even within this class, there exist several subclasses of possibly differing etiology). Table 2 gives the appropriate estimates. The *A* values are half those given in ALH's table 1 (since ALH's values were obtained by doubling the estimates for trisomy 21), the *B* values are unchanged, and the *C* values are taken directly from Hassold et al. Even without formal statistical tests, it is apparent that there is no evidence of a significant trend in the probability of spontaneous abortion with increasing maternal age. (Note also that several of these estimates are based on very small numbers of abortions and are, consequently, subject to a substantial negative statistical bias; this probably explains the low figure at maternal age $<$ 20, and could also affect the estimates at 25–29, 35–39, and $\geq$ 40.)

For XXX, XXY, trisomy 13, and trisomy 18, no estimates are possible without making the same assumptions as ALH, while for XXX and XXY, additional assumptions are needed since no data relating to their frequencies among spontaneous abortions were given by Hassold et al.

In short, the conclusions drawn by ALH can be largely, if not entirely, attributed to a spurious arithmetical artifact arising from the pooling of heterogeneous classes of data. When analysis is confined to trisomy 21, the evidence for a maternal-age-related trend in the embryonic selection rate is greatly diminished and ceases to be statistically significant.

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REFERENCES

1. AYMÉ S, LIPPMAN-HAND A: Maternal-age effect in aneuploidy: Does altered embryonic selection play a role? *Am J Hum Genet* 34:558–565, 1982
2. LENZ WV, NOWAKOWSKI H, PRADER A, SCHIRREN C: Die Äetiologie des Klinefelter-Syndroms. Ein Beitrag zur Chromosomenpathologie beim Menschen. *Schweiz Med Wochenschr* 89:727–731, 1959
3. HAMERTON JL: *Human Cytogenetics. Clinical Cytogenetics*, vol II. New York and London, Academic Press, 1971
4. HAMERTON JL, CANNING N, RAY M, SMITH S: A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. *Clin Genet* 8:223–243, 1975
5. CAROTHERS AD, COLLYER S, DE MEY R, FRACKIEWICZ A: Parental age and birth order in the aetiology of some sex chromosome aneuploidies. *Ann Hum Genet* 41:277–288, 1978
6. HASSOLD T, JACOBS P, KLINE J, STEIN Z, WARBURTON D: Effect of maternal age on autosomal trisomies. *Ann Hum Genet* 44:29–36, 1980

IN UTERO SELECTION AGAINST FETUSES WITH TRISOMY

To the Editor: In their article in the July 1982 issue of this journal, Aymé and Lippman-Hand [1] attempted to estimate the age-specific rates of in utero selection against fetuses with trisomy (r_a). They conclude that the increasing risk with maternal age for trisomy among live births may be due, at least in part, to a decreasing probability of aborting trisomic conceptions with increasing age. Al-

TABLE 1

FREQUENCY OF TRISOMY 21 AND ALL TRISOMIES AMONG SPONTANEOUS ABORTIONS OF 4–28 WKS GESTATION

	NEW YORK SERIES					HAWAII SERIES*			TOTAL		
MATERNAL AGE	No. spontaneous abortions	No. trisomy 21	%(SE)	NO. ALL TRISOMIES	%(SE)	No. spontaneous abortions	No. trisomy 21	%(SE)	No. spontaneous abortions	No. trisomy 21	%(SE)
< 20	197	1	0.51(0.50)	21	10.7(2.20)	102	0	...	299	1	0.33(0.33)
20–24 ...	406	1	0.25(0.25)	48	11.8(1.60)	221	7	3.17(1.18)	627	8	1.28(0.45)
25–29 ...	416	3	0.72(0.41)	78	18.8(1.92)	280	5	1.72(0.78)	706	8	1.13(0.40)
30–34 ...	341	8	2.35(0.82)	79	23.2(2.29)	240	9	3.75(1.23)	581	17	2.93(0.60)
35–39 ...	194	5	2.58(1.14)	67	34.4(3.41)	120	3	2.50(1.43)	314	8	2.55(0.89)
40+	66	5	7.58(3.26)	24	36.4(5.92)	26	2	7.69(5.23)	92	7	7.61(2.76)

*From [4] and T. Hassold et al., personal communication, 1983 concerning maternal ages of chromosomally normal abortions

though the model that we proposed in 1975 provides a simple method for estimating the probability of abortion for trisomic conceptions, the calculations presented by Aymé and Lippman-Hand do not provide convincing evidence for a decrease in the probability of in utero selection against trisomy with maternal age.

