RELATIVE FREQUENCIES AND SEX DISTRIBUTIONS OF HUMAN MULTIPLE BIRTHS

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Hellin (1895) published evidence indicating that the relative frequencies of multiple births conform to a simple mathematical relationship which may be expressed thus:

The frequency of triplet maternities is equal to the square of the frequency of twin maternities, and the frequency of quadruplet maternities is equal to its cube.

Stated in general terms, if f is the frequency of twin litters, the frequency of litters of size n is equal to f^{n-1} . This expression has since been tested many times. Although discrepancies between predicted and observed values have been noted (Strandskov, 1945), they appear not to have dispelled belief in the validity of the relationship which, it would appear, has now acquired the status of a "law".

EXAMINATION OF THE VALIDITY OF HELLIN'S LAW

(1) STATISTICAL.—There is, perhaps, little objection to the use of Hellin's law as a crude method of predicting the incidence of multiple births. But its acceptance leads to the inference that triplet production can be understood as the random operation of a second twinning process in a twin conception. In a similar way, quadruplets can be explained as arising from a triplet conception in which further twinning occurs. Representing the frequencies of dizygous and monozygous twin maternities respectively by a and b , we should predict from Hellin's law that the frequency of triplet maternities is $(a + b)^2$. The successive terms of this expression, a^2 , $2ab$, and b^2 , represent the frequencies of trizygous, dizygous, and monozygous triplets respectively. Hellin's law, therefore, leads us to conclude that trizygous triplets result from a repetition of the process of dizygous twinning, that dizygous triplets represent the simultaneous occurrence of dizygous and monozygous twinning, and that monozygous triplets arise from a repetition of the process of monozygous twinning.

This use of Hellin's law was exploited by Jenkins and Gwin (1940) in their analysis of the interrelations of the frequencies of plural births based on 25 million births which occurred in the United States Birth

Registration Area in the years 1923-24 and 1927-36. By plotting, for each maternal age group, the triplet frequency (y) against the square of the twin frequency (x), they obtained a straight line of equation

$$y = 0.656x + 0.00001318.$$

Substituting $(a + b)^2$ for x , this was written

$$y = 0.656a^2 + 0.656(2ab) + 0.656b^2 + 0.00001318.$$

Values for a and b were estimated by Weinberg's method from the sex distributions of twins at each maternal age group. Thus estimates of the trizygous triplet frequency ($0.656a^2$) and of the dizygous triplet frequency ($0.656 \times 2ab$) were obtained. Since the rate of monozygous twinning is only slightly dependent on maternal age, it was concluded that the constant term formed part of the monozygous triplet frequency, its total value being $0.656b^2 + 0.00001318$. (Jenkins and Gwin erroneously used $b^2 + 0.00001318$ in calculating the frequency of monozygous triplets.) The proportion of like-sexed triplet sets was derived from the relative proportions at each age group of trizygous, dizygous, and monozygous sets, assuming one quarter of the trizygous, one half of the dizygous, and all of the monozygous to be of like sex. The close agreement between observed (51.85) and predicted (51.74) values of the percentage of like-sexed sets was offered as confirmation of the accuracy of the equation. Jenkins and Gwin concluded that the occurrence of trizygous triplets may be understood as a double instance of dizygous twinning, and that of dizygous triplets as the simultaneous occurrence of dizygous and monozygous twinning, the coefficient 0.656 being interpreted as the *in utero* survival rate of trizygous and dizygous triplets as compared with dizygous twins. They considered the occurrence of monozygous triplets to be "a related but independent phenomenon governed by its own constant".

Applying the same method to births registered in England and Wales in the period July, 1938, to December, 1948, Waterhouse (1950) derived a monozygous triplet frequency equal to $0.596b^2 + 0.00000742$.

Substituting for b in this expression, he obtained a value for the monozygous triplet frequency in excess of b^2 . He concluded:

Such an outcome appears unlikely, for it would imply either that spontaneous division of a single fertilized ovum at some stage of its development into three resultant embryos occurs rather more frequently than probability dictates, or that monozygous triplet embryos are more viable not only than other types of triplets but than monozygous twins.

(a) *Observed Frequencies of Triplets and Quadruplets compared with Expected Frequencies derived from Hellin's Law.*—Since July 1, 1938, when the Population (Statistics) Act, 1938, came into operation, the Registrar-General for England and Wales has published in his Statistical Review (Pt. II, Civil) details of all registered live births and stillbirths. The data include maternal age, and the sexes of infants of multiple maternities. During the 11½-year period ending December 31, 1949, for which these data are now available, 8,224,585 maternities were registered; of these 99,971 resulted in twins, 842 in triplets, and 16 in quadruplets (Table I). Although

less extensive than the United States series used by Jenkins and Gwin, the statistics for England and Wales are more satisfactory, since they include all stillbirths (the United States series excluded multiple maternities in which all the foetuses were born dead) and they give the sex distribution of multiple births at each maternal age group.

