An Explanation of Twins

From the standpoint of the biologist single births are just as remarkable as multiple births, but the latter provide a clue to the processes responsible for both

by Gunnar Dahlberg

THE birth of twins is apt to cause excitement because our wonder and curiosity are aroused by the uncommon. If twin births were the rule and single births the exception, we would be incredulous over the birth of merely one child—just as, things being as they are, we would be amazed at the birth of a single kitten or a single puppy. Actually the birth of twins is no more wonderful than the fact that in the overwhelming majority of cases the female of our species bears but a single child. From a scientific point of view the latter phenomenon is as challenging and exciting as the former; both are part of one and the same problem.

We do not know what causes twins to be born. The explanations offered by scientists are still only hypotheses. I shall present here my own theory, based on physiological observations and on certain more or less probable assumptions.

We know that twins occur about once in 80 human births; triplets once in 80 times 80, or 6,400, and quadruplets once in 80 times 80 times 80, or 512,000. Of the birth of quintuplets only about 30 instances have been recorded in all history. There are three fully substantiated cases of the birth of sextuplets. One is vouched for by a missionary in Africa who visited the Negro tribal village where rumor said the event had taken place. When he arrived at the mother's hut, he found only five infants; the natives said the sixth was dead and already buried. He offered a small payment if he could see it. A woman went to a corner of the hut and upturned a basket; out of it rolled the dead sixth. The missionary photographed the sextuplets together. No case of septuplets has ever been authenticated, but in the small German town of Hammel an der Weser stands a tombstone said to be in memory of a woman who died in labor while bearing seven; on the tombstone are depicted the mother and seven fetuses representing the birth.

The mortality of twins and other multiple births is well known to be higher than that of single children; they are often born prematurely, and even those at full term are generally more feeble at birth. The famous Dionne quintuplets are the largest multiple birth known to have survived.

It is estimated that about 20 per cent of the women in a population have a propensity for twins. A woman who has borne twins once has one chance in 17 of bearing twins again. As women grow older, the likelihood of twins rises: for a pregnant woman of 40 the probability of a twin birth is three to four times as high as for a woman of 20. Twin births vary with populations, probably in part because of racial differences. They are more common in Northern Europe than in Southern Europe.

NOW what are the biological clues to the origin of twins? As almost everyone knows, there are two kinds: those that come from a single egg, commonly known as identical twins, and those that spring from two separate eggs which are discharged and fertilized at the same time. Two-egg twins, apart from the fact that they are of the same age, are no more alike than any other brothers or sisters. As often as not they are of different sexes. Twins that develop from the same egg, on the other hand, are as alike as the left and right half of an individual's body. They are always of the same sex and often very difficult to distinguish from one another. About one pair of twins in four is of this single-egg type.

Suppose we start with the simple hypothesis that twins arise from a tendency of some eggs to double, *i.e.*, divide into two normal eggs. This would certainly seem to be true of all one-egg twins: the egg from which they come doubles *after fertilization* to produce two complete individuals. The doubling process could also account for some two-egg twins. An occasional egg may have so strong a tendency to double that it divides even before fertilization. In that case both eggs can be fertilized separately and two embryos can develop simultaneously. This hypothesis, which I first formulated in 1926, seems to be supported by certain statistical facts. If the assumption is correct, a mother whose eggs have a disposition to double might at different times bear two-egg twins and one-egg twins. A study I made of a number of mothers in Sweden who had borne more than one set of twins, and later studies by others, indicate that such mothers do indeed tend to have both kinds of twins.

This theory of a doubling tendency can account for the various degrees of separation observed in human and animal births. If the doubling takes place before fertilization, we have a pair of two-egg twins. If it occurs after fertilization, the result is a pair of one-egg twins. If the tendency to double is less pronounced or occurs very late, the twins may be more or less joined together, as Siamese twins are. It is well known that great variations in the degree of conjunction of twins are actually observed.

But it seems that doubling of the egg cannot account for all twin births. The reasoning behind this conclusion is as follows: The probability of one-egg twin births, which clearly arise from egg-doubling, remains fairly constant throughout a woman's childbearing life. This suggests that the egg-doubling tendency does not vary with increasing age. On the other hand, the frequency of two-egg twin births goes up rapidly with women's age, reaching a maximum at approximately 37 years. We must therefore find some explanation other than egg-doubling for some of the two-egg twin births, particularly those that occur at the later ages.

THE explanation may well lie in the fact that the ovaries sometimes discharge two eggs at once, instead of the usual one. The ovaries contain somewhere between 100,000 and 400,000 eggs. Of these about 400 ultimately mature. Normally only a single egg matures at a time; it is then discharged during the short monthly ovulation period from its Graafian follicle into the Fallopian tubes, where it becomes available for fertilization. But it is known that occasionally two eggs may be discharged simultaneously from separate Graafian follicles.

