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Human Monozygotic and Plurizygotic Multiple Births: Heredity and Hormone Action

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I. Introduction

The twinning phenomenon is often explained in terms of *polyembryony* or of *polyovulation*. By the first term, reference is made to the case of identical twins, deriving from a single fertilized egg which produces two, or more, embryos. On the other hand, the second term refers to the case of nonidentical twins, deriving from two, or more, fertilized eggs.

Strictly speaking, the two terms, polyembryony and polyovulation, are not actually opposites, each of them referring to a different stage of the reproductive process. In fact, polyembryony concerns a stage *following* conception, whereas polyovulation concerns a stage *prior to* the conception of twins, which, however, does not necessarily take place whenever polyovulation occurs.

If we want to make an exact comparison to establish a clear-cut difference between the two types of twinning, we have to refer to their genetic equality or diversity; this depends from their deriving from one and the same zygote, or from two different zygotes. Therefore, rather than to polyembryony and polyovulation, we shall refer to monozygosity and dizygosity, as the criteria for a classification of twins.

Such a classification reflects the qualitative variability of human twinning. One should consider, however, that there also exists a quantitative variability, which expresses itself in the number of embryos (two, three, or more). Multiple births involving more than two embryos ("supertwins") exhibit various degrees of qualitative variability.

In the human species, multiple births are always an exception, though not very rare. The normal delivery consists in only one ("single-born") child.

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The phenomenon of the generation of twins is referred to as *twinning*, or *gemellogenesis*, while we adopt the term *gemellology* for that branch of biological sciences dealing with multiple births in general.

Concerning the derivation of identical twins from a single zygote, experience teaches us the usefulness of a terminology introduced by Gedda, in order to differentiate a twinning zygote from a usual zygote. Cleavage of the former produces two further zygotes, while cleavage of the latter produces the first two blastomeres of a new organism. Therefore, we shall use the term *protozygote* for the zygote responsible for monozygotic twinning, and the term *primary isozygote* for those deriving from the protozygote. If one, or both, primary isozygotes subdivide to form two, or four, further zygotes, these shall be called *secondary isozygotes*, and so forth.

II. Synthetic analysis of pertinent literature

The dawn of gemellology, i. e. the first scientific observations dealing with the inheritance of twinning, began with A. Bassi, the Italian naturalist who discovered the fungus causing lime disease in the silkworm. His observations, however, did not concern the human species, but sheep; they are so rigorous in their simplicity that they deserve being quoted:

" Nearly all my ewes producing two lambs in one delivery (they are generally not less than fifteen for every hundred) deliver well, on their own and without any assistance. For several years, the number of twins has been increasing progressively in my flock, due to the care I take in promoting the circumstances which, in my opinion, have an influence on twinning. By means of numbering the ewes, and by giving them only one ram at a time for mating, I have in several years ascertained that:

1. Twinning never or very rarely takes place with rams that are too young (i. e. aged about one year or one year and a half) even when they are mated with older ewes;

2. Ewes of the same approximate age, that is to say those lambing between twelve and twenty months, hardly ever have twins, even when mated with proven rams. Not one of the many ewes between about seven and fifteen months of age I mated for various experiments ever produced twins;

3. Proven ewes fertilized by likewise proven rams easily have twins;

4. To obtain the greatest possible number of twins, it is advisable to mate rams and ewes of medium age, of greater corpulence, of best constitution and being, above all, copiously fed;

5. Twins ewes of sound constitution and their daughters have twins more easily. At least, this is what I deduce from observations I have registered (A. Bassi: *Il Pastore ben istruito.* Milano, De Stefanis, 1812).

The special attention Bassi gave to twinning was, perhaps, stimulated by his being a twin himself.

Other observations concerning the inheritance of twinning are based on the study

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of families in which multiple births occurred with particular frequency (Curgenven, 1868; Masson, 1876; Coehlert, 1879; Grigg, 1890; Lauritzen, 1891; Mirabeau, 1894; Spyr, 1894; Wakley, 1895; Cory, 1895; Stoker, 1896; Jullien, 1897; Féré, 1898).

The rediscovery of Mendel's principles (1900) and the definite adoption of the term "Genetics" (1906) induced Weinberg in 1909 to re-elaborate the demographic twin material he had previously collected (1902) in Stuttgart and four Württemberg villages. Weinberg was therefore the first Author who attempted to apply the mendelian models to twinning.

Starting with Weinberg the publications concerning the genetics of twinning are numerous but not concordant. Roughly speaking, we could say that the solutions advanced by the various Authors are three.

First of all, there are those who deny the existence of an individual hereditary phenomenon, and maintain that the determining mechanism is due to environmental factors. One was Wilson, whose genealogical research (1930) concerned mothers of same-sexed twins, but was limited to their parents and grandparents. Another one was Lenz (1933), who maintained that twinning is one of the possible manifestations of the predisposition of the human species, and that all women may conceive and bear twins under the influence of environment.

According to a second group of Authors it is possible to speak of a hereditary phenomenon limited to one type of twinning, which most of them hold to be that of dizygotic (DZ) twins. Such was the opinion expressed by Weinberg who, in 1909, limited the phenomenon to maternal inheritance, while in 1927 he extended it to paternal inheritance as well. Ecker (1928) was of the same opinion. Others who advocated heredity in DZ twinning were Bonnevie (1919), Hofsten (1919) and Siemens (1923). On the other hand, Weitz (1924) considered only monozygotic (MZ) twinning to be hereditary.

A third group may be formed of those who hold that the entire phenomenon of twinning is controlled by heredity. Still, a number of Authors, such as Melmann (1910), Bumm (1912), Gall (1914), Brattström (1914), Peiper (1923) and Meyer (1932) admitted that such a heredity is only transmitted through the father. Danforth (1916) considered both types of twinning as hereditary, the inheritance being maternal in DZ, maternal and paternal in MZ cases. Davenport (1919, 1920, 1927) did not only think that twinning *in toto* depends on hereditary factors, but also that such factors are inherited both maternally and paternally in MZ as well as DZ twinning. On the basis of a study of zygotic combinations in supertwins, Yenkins (1927) concluded that the inheritance of twinning could be ascribed to one single factor. Greulich instead (1934), having noted that twinning was much more frequent in the families of DZ than MZ twins, concluded that the two types of twinning are independent as to their respective causal factors.

Dahlberg, who in 1926 was inclined to consider as hereditary only the tendency to DZ twinning, extended in 1930 the hereditary interpretation to the twinning phenomenon as a whole, with the statement: that researches carried out up to then upheld, to a certain extent, the assertion that not only DZ, but also MZ twin

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pregnancies are hereditary. He maintained that one can demonstrate that mothers with a tendency to DZ twinning also have a tendency to MZ twinning, and this should, in a certain manner, indicate that MZ twin pregnancies are also hereditary.