Using these data firstly in a simple examination of the validity of Hellin's law (Table II, col. *a*), we may note that the observed and predicted values of the quadruplet frequencies are roughly similar, but that the observed triplet frequency is substantially below the predicted value. The discrepancy could be accounted for by assuming that *in utero* mortality of triplets is considerably in excess of that of twins. But the mortality of quadruplets might reasonably be expected to be at least as great as that of triplets, and we should not therefore be misusing Hellin's law if we estimated the maximum quadruplet frequency by multiplying the observed triplet frequency by the twin frequency. This estimate of the quadruplet frequency is 1·244 per million maternities which is substantially lower than the observed value of 1·945 per million.

TABLE I
NUMBERS OF TWIN, TRIPLET, AND QUADRUPLET MATERNITIES ACCORDING TO MATERNAL AGE
(ENGLAND AND WALES, JULY, 1938–DECEMBER, 1949)

Maternities	Maternal Age						Total Maternities of Known Age	Age not Stated	Total
	Under 20	20–	25–	30–	35–	40 and Over			
<i>Twin</i>									
MM	747	6,426	9,746	8,820	5,762	1,476	32,977	113	33,090
FF	717	6,000	9,257	8,228	5,482	1,448	31,132	128	31,260
MF	447	5,521	10,481	10,240	7,195	1,619	35,503	118	35,621
Total	1,911	17,947	29,484	27,288	18,439	4,543	99,612	359	99,971
<i>Triplet</i>									
MMM	4	23	59	56	43	7	192	2	194
FFF	1	42	49	55	42	10	199	—	199
MMF	2	29	48	53	48	14	194	1	195
MFF	2	30	66	87	62	6	253	1	254
Total	9	124	222	251	195	37	838	4	842
<i>Quadruplet</i>									
Like-sexed	—	1	4	1	—	—	6	—	6
Total	—	2	8	1	4	1	16	—	16
Total Maternities (Single and Multiple) ..	310,101	2,068,410	2,504,221	1,858,839	1,087,986	358,796	8,188,353	36,232	8,224,585

TABLE II
INCIDENCE OF MULTIPLE MATERNITIES

Maternities		England and Wales (1938–49)		Eighteen Countries (Greulich, 1930) (c)
		(a) All Maternal Ages	(b) Known Ages*	
<i>Twin</i>	Observed (x)	12·1551 per thousand	12·1651 per thousand	11·7687 per thousand
<i>Triplet</i>	Observed (y)	102·38 per million	102·34 per million	118·59 per million
	Predicted (x ²)	147·75 per million	156·96 per million	138·50 per million
<i>Quadruplet</i>	Observed	1·945 per million	1·954 per million	1·809 per million
	Predicted (x ³)	1·796 per million	2·127 per million	1·630 per million
	Predicted (xy)	1·244 per million	1·368 per million	1·396 per million
Total Maternities		8,224,585	8,188,353	59,143,098

* Predicted frequencies in column (b) are derived from the sum of the calculated number of multiple births at each maternal age group.

It was suggested by Jenkins (1927) that agreement between observed frequencies of multiple births and values predicted by Hellin's law is closer if the calculation is carried out separately for each maternal age group and the results then summed. In view of the variation of twin frequency with maternal age this modification is obviously desirable, but when applied to data for England and Wales, the inconsistencies revealed by the simpler treatment are not eliminated (Table II, col. *b*).

A similar examination of more extensive data collected by Greulich (1930) is also shown in Table II (col. *c*). Greulich's original series, derived from birth statistics of 21 countries, is marred by the fact that nearly half the series was derived from births which occurred in Italy in the years 1872-1925. Greulich showed that these births were not representative and suggested that the statistics for the period 1872-1911 may have been faulty. The Italian data have therefore been excluded. Data for Bulgaria and Poland have also been excluded since the number of quadruplets is not known. Results derived from this series are similar to those noted for England and Wales. For quadruplet maternities there is reasonable agreement between the observed frequency and that predicted by Hellin's law, but for triplet maternities the predicted frequency is greater than that observed. The product of the twin and triplet frequencies again gives a value for the quadruplet frequency considerably below the observed value. Since no details of maternal age are available for this series, Jenkin's modification cannot be applied.

