segregation in the propensity to spontaneous abortion in the human female. *Ann. Hum. Genet.* 25: 207-213.

JAMES, W. H. 1962. On the probability that an untreated habitual aborter will abort a current pregnancy. *J. Obstet. Gynaec. Brit. Comm.* 69: 606–607.

JAMES, W. H. 1963. The problem of spontaneous abortion. X. The efficacy of psychotherapy. *Amer. J. Obstet. Gynec.* 85: 38-40.

JAVERT, C. T., FINN, W. F., AND STANDER, H. J. 1949. Primary and secondary spontaneous habitual abortion. *Amer. J. Obstet. Gynec.* 57: 878–889.

KARN, M. N., LANG-BROWN, H., MACKENZIE, H., AND PENROSE, L. S. 1950. Birth weight, gestation time and survival in sibs. *Ann. Hum. Gynet.* 15: 306–322.

KING, A. G. 1953. Threatened and repeated abortion. *Obstet. Gynec.* (N. Y.) 1: 104-114.

LASH, A. F., AND LASH, S. R. 1950. Habitual abortion: the incompetent internal os of the cervix. *Amer. J. Obstet. Gynec.* 59: 68-76.

LEVENE, H., AND ROSENFIELD, R. E. 1961. ABO incompatibility. *Progr. Med. Genet.* 1: 120-157.

MALPAS, P. 1938. A study of abortion sequences. *J. Obstet. Genaec. Brit. Emp.* 45: 932-949.

MANN, E. C. 1956. Psychiatric investigation of habitual abortion. *Obstet. Gynec.* (N. Y.) 7: 589-601.

MATSUNAGA, E., AND ITOH, S. 1958. Blood groups and fertility in a Japanese population,

with special reference to intra-uterine selection due to maternal-foetal incompatibility. *Ann. Hum. Genet.* 22: 111-131.

McDONALD, A. D. 1958. Maternal health and congenital defect. A prospective investigation. *New Eng. J. Med.* 258: 767-773.

METRAKOS, J. D., AND METRAKOS, K. 1961. Genetics of convulsive disorders. II. Genetic and electroencephalographic studies in centrencephalic epilepsy. *Neurology* (Minneap.) 11: 474-483.

MILLIS, J. 1958. The influence of maternal age and birth order on the outcome of pregnancy in poor Chinese women. *Ann. Hum. Genet.* 22: 362-369.

MORTON, N. E. 1959. Genetic tests under incomplete ascertainment. *Amer. J. Hum. Genet.* 11: 1-16.

NEEL, J. V., AND SCHULL, W. J. 1956. *The Effect of Exposure to the Atomic Bomb on Pregnancy Termination in Hiroshima and Nagasaki.* Washington: Publ. 461, Nat. Acad. Sci.

PAYNE, R., AND ROLFS, M. R. 1958. Fetomaternal leukocyte incompatibility. *J. Clin. Invest.* 37: 1756-1763.

PENROSE, L. S. 1956. Mutation in man. *Acta Genet.* (Basel) 6: 169-182.

REED, T. E., AND KELLY, E. L. 1958. The completed reproductive performances of 161 couples selected before marriage and classified by ABO blood group. *Ann. Hum. Genet.* 22: 165-181.

RUCKER, M. P. 1952. Spontaneous abortions: Too many or too few? *J. Internat. Coll. Surg.* 17: 328-332.

SLATIS, H. M., REIS, R. H., AND HAENE, R. E. 1958. Consanguineous marriages in the Chicago region. *Amer. J. Hum. Genet.* 10: 446-464.

SLIZYNSKI, B. M. 1960. Sexual dimorphism in mouse gametogenesis. *Genet. Res.* (Camb.) 1: 477-486.

SPEERT, H. 1954. Pregnancy prognosis following repeated abortion. *Amer. J. Obstet. Gynec.* 68: 665.

STEINBERG, A. G. 1959. Methodology in human genetics. *J. Med. Educ.* 34: 315-334.

STEVENSON, A. C., DUDGEON, M. Y., AND MCCLURE, H. I. 1959. Observations on the results of pregnancies in women resident in Belfast. II. Abortions, hydatidiform moles and ectopic pregnancies. *Ann. Hum. Genet.* 23: 395-414.

TIETZE, C., GUTTMACHER, A. F., AND RUBIN, S. 1950. Unintentional abortion in 1,497 planned pregnancies. *J. Amer. Med. Assoc.* 142: 1348-1350.

TIETZE, C., AND MARTIN, C. E. 1957. Foetal deaths, spontaneous and induced, in the urban white population of the United States. *Population Studies* 11: 170-176.

TUPPER, C., AND WEIL, R. J. 1962. The problem of spontaneous abortion. IX. The treatment of habitual aborters by psychotherapy. *Amer. J. Obstet. Gynec.* 83: 421-424.

WARBURTON, D., AND FRASER, F. C. 1961. On the probability that a woman who has had a spontaneous abortion will abort in subsequent pregnancies. *J. Obstet. Gynaec. Brit. Comm.* 68: 784-787.

WHITEHOUSE, F. 1929. Discussion on the causes of early abortion and sterility. *Proc. Roy. Soc. Med.* 23: 241-250.

ADDENDUM

Since this paper was submitted for publication, an article by W. H. James has appeared (Notes toward an epidemiology of spontaneous abortion. *Amer. J. Hum. Genet.* 15: 223-240.), which raises several points relevant to the present paper.

First, contrary to James's statement, we do not question the idea that women differ in their propensity to abortion. The increase in risk after at least one previous abortion is indisputable. However, our results do not support his claim that the abortion probability remains constant within a given woman, or that women with three previous abortions have a much higher risk of aborting than do women with only one or two previous abortions. Further data are needed to resolve these discrepancies.

The effect of family limitation, or lack of it, on the distribution of families with given numbers of abortions had been overlooked by us, and we agree with James that it probably invalidates our attempts to fit theoretical distributions to our family data.

We noted, as James did, the relationship between family size and abortion frequency and its probable explanation as a compensation phenomenon. We also agreed in pointing out that at least a part of the parental age–birth order effect is a statistical artifact, due to the large proportion of women pregnant at late ages who have previously aborted and have a relatively high risk of aborting again (see table 9). James believes this is merely the result of the tendency of women with abortions to undertake more and later pregnancies than they otherwise would. This seems credible to us, although the interpretation given in our paper is also valid.

The data in our table 9 show that, at least in our sample, the maternal age effect is not all artifact. There is a significant regression of abortion frequency on maternal age in the pregnancies of women who had never previously had an abortion. The women in this group who were pregnant at late maternal ages were not compensating for aborted pregnancies, yet they had a higher risk of abortion at late ages than at early ages.