Wehefritz (1925) admitted the existence of a predisposing factor, inherited as a recessive, exhibiting a variability of expression under the influence of environmental factors. Fisher (1928) maintained that DZ twinning is less conditioned by heredity than MZ twinning, and that hereditary transmission from the paternal side occurs in the latter only.

The German school, with v. Verschuer (1927) and Curtius (1927) and later with v. Verschuer and Curtius (1931), also came to the following conclusions: (1) In brothers and sisters of parents of twins the predisposition to generate twins appears with equal frequency, while the frequency of twinning is somewhat increased only in sisters of mothers of opposite-sexed pairs; (2) In the brothers of fathers of twins the predisposition to generate twins appears just as frequently as in the brothers of mothers of twins; (3) The predisposition to generate twins appears to be similar in the brothers of parents of MZ and DZ twins; in the families of MZ twins it appears slightly more rarely; (4) Both types of twins are equally frequent in the families of MZ, same-sexed DZ and opposite-sexed DZ twins.

On the basis of accurate population studies, Yerushalmy and Sheerar (1940) maintained that differences in the frequencies of the twin phenomenon should be ascribed to hereditary racial factors.

Gedda (1951) compiled a detailed analysis of pertinent literature (which may be consulted for further information) implementing it with studies of his own school (Gedda and Capelli, Gedda and Cherubini). His findings indicated that the frequency of twinning in both paternal and maternal ascendancies of MZ as well as DZ twins appears to exceed significantly the corresponding frequencies observed in a random sample of families from Rome (77% and 23% respectively). It is Gedda's opinion that both mother and father may carry the trait responsible for both MZ and DZ twinning, the maternal contribution being more relevant. The finding that both MZ and DZ twinning may occur in the same families led Gedda to conclude for the singleness of the tendency to twinning, to be ascribed to a single " gemellogenetic factor " or " G factor ".

III. Studies on the heredity of the twinning phenomenon

a - ***Is the twinning phenomenon hereditary?***
b - ***If twinning is hereditary, what is its mode of inheritance?***

On the occasion of the tenth anniversary of the inauguration of the Mendel Institute in Rome, we have decided to make use of our increased twin material collected up to date, in order to re-examine the problems referring to the causes and the mechanism of twinning.

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Our material is collected in the twin register we call the Mendel Institute's " Gemelloteca ". The Gemelloteca represents the archives of the clinical histories and other documents of all the 7,218 twin pairs studied by the Institute.[1] The data concerning each pair are transferred onto punched cards and then analyzed by an IBM 444 machine.

The material, thus treated, was used for a research program intended to answer the following questions:

a) Is the twinning phenomenon hereditary?

b) If so, which would be its mode of inheritance?

To answer these questions we sifted the 7,218 records to find those referring to pairs presenting other twin cases in their ascendancies. This sifting excluded 3,841 pairs, for which precise information was lacking. Thus we limited our survey to 3,377 twin pairs with other twin pairs in the paternal branch of their family tree, or in the maternal branch, or in both, or even in an unspecified genealogical location.

For our research we did not take into consideration the case of other twin pairs existing among the sibs and descendants of our index cases. Moreover, in taking down data, we did not consider the *number* of twin pairs among the paternal or maternal branches, but only their *presence* or *absence*.

The twin cases selected from the Gemelloteca were thus distributed as follows:

a) with twinning in the paternal branch	656
b) with twinning in the maternal branch	1,036
c) with twinning in both the paternal and the maternal branches	324
d) without twinning in the family area	1,205
e) with twinning unspecified as to genealogical location	156
Total cases	3,377

In view of the structure of our research, we had to exclude the 156 twin pairs belonging to group *e*. In fact, we could not give these cases a positive value for mathematical analysis. Thus, the material on which we did base the present research program consists of 3,221 twin pairs distributed as shown in Tab. 1.

Tab. 1. Distribution of twinning in the parental branches

		Paternal branch		
		Yes	No	Total
Maternal branch	Yes	324	1036	1360
	No	656	1205	1861
	Total	980	2241	3221

This material was used to answer the two questions posed in this research program.

[1] At the date of publication (May 1965) the Gemelloteca includes 9,515 cases.

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a - *Is the twinning phenomenon hereditary?*

In this first research, only the existence of other twin cases in the family area (regardless of whether paternal or maternal) was taken into consideration. The problem was to establish whether the number of twin pairs with twinning in the family area found in the sample corresponds to the number of pairs we would have found if the distribution of twinning in a similar sample had taken place at random and according to the population frequencies. The theoretical distribution was calculated on the basis of the fact that the survey of the Gemelloteca concerning twinning included the sibships of the parents and the grandparents (6 sibships in all of each twin index case), and that the size of the average Italian sibship has been oscillating around 4 persons during the last 100 years.

Given that the Italian population shows a twinning frequency generally corresponding to .0125, it is possible to calculate the probability of random occurrence of one, or more, twin deliveries in a four-sibling sibship. Such a probability is $p = .0469$. Thus, the probability of random occurrence for one, or more, twin deliveries in a family area, equivalent to that of the pairs in our sample (i. e. in one, or more, of the six examined sibships), turns out to be the following:

Twinning in 1 sibship	$p = .2814$
Twinning in 2 sibships	$p = .0328$
Twinning in 3 sibships	$p = .0020$
Twinning in 4 sibships	$p = .0007$
Twinning in 5 or 6 sibships	$p = .0001$
Total probability	$p = .3170$

The calculation of total probability (i. e. .3170) when referred to the 2,016 pairs examined leads to the theoretical distribution given in Tab. 2, which shows that the pairs with twinning in the ascendancies should be 1,021. Therefore, 31.70% of the index pairs should have shown at least one twin delivery in the six sibships of the

Tab. 2. Theoretical and experimental distribution of twinning in the family area of the 3,221 index pairs

	Pairs with twinning in the family area	Pairs without twinning in the family area
Theoretical	1021	2200
Experimental	2016	1205

family area. In fact, the eperimental data prove the presence of nearly twice this number of pairs showing other cases of twinning in the family area. This actually takes place in 2,016 pairs, equal to 62.59% of the sample.