The data for England and Wales have also been examined by the method of Jenkins and Gwin (1940). The results (Table III) compare at each maternal age group the observed proportion of like-sexed triplet sets with the values calculated by this method. That agreement is not close is obvious, but numbers are not large enough to justify the view that the discrepancies cannot be accounted for by chance.

TABLE III
PERCENTAGE OF TRIPLET MATERNITIES OF LIKE SEX
ACCORDING TO MATERNAL AGE
(ENGLAND AND WALES, 1938-1949)

Maternal Age		Under 20	20-	25-	30-	35-	40 and Over
Percent-ages	Observed	55.56	52.42	48.65	44.22	43.59	45.95
	Calculated by method of Jenkins and Gwin	71.62	57.78	48.08	43.03	40.13	46.62

(*b*) *Examination of the Proportion of Like-Sexed Litters in Quadruplet and Quintuplet Maternities.*—A further reason for doubting the implications of Hellin's law is provided by an examination of a series of 114 quadruplet maternities, assembled from the following sources:

- (i) 29 sets born in England and Wales in the period 1931-51, details of which have been published elsewhere (McKeown and Record, 1952).
- (ii) 26 sets collected from the literature (McKeown and Record, 1952).

- (iii) Eleven sets recorded in the literature. (The eleven references are listed separately at the end of this paper.)
- (iv) 48 sets which occurred in the United States in the period 1915-30 (Hamlett, 1935).

The sex distributions are shown in Table IV; 37.7 per cent. were like-sexed. By Hellin's law, we should expect the frequency of quadruplet maternities to be $(a + b)^3$. Assuming that males and females are conceived in equal numbers we should expect the proportion of like-sexed sets to be $\frac{(\frac{1}{2}a + b)^3}{(a + b)^3}$. By equating this expression with the observed value (0.377), we derive a value for *b* in terms of *a* which indicates that the proportion of twins which are monozygous is 44.5 per cent. This greatly exceeds any estimate so far recorded in Europe or the United States.

TABLE IV
SEX DISTRIBUTIONS OF QUADRUPLLET MATERNITIES

Sex	Source			Total
	England and Wales (1931-1951)	U.S.A. (1915-30) (Hamlett, 1935)	Literature*	
MMMM	4	13	3	20
MMMF	9	6	11	26
MMFF	7	12	6	25
MFFF	3	7	10	20
FFFF	6	10	7	23
Total ..	29	48	37	114

* See text for details.

In the same way, we can use data on the 45 quintuplet maternities assembled from the literature by MacArthur and Ford (1937). Of the forty sets of known sex, eight were entirely male and eight entirely female, the proportion of like-sexed sets therefore being 40 per cent. The expected proportion is $\frac{(\frac{1}{2}a + b)^4}{(a + b)^4}$. Equating this expression as before with the observed value (0.4), we obtain 59.1 per cent. for the proportion of monozygous twins.

The high incidence of like-sexed sets (quadruplets and quintuplets) could be accounted for if:

- (a) Most quadruplets and quintuplets were born to women at the extremes of the reproductive period. The data do not support this view.
- (b) Pre-natal mortality of litters of unlike sex were greater than that of litters of like sex.

No evidence on this point is available, but it is not easy to give any reasons for expecting a considerable differential mortality.

(2) BIOLOGICAL.—We now consider the biological implications of the use of Hellin's law. If the frequencies of dizygous and monozygous twin maternities are respectively *a* and *b*, the expected frequency of triplet maternities is $(a + b)^2$ and of quadruplet maternities $(a + b)^3$. Assuming that

there is no differential pre-natal loss, we may infer from expansion of these expressions that polyovulation, polyembryony, and a combination of the two processes occur with predictable frequencies.

(a) *Polyovulation*.—The above expressions imply that the frequencies of release of two, three, and four ova at one ovulation are respectively a , a^2 , and a^3 . From what is known concerning the endocrine control of follicle maturation, it seems unlikely that polyovulation is the chance phenomenon indicated by these terms. The problem is further complicated by occasional liberation of two or more ova from a single follicle (Arnold, 1912). On the scanty evidence at present available, it is concluded that no judgment on the frequency of human polyovulation is yet possible.

(b) *Polyembryony*.—Hellin's law implies that the frequency with which two, three, and four embryos may develop from a single zygote are respectively b , b^2 , and b^3 . Consideration of the biological justification for these relationships may be assisted by a brief review of contemporary opinion on the mechanism of polyembryony in mammals. Four methods are usually described:

(i) By cleavage of the developing ovum at the morula stage, each half giving rise to a separate embryo with its own chorion and amnion. Some idea of the frequency of this occurrence in man may be derived from the fact that a dichorial condition was found in three out of seven sets of identical twins by Curtius, and in five out of fourteen sets of identical twins by Lassen (cited by Newman, Freeman, and Holzinger, 1937). It is relevant to the present discussion to enquire whether a second cleavage of the morula, resulting in triplets, is possible. There seems to be no reason for rejecting this possibility on biological grounds, but until a series of sets of trichorionic identical triplets has been collected no opinion on the frequency of this phenomenon can be expressed.