Why, one may ask, does this happen? There is no valid reason, as I have already suggested, for posing the question in that form. We really ought to ask why as a rule only one egg is discharged at a time. Taken by itself the rule is just as mystifying as its exceptions, and we cannot explain these exceptions until

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we understand the normal mechanism.

We may be able to get a clearer picture of the situation by considering an analogy. Suppose that a large number of sheep are penned in a fold and once a month a single sheep leaves the fold. Now there are two possible explanations. It is conceivable that regularly each month, one and only one, sheep is moved to seek escape, while the rest have no such impulse. If this possibility seems absurd, we must accept the alternative explanation: namely, that once a month a gate is opened and many sheep try to get out but only one succeeds, the gate closing as soon as it escapes.

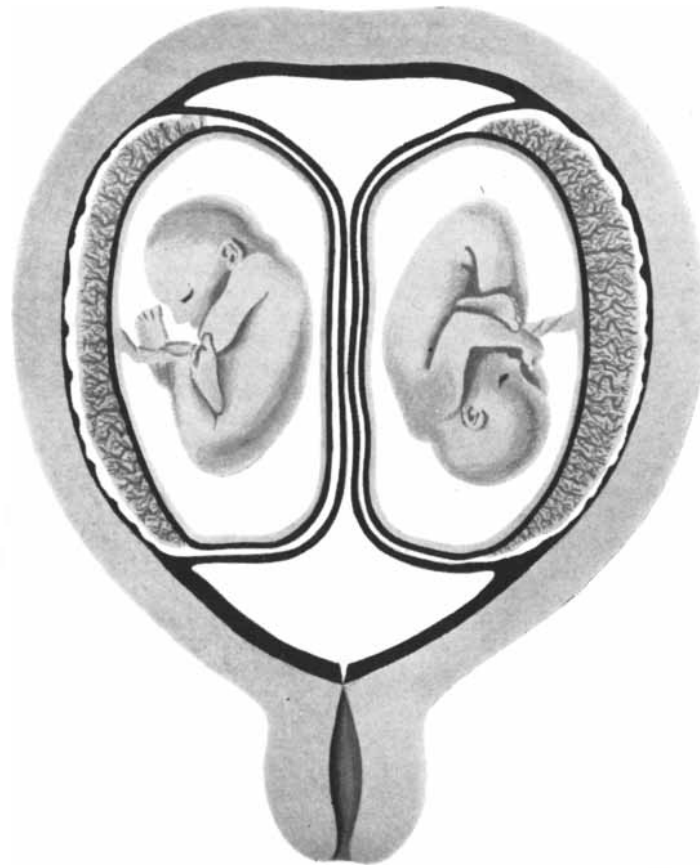
Evidently this is the case in the ovary. It is extremely improbable that the individual eggs are predestined to mature in a certain order and at the rate of precisely one each month. It is much more likely that the eggs strive to mature in crowds. This being so, there must be some kind of valve mechanism that lets through only one egg of the crowd. This mechanism cannot be controlled by the nervous system, for no nerves pass from the ovaries to the Graafian follicles. Furthermore, the mechanism must be such that it acts on both ovaries at the same time. The possibility nearest at hand is that some chemical substance plays a role in the development of the eggs. In a given group of developing eggs the one that wins the race to maturity must cause some substance to be excreted into the blood which prevents the remaining eggs from developing fully. Sometimes, however, two eggs may finish in a dead heat and cross the critical boundary simultaneously. Then we get a pair of twins.

THUS FAR we have analyzed the problem strictly by the process of logic. Students of the natural sciences, however, possess a healthy disbelief in bare logic. They like to see logical deductions verified by experiment. In this case the problem is to demonstrate that a fully developed egg possesses some substance which inhibits ovulation of the other eggs. This substance should be found in the liquid which fills the Graafian follicle that holds the egg.

My first efforts to find such a substance were frustrated by certain technical difficulties. But the discovery of the Zondek-Aschheim pregnancy test in the 1930s provided a ready means of investigating the question. In this test urine from a woman believed to be pregnant is injected into an immature female mouse. If the woman is actually pregnant, the eggs in the mouse's ovary develop. This is because a pregnant woman's urine contains a pituitary hormone that stimulates ovulation. Now if the liquid in Graafian follicles contains a substance that inhibits ovulation, then the addition of small quantities of the liquid should cancel the ovulation-stimulating effect of a pregnant woman's