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Fig. 1 shows more clearly that the observed frequency of cases with twinning in the family area corresponds to about twice what we could have expected from a random distribution. Therefore the pairs are not distributed at random in the family

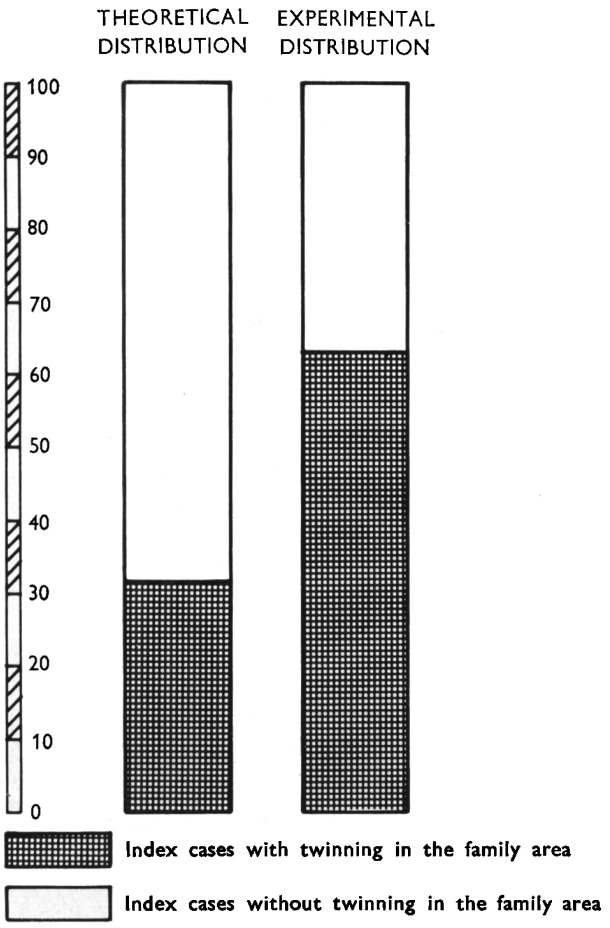

Fig. 1

area, but follow a causal factor which groups in the families of twin pairs a number of twin cases greater than expected.

This greater frequency tends to exclude that twinning depends only from external factors operating at random, thus indicating that the phenomenon is due to a cause inherent to the family biology, i. e. to a genetic factor. Therefore this first analysis enables us to conclude that twinning is a familial trait, which fits the hypothesis of genetic control.

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b - *If twinning is hereditary, what is its mode of inheritance?*

The same data from the Gemelloteca were analyzed in order to discriminate parental contributions to the heredity of twinning. For this purpose, information was used which referred to the location of other twin pairs in the family area of each index pair, i. e. whether they belonged to the paternal or the maternal branches, or both. In order to verify the hypothesis of equal probability of the occurrence of twinning in both parental branches, we have calculated a theoretical distribution to be compared with the experimental one (Tab. 1) by means of the χ^2 test. In the following table (Tab. 3) p indicates the frequency of pairs with twin deliveries in either

Tab. 3. Theoretical distribution of index cases in the hypothesis of equal probability of twin deliveries in either parental branch

		Paternal branch		
		Yes	No	Total
Maternal branch	Yes	p^2	pq	$p(p + q)$
	No	pq	q^2	$q(p + q)$
	Total	$p(p + q)$	$q(p + q)$	$(p + q)^2$

branch of the family, while q indicates the frequency of pairs without twinning in the parental branches.

On the basis of the values of $(p + q)^2$ and p^2, the former corresponding to the total 3,221 considered cases and the latter to the observed frequency of pairs with twinning in both parental branches (324), we calculated the values of p and q as follows:

$$p = \sqrt{p^2} = \sqrt{324} = 18.00$$

$$q = \sqrt{(p + q)^2} - \sqrt{p^2} = \sqrt{3221} - \sqrt{324} = 56.75 - 18.00 = 38.75$$

from which we have calculated all the values of the theoretical distribution as shown in Tab. 4.

Tab. 4. Expected frequencies in our sample according to the distribution in Tab. 3

		Paternal branch		
		Yes	No	Total
Maternal branch	Yes	324	698	1022
	No	698	1501	2199
	Total	1022	2199	3221

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The comparison between the experimental and theoretical distributions by means of the χ^2 test yields the values shown in Tab. 5.

Such comparison reveals a considerable excess in the observed number of pairs with twinning in the maternal branch and, on the other hand, no excess in the

Tab. 5. Comparison of the experimental and theoretical distributions of twinning in the parental branches

		Paternal branch			
		Yes		No	
Maternal branch	Yes	Experimental	Theoretical	Experimental	Theoretical
		324	324	1036	698
		$\chi^2 = 0.000$		$\chi^2 = 125.524$	
	No	Experimental	Theoretical	Experimental	Theoretical
		656	698	1205	1501
		$\chi^2 = 2.527$		$\chi^2 = 76.112$	

$\chi^2 = 204.163$ with one D. F., $p < .001$

observed number of pairs with twinning in the paternal branch. This indicates that the highest frequency of twinning concerns only the maternal branch, while the cases found in the paternal branch correspond to those expected in an unselected sample in proportion to the population frequency of the phenomenon.

Fig. 2 clearly shows the relevant positive difference between the observed and the expected frequencies, as revealed by our research in the case of pairs with twinning in the maternal branch.

These results serve to clarify the genetic significance of the phenomenon. In fact, on the basis of our results, we may state that the higher concentration of the phenomenon in the maternal branch may be explained only in terms of a hereditary trait being manifested by the mother, since her twin children are nothing but the extra-individual result of such trait. We are dealing here with a special case of sex-limited inheritance which, at the present state of our knowledge, can be detected only in the filial generation. For the sake of clarity, we wish to stress the fact that a woman manifesting the trait may have inherited it through her father as well as through her mother (or even through both). Therefore, the higher frequency of the phenomenon in the family, resulting from its being hereditary, may be better stressed if, as indicated in Fig. 3, the research is started at the level of the mother of twins (section α'), rather than of her twin children (section α).

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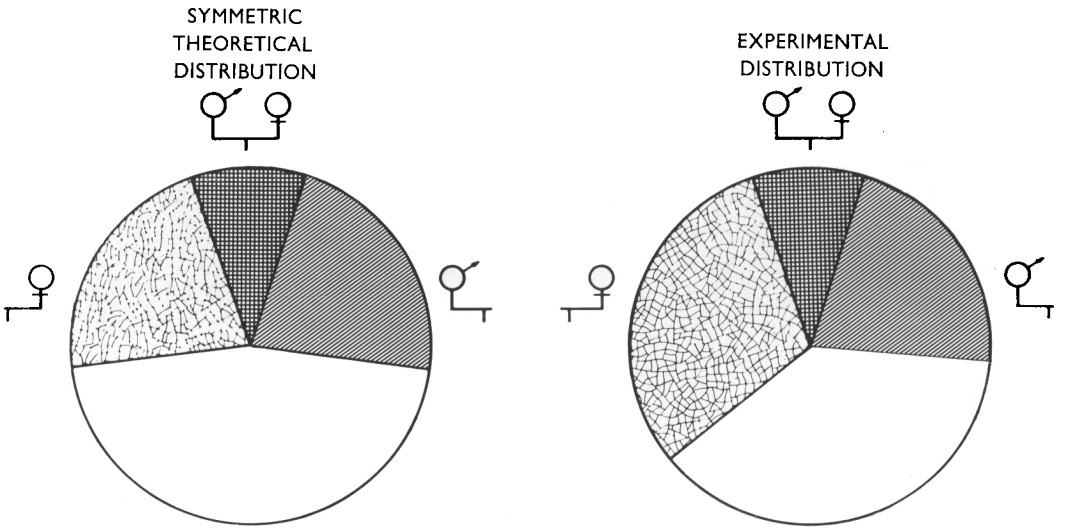