(ii) By fission of the inner cell mass of the blastocyst to produce two blastodisks, resulting in monochorionic diamniotic twins. There is little evidence that this process occurs in man, and still less that it may be repeated to form monozygotic triplets.

(iii) By budding of the blastoderm. This process, demonstrated in *Tatusia novemcincta* (Patterson, 1913), is initiated by a thickening of the wall of the ectodermal vesicle at two points. Each of the two primary buds thus formed grows and gives rise to a pair of secondary buds. In the Texas armadillo, polyembryony ceases at this stage, so that four embryos (one from each bud) result. But in the South American armadillo it is presumed that each of the secondary buds gives rise to two tertiary buds, eight embryos thus resulting from a single egg. In these species polyembryony is not a simultaneous process, but occurs in consecutive stages. The embryos

at first share a common amniotic cavity, but subsequent proliferation of the amnion is extensive enough to invest each embryo, which therefore appears to be contained in its own amniotic sac. It is commonly believed that the origin of human monochorionic diamniotic monozygous twins can be explained in this way. It is presumed that in man the process usually ceases when two buds have been formed, but it is probable that, as in *Tatusia*, each bud has the capacity to originate a pair of secondary buds, thus leading to development of monozygous triplets and quadruplets. This suggests that the opportunity for further budding depends on the number of buds already present. It seems unlikely, therefore, that the terms b^2 , b^3 , etc., represent the frequencies of triplets, quadruplets, etc., derived by this process.

(iv) By longitudinal fission of the embryonic axis. This method has been advanced to account for situs inversus viscerum, conjoined twins, and other monoamniotic twins. In view of the rarity of these conditions in man, it need not be considered further in this context.

(c) *Polyovulation associated with Polyembryony*.—There appears to be no biological reason for supposing, even in normally monotocous animals, that polyovulation and polyembryony are mutually inhibitive. It is not unreasonable to assume, therefore, that if two ova are liberated, diembryony may occur in each with the same frequency, as it would in a single ovum. The expression $2ab$, derived from Hellin's law for the frequency of dizygous triplets, appears at first sight to be acceptable. But this underestimates the frequency, since it represents only that of diembryony in a dizygous twin conception. Obviously dizygous triplets may result also from the random association of a further ovulation (frequency a) with monozygous twins (frequency b), the frequency of this combination of events being ab . If, therefore, the twin frequency is $a + b$, the frequency of dizygous triplets may be expected to be $3ab$.

CONCLUSION

This examination of Hellin's law appears to justify three conclusions:

- (1) Predicted frequencies of multiple births do not approximate closely to observed values.
- (2) Development of the law to estimate the proportion of like-sexed litters gives results inconsistent with observed proportions.
- (3) There are biological grounds for doubting the implications of Hellin's law.

It may be considered that any attempt to derive a meaningful algebraic expression for the frequency relationships between litters of various sizes is unwise in the present rudimentary state of knowledge

of the mechanism of polyovulation and polyembryony. The temptation to obtain a reliable expression is great, since understanding of these phenomena would thereby be advanced considerably. But its formulation is hampered by lack of knowledge of the sex ratio at conception as well as of the relation between pre-natal mortality rates and the size and type of litter. These difficulties are encountered at the outset in derivation of monozygous and dizygous twinning rates by Weinberg's differential method. As a first step in modifying Hellin's law, therefore, attention may be directed most usefully to a critical examination of this method by comparing observed with predicted frequencies of monozygous and dizygous twin births. Physical methods of twin differentiation are now, perhaps, sufficiently advanced to permit this approach.

SUMMARY

According to Hellin's law, if the frequencies of monozygous and dizygous twins are represented by a and b respectively, the expected frequency of triplets will be $(a + b)^2$, of quadruplets $(a + b)^3$, and of litters of size n , $(a + b)^{n-1}$. Data for triplets and quadruplets born in England and Wales (1938-49) and for quadruplets and quintuplets collected from the literature are shown to be inconsistent with this hypothesis. Biological grounds are also advanced for doubting its validity.

It is suggested that in the present state of biological knowledge an accurate expression relating the frequencies of multiple births is not possible. Solution of the problem may be furthered by a reliable estimate of monozygous and dizygous twin frequencies based on the physical examination of a large series of twin births.

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