Because of the sparsity of data on single trisomies among abortions, Aymé and Lippman-Hand estimated r_a in 5-year maternal-age groups for all trisomies considered together, rather than for only those trisomies compatible with survival to term. In taking this approach, they are assuming, as they point out, that the probability of abortion is similar for all trisomies, and that the relation with maternal age is similar for all trisomies. Neither of these assumptions is true. With regard to the first assumption, for most autosomal trisomies, r_a is essentially 100%; for sex-chromosome trisomies, r_a may not be raised over that for chromosomally normal abortions; for the few trisomies that are compatible with survival to term, r_a is less than 100%, and it is this probability that is of interest. The second assumption is also known to be false; for example, the increasing risk of trisomy 16 among abortions with maternal age is less steep than that for trisomy 21 [2] and Hook et al. [3] recently demonstrated that trisomy 13 and trisomy X live births also have a less marked increase in rates with maternal age than trisomy 21 live births.

Since the real interest is in selection against fetuses with trisomy 21, it would be much more satisfactory to estimate r_a for this trisomy alone. Age-specific rates of trisomy 21 in spontaneous abortions are now available from two large series, that of Hassold et al. from Hawaii [4] and our series from New York City ([5] and our unpublished data, 1983). Table 1 presents data from these studies for 5-year maternal-age groups. For the New York series, the frequency of all trisomies combined is also shown. Maternal-age specific rates for trisomy 21 among live births are consistent across a wide variety of settings, and we can use the same estimates for this parameter as did Aymé and Lippman-Hand.

TABLE 2

FREQUENCY OF SPONTANEOUS ABORTION BEFORE 28 WKS GESTATION

MATERNAL AGE	A-LH AVERAGE FROM RETROSPECTIVE STUDIES*	NEW YORK CITY		
	% SPONTANEOUS ABORTIONS	No.	% spontaneous abortions	SE
> 20	10.1	1,428	9.9	0.8
20–24	12.1	3,086	10.7	0.6
25–29	14.1	4,069	9.2	0.2
30–34	15.1	2,669	11.2	0.6
35–39	17.3	1,064	16.3	1.1
40+	24.4	285	34.0	2.8

*These values differ slightly from those presented by Aymé and Lippman-Hand (A-LH), possibly due to differences in the no. significant figures used in calculating the pooled averages from the three studies. We included women aged greater than 45 years in the 40+ age group since the trisomy data include women in this age group; women of this age group appear to have been omitted from the pooled rates presented by Aymé and Lippman-Hand.

TABLE 3

ESTIMATES OF r_a FOR TRISOMY 21 USING DIFFERENT ESTIMATES OF THE FREQUENCY OF ABORTION AND THE FREQUENCY OF TRISOMY 21 AMONG ABORTIONS

Frequency of abortion estimated from ...	NYC*		A-LH*		A-LH	
Frequency of trisomy 21 in abortions estimated from ...	NYC		NYC		NYC + Hawaii	
	r_a	95% confidence limits†	r_a	95% confidence limits	r_a	95% confidence limits
Maternal age:						
< 20	.434	.098–.845	.440	.100–.847	.337	.066–.785
20–24	.300	.058–.750	.330	.066–.774	.716	.558–.834
25–29	.453	.211–.720	.573	.303–.806	.678	.513–.808
30–34	.698	.536–.823	.766	.621–.867	.803	.717–.867
35–39	.579	.363–.768	.596	.381–.779	.593	.422–.745
40+	.722	.519–.862	.619	.405–.796	.620	.436–.776

*NYC = New York City, data from table 1; A-LH = Aymé and Lippman-Hand.

†We thank Dr. Bruce Levin for calculating the confidence limits about r_a, using the ∂-method, and taking into account the standard errors about both the frequency of abortion and the frequency of trisomy among abortions.

†Data from table 1.

Estimation of the appropriate age-specific rates of spontaneous abortion is more difficult. Aymé and Lippman-Hand use three series of retrospectively collected reproductive histories to derive pooled estimates of abortion risks in 5-year maternal-age categories. They considered these to be "true" values, not estimates, because "they were based on large populations." However, the total number of pregnancies from all three studies in the crucial "maternal age of 40 or over" was actually only 386, with 95% confidence limits about the estimate of abortion frequency being .201–.287. It is not valid to ignore this variability when calculating confidence limits about r_a. Furthermore, these estimates are not derived from the same time period (all, for example, preceded legalized abortion), the same geographical region, or the same ascertainment source as those data used to estimate the frequency of trisomy among abortions. The latter derive from hospital-collected consecutive abortions, which may differ from those collected by maternal interview because gestation, maternal age, and social class may affect the likelihood that a woman seeks hospital care for spontaneous abortion. Table 2 compares the maternal-age specific rates of spontaneous abortion derived from the pooled retrospective data with cross-sectional rates at three New York City hospitals. The New York City rates were calculated by dividing the number of spontaneous abortions attended at the hospital by the total number of deliveries at the same hospital over all gestations (data in [6]). These estimates will provide an accurate description of the changing rate of abortion with age if women using the hospital for spontaneous abortions are drawn from the same population as those using it for full-term deliveries; we do not know if this assumption is true. The hospital-based rates appear to be more stable at lower maternal ages than those based on retrospective histories, although higher in the oldest age group.