Fig. 2

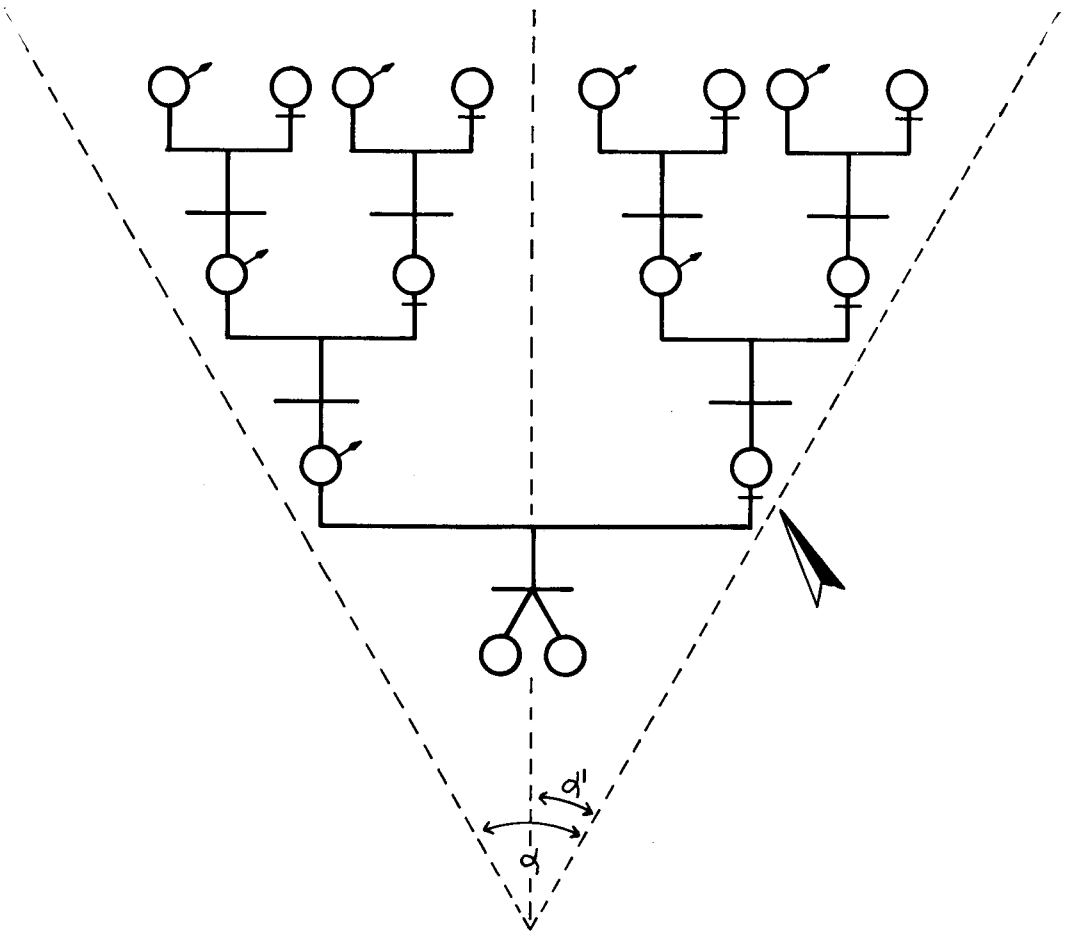

Fig. 3

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The answer to both questions, as obtained from the Gemelloteca's material, thus confirms the assumption that twinning corresponds to the manifestion of a hereditary trait in the mothers of twins, which the term " Gemellogenetic Factor ", or " G Factor ", proposed by Gedda in 1951, may suitably express.

IV. Studies on the singleness of MZ and DZ twinning inheritance

A second research program was based on material published by ISTAT. This research deals with the qualitative variability of the twin phenomenon, expressed by the existence of identical (or monozygotic) and nonidentical (or dizygotic) twins. Already in 1951 the senior Author had pointed out the frequent finding, in the genealogy of individual twin pairs, of multiple births differing as to quality (MZ and DZ) and even to quantity (twins, triplets, quadruplets etc.). Such findings, once established that twinning fits the hypothesis of genetic control, prompted us to pose the following question: should twin types differing as to zygosity (frequently found in the same family area) be ascribed to the chance association of different, independent hereditary traits, or do they represent the variability of expression of a single hereditary trait? The answer to this question has been sought by us in the study of " supertwins " (triplets, quadruplets etc.). Such multiple births afford the occurrence of the various zygotic combinations reflecting the phenomenon's qualitative variability.

The material we analyzed consists of all triplet births registered in Italy in the years 1952-1961 (ISTAT records list births by multiplicity and by sex).

In the model we adopt, the frequencies observed in this material are compared with the frequencies expected in the hypothesis of chance combination of the two types of zygosity in a similar theoretical sample. Under this model, qualitatively different types of triplet births should be interpreted as chance combinations of MZ and DZ twinning events. A triplet birth may therefore derive from any of the following possibilities (Fig. 4).

1. *Triplet monozygosity*, deriving from two subsequent events of MZ twinning, concerning respectively the protozygote and one of the two deriving primary isozygotes. The latter, in turn, produces two secondary isozygotes. In this case

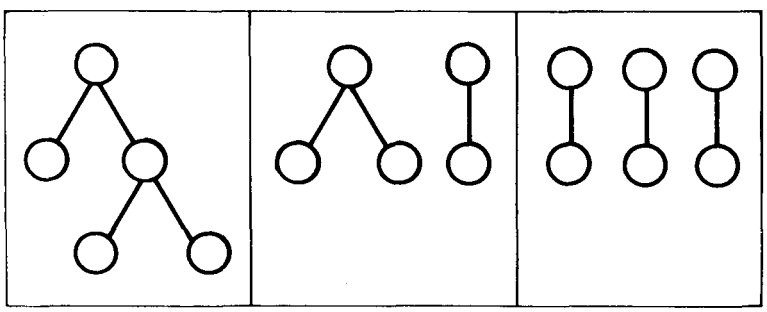

Fig. 4

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a triplet birth may be interpreted as due to a single zygote and may therefore be called monozygotic. The frequency of triplet monozygosities (MZ_t) in a triplet population should equal the product of the frequencies of two subsequent monozygotic events, or: $MZ_t = MZ \cdot MZ = MZ^2$.

2. *Triplet dizygosity*, deriving from the combination of a monozygotic event, originating two primary isozygotes, with a normal zygote; such a triplet birth is dizygotic. The frequency of triplet dizygosities (DZ_t) in a triplet population should be: $DZ_t = 2 \cdot MZ \cdot DZ$.

3. *Triplet trizygosity*, deriving from three independent zygotes, none of which undergoes duplication: such a triplet birth is trizygotic. The frequency of triplet trizygosities (TZ_t) in a triplet population should be: $TZ_t = DZ \cdot DZ = DZ^2$.

The above interpretation of triplet births affords the possibility of determining the frequency with which monozygosities and dizygosities (the two basic phenomena of twinning) would combine if they were independent hereditary phenomena, associated at random in triplet phenogenesis. In fact, from the three above mentioned formulae, we can derive the following comprehensive formula expressing the frequency of zygosities in a triplet population:

$$MZ^2 + 2 \cdot MZ \cdot DZ + DZ^2 = (MZ + DZ)^2.$$

Zygosity and sex are reciprocally related, since the two products of a monozygotic event are necessarily of the same sex, while in dizygotic events the sex of each product is determined by chance. As a consequence, indicating by p and q the respective probabilities of male and female births, we can calculate the possible sex combinations, and their probabilities, within each type of zygotic combination resulting in a triplet birth. Such combinations are:

1. *Monozygotic triplet births* (probability = MZ^2)	Three-male monozygosity (probability = p) Three-female monozygosity (probability = q)
2. *Dizygotic triplet births* (probability = $2 \cdot MZ \cdot DZ$)	Two-male monozygosity + one male zygote (probability = p^2) Two-male monozygosity + one female zygote (probability = pq) Two-female monozygosity + one male zygote (probability = qp) Two-female monozygosity + one female zygote (probability = q^2)
3. *Trizygotic triplet births* (probability = DZ^2)	One male zygote + one male zygote + one male zygote (probability = p^3) One male zygote + one male zygote + one female zygote (probability = $3p^2q$) One male zygote + one female zygote + one female zygote (probability = $3pq^2$) One female zygote + one female zygote + one female zygote (probability = q^3)

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Grouping together the frequencies of the various combinations of zygosity and sex, originating the same sex combinations, we obtain, in the hypothesis of independence between sexes and zygosities, the distribution shown in Tab. 6.

In order to apply the formulae of Tab. 6, we must obviously substitute the numerical values for MZ, DZ, p and q. Since MZ and DZ frequencies cannot be di-

Tab. 6. Theoretical distribution of triplet births according to sex combinations

$$\begin{aligned}
♂♂♂ &= MZ^2\ p + 2\ MZ\ DZ\ p^2 + DZ^2\ p^3 \\
♂♂♀ &= 2\ MZ\ DZ\ pq + DZ^2\ 3\ p^2\ q \\
♂♀♀ &= 2\ MZ\ DZ\ pq + DZ^2\ 3\ pq^2 \\
♀♀♀ &= MZ^2\ q + 2\ MZ\ DZ\ q^2 + DZ^2\ q^3
\end{aligned}$$

rectly obtained from vital statistics, we choose to apply Weinberg's differential method, where the respective frequencies are obtained by the following formulae:

$$DZ = \frac{2 \cdot f(♂♀)}{N} \quad \text{(where N = total number of pairs)}$$

and

$$MZ = 1 - DZ$$

These formulae have been applied to ISTAT data (Tab. 7) concerning male and female single births, twin births in the three possible sex combinations, triplet births in the four possible sex combinations, as well as other multiple births in the years 1952-61.

Tab. 7. Single and multiple births in Italy in 1952-1961

	Single births			Twin births				Triplet births					Other		
	♂	♀	Total	♂♂	♀♀	♂♀	Total	♂♂♂	♂♂♀	♂♀♀	♀♀♀	Tot.	♂	♀	Tot.
1952	437061	411908	848969	3885	3670	3411	10974	25	17	35	27	105	9	4	13
1953	448701	423569	872270	3824	3757	3451	11032	22	34	24	39	119	3	1	4
1954	449226	425247	874473	3857	3693	3558	11108	22	26	18	29	95	10	2	12
1955	434507	408475	842982	3832	3573	3457	10862	28	33	26	31	118	4	0	4
1956	450250	425381	875631	3853	3681	3506	11040	27	30	34	26	117	3	1	4
1957	452971	427586	880557	4009	3750	3530	11289	16	17	38	30	101	7	5	12
1958	447966	422987	870953	3864	3715	3613	11192	28	22	26	27	103	8	4	12
1959	464607	437136	901743	3820	3839	3542	11105	36	36	29	29	130	0	4	4
1960	468644	442270	910914	3827	3667	3395	10889	21	32	27	32	112	7	1	8
1961	477940	451571	929511	3846	3657	3489	10992	25	27	25	28	105	0	0	0
Total	4531873	4276130	8808003	38617	36910	34956	110483	250	275	282	298	1105	51	22	73

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Calculating the frequencies p and q directly from male and female births, and the frequencies of twin births of the two zygosity types by means of Weinberg's formulae, we obtain, for the period under examination, the following values:

$$\text{Total male births} = 4{,}645{,}982; \quad p = \frac{4{,}645{,}982}{9{,}032{,}357} = .514$$

$$\text{Total female births} = 4{,}386{,}375; \quad q = \frac{4{,}386{,}375}{9{,}032{,}357} = .486$$

$$\text{Total births} \quad 9{,}032{,}357$$

$$\text{Same-sexed twin births} = 71{,}866; \quad MZ = \frac{110{,}483 - 2 \cdot 38{,}617}{110{,}483} = \frac{33{,}249}{110{,}483} = .301$$

$$\text{Opposite-sexed twin births} = 38{,}617; \quad DZ = \frac{2 \cdot 38{,}617}{110{,}483} = \frac{77{,}234}{110{,}483} = .699$$

$$\text{Total twin births} \quad 110{,}483$$

By substituting these values in Tab. 6, we obtain the results listed in Tab. 8.

Having thus obtained the expected frequencies of the various sex combinations in triplet births, we can compare them with the observed frequencies derived from Tab. 7. The comparison between theoretical and experimental distributions is shown

Tab. 8. Relative frequencies of sex combinations in the observed triplet sample

	♂♂♂	♂♂♀	♂♀♀	♀♀♀
Monozygotic	.046568914000000			.044032086000000
Dizygotic	.111173148408000	.110117023592000	.110117023592000	.099390804408000
Trizygotic	.066350424915144	.188208014642568	.177955437969432	.056087122472856
Total frequencies	.224092487323144	.293325038234568	.283072461561432	.199510012880856

in Tab. 9 and Fig. 5. This comparison indicates that the observed number of three-male and three-female triplet births exceeds the expected number by 35 and 77 units respectively, while the opposite occurs in two-sex triplet births, where the expected number exceeds the observed number by 74 (in the case of two males and one female) and by 38 (in the case of one male and two females).