Table 3 shows age-specific values of r_a for trisomy 21, using alternative estimates of the rates of spontaneous abortions, and the rates of trisomy 21 in abortions. In no case is there a consistent trend toward lower values of r_a with increasing maternal age. However, the confidence limits about these estimates of r_a are very

TABLE 4

ESTIMATES OF r_a FOR ALL TRISOMIES COMBINED USING DIFFERENT ESTIMATES OF THE FREQUENCY OF ABORTION

Frequency of abortion estimated from	NYC*		A-LH*	
Frequency of all trisomies in abortions estimated from	NYC		NYC	
	r_a	95% confidence limits	r_a	95% confidence limits
Maternal age:				
< 20	.890	.838–.926	.892	.845–.925
20–24	.910	.883–.931	.921	.899–.938
25–29	.915	.896–.931	.946	.934–.956
30–34	.920	.901–.935	.942	.929–.952
35–39	.901	.877–.922	.908	.887–.925
40+	.862	.807–.903	.796	.725–.853

*NYC = New York City; A-LH = Aymé and Lippman-Hand.

large when the standard errors of each of the estimated parameters is taken into account. Thus, we cannot rule out large differences among maternal-age groups.

For comparison with the data presented by Aymé and Lippman-Hand, table 4 shows the estimates of r_a for all trisomies combined, using updated estimates of the rates of trisomy among spontaneous abortions (table 1, New York City), and the two alternative estimates of the frequency of abortion. As Aymé and Lippman-Hand found, there is a statistically significant decrease in r_a for maternal ages 35–39 and 40+ when abortion rates derive from retrospective histories. This effect is less marked and no longer statistically significant when the cross-sectional hospital data are used to estimate the frequency of spontaneous abortion. Given that r_a is sensitive to rather small changes in the rate of abortion, and that it is unclear which estimate, if either, is the most appropriate, it seems premature to try to estimate r_a from the data at hand. Any decrease in r_a with maternal age when all trisomies were combined would also be difficult to interpret in the absence of a demonstrable similar effect for trisomy 21 alone.

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REFERENCES

1. AYMÉ S, LIPPMAN-HAND A: Maternal-age effect in aneuploidy: Does altered embryonic selection play a role? *Am J Hum Genet* 34:558–565, 1982
2. HASSOLD T, JACOBS PJ, STEIN Z, WARBURTON, D: Effect of maternal age on autosomal trisomies. *Ann Hum Genet* 44:29–36, 1980
3. HOOK EB, CROSS PK, SCHREINMACHERS D: Rates of cytogenetic abnormalities in older women at mid trimester amniocentesis and in livebirths. *J Am Med Assoc*. In press, 1983
4. HASSOLD T, CHEN N, FUNKHOUSER J, ET AL.: A cytogenetic survey of 1000 spontaneous abortions. *Ann Hum Genet* 44:151–178, 1980
5. WARBURTON D, STEIN Z, KLINE J, SUSSER M: Chromosome abnormalities in spontaneous abortion: data from the New York City Study, in *Human Embryonic and Fetal Death*, edited by PORTER IA, HOOK EB, New York, Academic Press, 1980, p 261
6. STEIN Z, KLINE J, SUSSER E, SHROUT P, WARBURTON D, SUSSER M: Maternal age and spontaneous abortion, in ibid., p 107

MATERNAL AGE AND ALTERED EMBRYONIC SELECTION: A REPLY TO CAROTHERS AND TO WARBURTON, STEIN, AND KLINE

To the Editor: We are grateful to our colleagues for providing us with an opportunity to elaborate on our original report [1]. It appears that Carothers' [2] major concern is the extent to which statistical artifact could explain our results, and his table 1 does illustrate one way in which a spurious association between selection and maternal age could arise. However, even though the numbers "are not intended to be entirely realistic," the situation Carothers hypothesizes appears substantially

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