The χ^2 test indicates that the chance probability is $p < .001$, thereby leading us to reject the hypothesis of the experimental distribution being a random sample of the theoretical distribution. In other words, the experimental distribution must be conditioned by a cause which, being necessarily unrelated to the distribution of sexes

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Tab. 9. Comparison of experimental and theoretical distributions of triplet births in Italy (1952-1961) according to sex combinations

	♂♂♂	♂♂♀	♂♀♀	♀♀♀	Total
Experimental distribution (A)	282	250	275	298	1105
Theoretical distribution (B)	247	324	313	221	1105
Difference A-B	+35	—74	—38	+77	0
χ^2	4.96	16.90	4.61	26.83	53.30

Total $\chi^2 = 63.30$ with three D. F., $p<.001$.

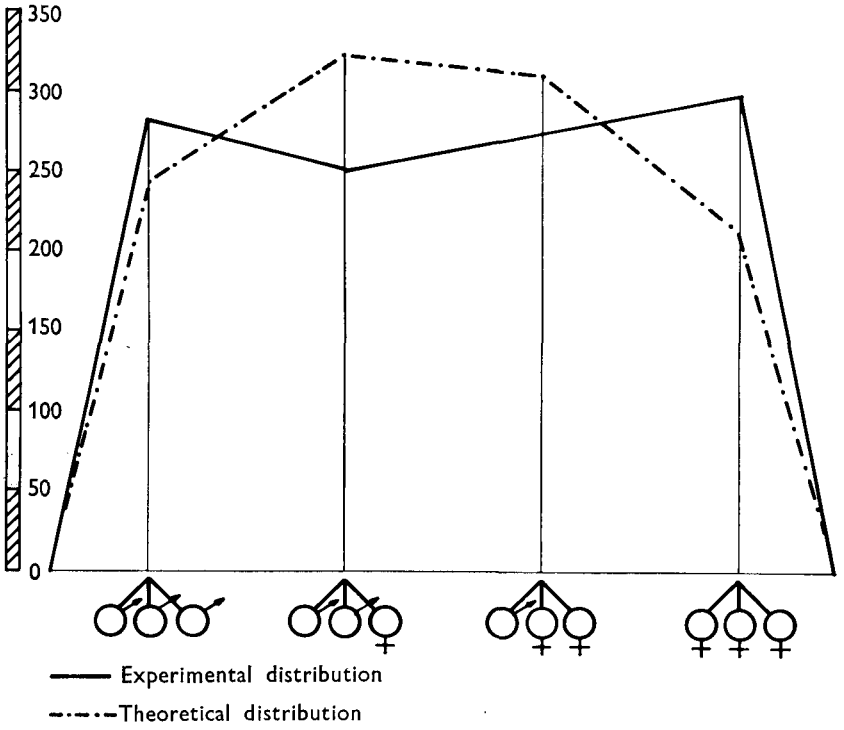

Fig. 5

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(since the latter are inherited independently), must be related to the distribution of zygotic variability (MZ and DZ).

It is clear that the chance event is altered by an increase of the classes including monozygotic triplet births and by the corresponding decrease of the classes formed by dizygotic and trizygotic triplet births (Tab. 9). In other words, the factors responsible for monozygosity and dizygosity do not behave as statistically independent events: they reveal a measure of interaction, i. e. of mutual conditioning.

Since we are dealing with a hereditary phenomenon, the explanation should be sought within the field of genetics, giving to the interaction between monozygosity and dizygosity the meaning of a possible variability of expression of the same hereditary unit.

V. The phenogenesis of twinning in the perspective of HMG-induced twinning

The conclusions we have reached in the preceding chapters are comparable to the loose *tesserae* of a mosaic which have to be assembled in a picture reflecting a hereditary and unitary concept of twinning.

It is not easy to proceed from such a concept to the study of its biological mechanisms, on account of both the complexity of the event and the unavailability of the experimental method. The main difficulty arises from the fact that the tendency to generate twins remains latent in the male, and remains latent in the female in the cases of nubility, sterility of the husband, birth control and so forth.

Medical science has recently registered events of great interest that should be pointed out and discussed in gemellology. These concern the use of the human gonadotropic hormone FSH in the cure of female sterility. It is known that animal gonadotropic hormones are unsuitable for an efficient cure of sterility in women, on account of immune reactions. Given that human FSH is difficult to extract *post mortem*, only the extraction of this hormone from the urine of women after menopause by Donini's method (Pergonal, or HMG, human menopausal gonadotropin) has permitted an adequate and sufficiently prolonged administration.

The first results of the treatment of female sterility with Pergonal were reported by C. A. Gemzell (Uppsala), R. L. Vande Wiele (New York), E. Rabau and B. Lunenfeld (Tel Aviv) in the medical press and at the Symposium held in Rome from May 14 to 16, 1965. These Authors reported the following clinical results concerning twinning due to Pergonal.

In 17 cases, Gemzell obtained 18 pregnancies, of which 7 were multiple: 2 quadruplet sets (one still-born) and 5 twin pairs. In 20 cases, Vande Wiele and Turksoy (New York) obtained 2 twin pairs and one set of quadruplets. In 37 cases, Rabau and Lunenfeld (Tel Aviv) obtained 12 pregnancies including 5 twin pairs. Gemzell, Vande Wiele and Lunenfeld gave the senior Author (also a lecturer at the Rome Symposium) diagnostic information concerning zygosity in multiple pregnancies obtained with Pergonal. The three Authors agreed that up to now they had obtained

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plurizygotic twins differing as to sex, blood groups and other significant traits. Until now, at least, Pergonal has not produced monozygotic but only dizygotic or plurizygotic multiple births.

In our opinion, this clinical documentation should be kept in mind while studying the phenogenetic mechanism of twinning. The case of sterile women becoming fertile following treatment with Pergonal can be explained by a quantitative and qualitative deficit of FSH. As a matter of fact, the same hormone, administered in adequate doses and for an adequate length of time, is able to overcome this deficiency.

What interests biology and gemellology is that in this substitutive function Pergonal is able to overcome a hereditary characteristic of the human species, i. e. the readying for conception of a single egg at a time.

According to current opinion, Pergonal may act by causing the simultaneous readying of two, or more, follicles, and therefore of two, or more, eggs.

However, another hypothesis may be advanced, i. e. that Pergonal causes a modification of the oogenesis, inasfar as it may lead to the maturation of two, or more, oocytes in the same follicle, thus avoiding the transformation into polar bodies of the product of maturative divisions, as it usually happens.

Moreover, FSH may be credited with an action which does not concern the follicle but more directly gamete production. In fact, the action of Pergonal has shown itself useful not only in removing female sterility in the above mentioned sense, but also in stimulating gametogenesis by reactivating male fertility, as demonstrated by the individual experiences of Pasetto, Debiasi, MacLeod and Lunenfeld. The latter Author, for instance, treating 15 azoospermic patients, obtained in 5 cases motile and vital spermatozoa.

Hence, our conclusion that FSH does not fully correspond to its name (which expresses only the action on the follicle) because follicles do not exist in the testicle. On the contrary, FSH seems to have a special stimulating function on the gamete-producing cells.

Wheter the one or the other is the Pergonal's mechanism of action as indicated above, either of them produces two, or more, genetically different zygotes. In fact, even before the amphimixis the possibility that ova from different follicles, or even from a single follicle, be genetically identical is irrelevant. Even by far more irrelevant is the same probability in the case of spermatozoa.

At this point one might wonder why the twinning phenomenon does not represent the rule in human generation. According to present knowledge, it seems that gonadotropic incretion is blocked by a hormone produced by the granular layer of the follicle during its transformation into a corpus luteum. This hormone is progestin, and its incretion is controlled, in turn, by another gonadotropic hormone (increted by the pituitary gland) called LH. After implantation, the task of continuing progestin incretion throughout pregnancy is transferred from the corpus luteum to the placenta. Thus we might have a complex mechanism, responsible for the singleness of normal human conception, which, on one hand, stimulates the maturation of more than one egg (FSH action) and, on the other, blocks such a readying of more than

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one egg (LH action). Three possible variations of this mechanism may lead to a dizygotic or pluriyzygotic pregnancy: (1) an excess of FSH incretion; (2) a primary deficit of progrestin incretion; (3) a secondary deficit of progestin incretion, caused by a primary deficit of LH incretion.

As is well known, hormones are closely related to the genotype, being generally activated by enzymes representing primary gene effects. Since definite evidence indicates that dizygotic twinning may result from hormone action, we may formulate the hypothesis that the tendency to generate twins of this type corresponds to either a deficit or an excess of a hormone system controlled by the genotype.

In other words, we may assume that the hereditary tendency to twinning depends from a genotype responsible for a primary excess of FSH incretion. Or else, we may assume that twinning depends from a genotype responsible for a deficit in LH incretion, and/or a deficit in progestin incretion resulting in a secondary excess of FSH. Since this seems to represent an expression of the balance between the two hypophyseal gonadotropic hormones (FSH and LH), twinning variability could also be explained as a result of the variability of the balance between the hypophyseal incretions of its two gonadotropic components.

The problem remains of how to include monozygotic twinning in such a mechanism, since our research on Italian triplets seemed to indicate the existence of a single genetic factor for twinning.

In this connection, we should point out that animal as well as human multiple births feature a blend of monozygotic and polyzygotic twinning. On this basis, we may assume that the same hereditary factor is able to ready more than one egg of different genic content, and/or to induce the transformation of a fertilized egg into a protozygote which then divides to give the primary isozygotes.

In this case the difference may be determined by the chronology of the FSH impact, i. e. by whether FSH strikes the ovum before or after fertilization.

An appropriate set of experiments has been devised to test the above hypotheses and is currently being carried out at the Mendel Institute.

From a general point of view, one may state that multiple births following administration of HMG (Pergonal) indicate the possibility of an external determination of the twinning phenomenon. Such kind of twinning may, in a certain sense, be considered as a phenocopy of spontaneous twinning.

These new data, obviously, do not alter our understanding of the hereditary nature of twinning: they clarify a large part of the phenogenetic chain, thus reducing the difficulties of interpretation of the hereditary mechanism.

Summary

The Authors take once more into consideration the problem of the hereditary nature of twinning on the basis of their own studies and of recent findings on human twinning induced by human menopausal gonadotropin (HMG).

Personal studies concern 3,221 cases of twinning drawn from the special files

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(" Gemelloteca ") of the Mendel Institute. On the basis of this material the Authors state that the occurrence of the cases of twinning in the paternal and maternal ascendancies of the twin index cases is significantly more frequent than would be expected in proportion to the frequency of twinning events in the Italian population.

This finding is in agreement with the hypothesis of the hereditary nature of the twinning phenomenon.

The same material is used to compare the frequency of twinning in the paternal and maternal families of twins. The observed frequency in the maternal families is significantly higher than in paternal families in which the frequency approximates population values. This finding leads the Authors to formulate the hypothesis that the twinning trait is limited to the female sex and is presently manifested by the occurrence of twins in the next generation. Thus studies on the frequency of twinning as a hereditary phenomenon should be based on the families of the mothers of twins.

Original studies also concern the 1,105 triplet sets born in Italy in the years 1952-1961. A study of the experimental and theoretical distribution of sex combinations in this triplet material allowed the Authors to prove that the experimental distribution differs from the theoretical one, based on the hypothesis of independence of the two types of zygosity (MZ and DZ). The absence of independence is considered a proof of the hereditary singleness of twinning.

The Authors further take into consideration cases of twinning induced in sterile women by administration of human menopausal gonadotropin (HMG): they observe that cases reported to date seem to be limited to dizygotic or plurizygotic twinning. These findings lead the Authors to believe that in this case hypophyseal FSH, responsible for ovulation, fails to find the usual pathway leading to standard uniparous pregnancy in the human species; the mechanism involved in such pathway is the object of some hypotheses of a hormonal nature. The Authors also believe that FSH stimulates not only the follicle but also follicular gametogenesis and even perhaps the division of the fertilized egg resulting in MZ twinning.

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RIASSUNTO

Gli AA. riprendono a trattare il problema della natura ereditaria della gemellazione in base alle loro ricerche e alle recenti acquisizioni della gemellazione umana provocata da somministrazione di ormone gonadotropico della menopausa (HMG).

Le ricerche personali riguardano 3.221 casi di gemellanza ricavati dall'archivio speciale (Gemelloteca) dell'Istituto Mendel. Gli AA., sulla base di questo materiale, affermano che la presenza di altri casi di gemellanza negli ascendenti paterni e materni dei gemelli è significativamente più alta di quella attesa in base alla frequenza dell'evento gemellare nella popolazione italiana. Questo comportamento si accorda con la natura ereditaria del fenomeno gemellare. Sul medesimo materiale viene confrontata la frequenza dell'evento gemellare nelle famiglie dei genitori, e si trova che nella famiglia della madre dei gemelli i valori sperimentali sono significativamente più alti che nella famiglia del padre dei gemelli, dove la frequenza si aggira intorno ai valori popolazionistici. Questo comportamento suggerisce agli AA. che la gemellazione corrisponde ad un carattere ereditario limitato al sesso femminile, che praticamente si manifesta con la presenza di gemelli nella generazione successiva. Perciò la ricerca della frequenza del fenomeno ereditario della gemellazione deve essere effettuata nella famiglia della madre dei gemelli.

Le ricerche personali degli AA. riguardano inoltre le 1.105 trigemellanze verificatesi in Ita-

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lia del 1952 al 1961. Studiando le combinazioni dei sessi in queste trigemellanze, sia dal punto di vista sperimentale che dal punto di vista teorico, gli AA. hanno potuto dimostrare che la distribuzione sperimentale non è conforme a quella teorica fondata sull'ipotesi dell'indipendenza tra i due zigotismi.

Essi ritengono che il comportamento interdipendente dimostri l'unicità del fenomeno gemellare rispetto alla sua genesi ereditaria.

Inoltre gli AA. prendono in considerazione le gemellanze prodotte da somministrazione in donne sterili di HMG e constatatano che fino ad oggi sembra trattarsi di gemellanze DZ o plurizigotiche.

In base a questi risultati, essi pensano che l'FSH dell'ipofisi, che ha il compito di provocare l'ovulazione, non trovi in questo caso dinanzi a sé il meccanismo che garantisce alla specie umana la normale gravidanza unipara, intorno al quale meccanismo essi formulano delle ipotesi di natura ormonale. Gli AA. pensano inoltre che l'ormone FSH non sia soltanto stimolante del follicolo ma anche della gametogenesi nel follicolo e forse anche della divisione dell'uovo fecondato che produce la gemellanza MZ.

RÉSUMÉ

Les AA. étudient de nouvau la question de la nature héréditaire du phénomène gémellaire sur la base de leurs recherches et des nouvelles acquisitions concernantes la naissance de jumeaux, suivant administration chez la femme de l'hormone gonadotropique de la ménopause (HMG).

Les recherches personnelles concernent 3.221 cas de naissances gémellaires tirés des archives spéciales (Gémellothèque) de l'Institut Mendel. Sur la base de ce matériel les AA. trouvent que la présence d'autres cas de jumeaux chez les ascendants paternels et maternels des jumeaux est significativement plus élevée de ce que l'on pourrait attendre d'après la fréquence du phénomène gémellaire dans la population italienne, ce qui est en accord avec l'hypothèse héréditaire du phénomène.

Les AA. comparent aussi la distribution de la fréquence du phénomène gémellaire chez les familles des parents: du côté maternel les valeurs expérimentales paraissent significativement plus élevées que du côté paternel, où la fréquence est très proche des valeurs de la population. Par conséquent, les AA. pensent que le phénomène gémellaire corresponde à un caractère héréditaire limité au sexe féminin, qui se manifeste pratiquement par la présence de jumeaux dans la génération suivante. La recherche de la fréquence du phénomène héréditaire gémellaire doit, donc, être effectuée partant de la mère des jumeaux.

Les recherches personnelles concernent aussi les 1.105 triplettes qui se sont vérifiées en Italie de 1952 à 1961. Par l'étude des combinaisons des sexes au sein de ces triplettes, soit au point de vue expérimental, soit au point de vue théorique, les AA. ont pu démontrer que la distribution expérimentale ne correspond pas à la distribution théorique, sur la base de l'indépendence de mono- e dizygotisme. Cette interdépendence démontrerait l'unicité héréditaire du phénomène gémellaire.

Les phénomènes gémellaires suivant administration de HMG chez des femmes stériles sont aussi considérés par les AA. qui constatent que, jusqu'à présent, il paraît s'agir de jumeaux dizygotiques ou plurizygotiques.

Ces résultats amènent les AA. à penser que l'FSH de l'hypophyse, qui a la tâche de déterminer l'ovulation, ne rencontre pas dans ce cas le mécanisme responsable de la grossesse unipare habituelle, à propos duquel ils formulent des hypothèses de nature hormonale.

Les AA. pensent aussi que l'FSH n'ait pas seulement une action stimulante du follicule, mais aussi bien de la gamétogenèse dans le follicule et, peut-être, aussi de la division ovulaire donnant lieu au phénomène gémellaire MZ.

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ZUSAMMENFASSUNG

Auf eigene Untersuchungen sowie auf neueste Forschungen gestützt, in denen menschliche Zwillingsbildung durch Verabfolgung von gonadotropem Hormon des Klimakteriums (HMG) hervorgerufen wurde, nehmen die Verf. das Problem der Erblichkeit des Zwillingsphänomens auf.

Die eigenen Untersuchungen beziehen sich auf 3.221 Zwillingsfälle, welche in dem Sonderarchiv (Gemellothek) des Mendelinstitutes geführt werden. Diesem Material gemäß behaupten die Verf., daß die Häufigkeit anderer Zwillingsfälle bei den väterlichen und mütterlichen Vorfahren der Zwillinge bedeutend höher ist, als auf Grund der Zwillingshäufigkeit in der italienischen Bevölkerung zu erwarten sei.

Dieses Verhalten bekräftigt die Hypothese, daß das Zwillingsphänomen erbbedingt ist.

An dem gleichen Material vergleichen die Verf. die Häufigkeit des Zwillingsvorkommens in den elterlichen Familien und finden, daß die experimentellen Werte in der mütterlichen Familie bedeutend höher sind als in der väterlichen Familie der Zwillinge, wo die Häufigkeit ungefähr derjenigen der Bevölkerung entspricht. Dieses Verhalten bringt die Verf. zur Annahme, daß das Zwillingsphänomen einem ans weibliche Geschlecht gebundenen Erbmerkmal entspricht, das sich praktisch in dem Vorkommen von Zwillingen in der folgenden Generation äußert. Daher muß die Häufigkeit des Erbphänomens der Zwillinge in der mütterlichen Familie der Zwillinge untersucht werden.

Die eigenen Untersuchungen der Verf. beschäftigen sich außerdem mit 1.105 Drillingsfällen, die sich in der Zeit von 1952 bis 1961 in Italien ereigneten. Durch Untersuchung der Geschlechtskombinationen dieser Drillinge sowohl vom experimentellen als vom theoretischen Standpunkt konnten sie beweisen, daß die experimentelle Verteilung nicht mit der theoretischen übereinstimmt, da letztere sich auf die Hypothese stützt, daß die beiden Eiigkeiten voneinander unabhängig sind. Die Verf. sind der Ansicht, daß das gegenseitig abhängige Verhalten die Einzigkeit des Zwillingsphänomens gegenüber seiner Erbgenese beweist. Verf. beschäftigen sich auch noch mit den Zwillingsfällen, welche durch Verabfolgung gonadotropen Hormons des Klimakteriums an sterile Frauen hervorgerufen wurde und stellen fest, daß es sich dabei bis heute um zwei- oder mehreiige Zwillingsformen zu handeln scheint.

Auf Grund dieser Resultate glauben sie, daß das FSH-Hormon der Hypophyse, welchem die Aufgabe der Ovulationsauslösung zukommt, in diesem Falle nicht den Mechanismus vorfindet, welcher der Species humana die normale Einlingsschwangerschaft gewährleistet und fragen sich, ob dieser Mechanismus hormoneller Natur sei. Verf. glauben außerdem, dass das FSH-Hormon nicht nur das Follikel stimuliere, sondern auch die Gametogenese darin und vielleicht auch die Teilung des befruchteten Eies, welche sodann die eineiige Zwillingsbildung bewirkt.

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