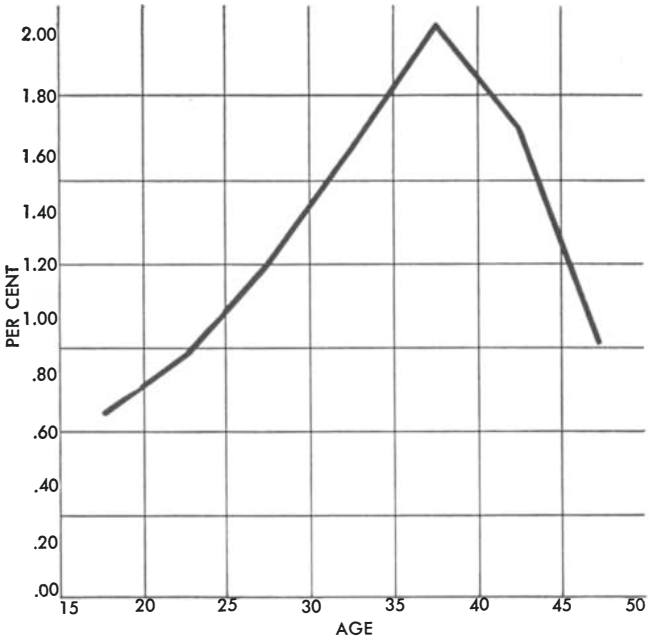
ONE-EGG OR IDENTICAL TWINS always develop from an egg which divides after fertilization. During gestation the twins have a common placenta.



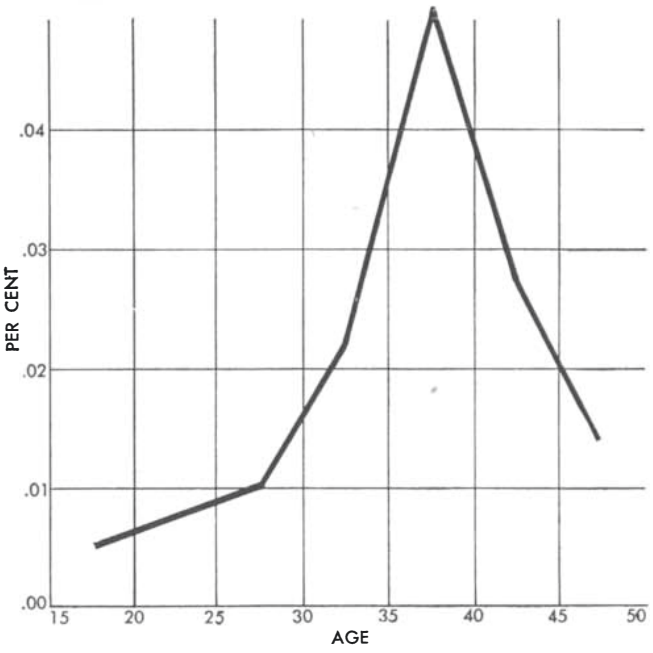
TWO-EGG OR FRATERNAL TWINS appear to develop from two eggs or an egg which divides before fertilization. The twins have separate placentas.

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LIKELIHOOD OF TWINS increases sharply with the age of the mother. The percentage of twins for mothers of 40 is three to four times that for mothers of 20.



LIKELIHOOD OF TRIPLETS increases even more sharply with the age of the mother. The percentage of triplets is about 10 times greater for older mothers.

urine. I proceeded to make this test, using part of a urine specimen from a woman known to be pregnant and liquid from the Graafian follicles of cows. Sure enough, the experiment had the predicted result: test animals that received the Graafian-follicle liquid showed no pregnancy reaction while control animals did.

I suspected that the inhibiting substance in the Graafian follicles might be the estrus-inducing hormone called folliculin or estrin, which is known to be secreted by mature eggs and by cells in the follicles. But the first experimental tests of this idea by myself and by Bernhard Zondek, the co-inventor of the pregnancy test, failed: the addition of pure estrin to the urine of pregnancy did not inhibit ovulation. Yet the idea seemed basically so sound that I refused to believe that these results were decisive. Perhaps pure estrin failed because it is absorbed quickly and produces only a transient effect. The estrin present in the follicle liquid, on the other hand, is absorbed slowly, on account of the presence of protein. Hence its effect, though less intense, is more lasting. If ovulation is to be inhibited, the effect must be continuous, to prevent the race of the eggs toward maturity from going so far that they cannot be stopped.

As a matter of fact, subsequent experiments indicated that estrin does indeed inhibit ovulation. It turned out that the doses we had used were too small; investigators who injected much larger estrin doses in mice obtained a sufficiently powerful and prolonged effect to inhibit ovulation in the Graafian follicles. Moreover, I found that when estrin is fed to young mice by mouth instead of by injection, so that it is absorbed more slowly, the hormone postpones ovulation as long as it is given.

So we have this picture of the normal cycle: Each month a group of eggs in the ovaries begin a race toward maturity. When one of the eggs arrives at a certain stage of maturity, winning the race, it causes the secretion of estrin, which halts the development of the rest. Now what happens to the losers of the race? Do they carry over to join the race at the next ovulation? This seems unlikely. Assume, for example, that 20 eggs enter the race at a given ovulation. If the 19 losers survived to join the 20 new eggs in the contest at the next ovulation, there would be almost twice as many contestants in the second month as in the first and therefore twice as high a probability for the birth of two-egg twins. During a single year the probability for twins would rise 12-fold. Actually the probability does not increase at anything like this rate.

Suppose, then, that only one new egg enters the race at each ovulation. This also is improbable, for it presupposes a precision and predestination in the development of individual eggs which we have already ruled out as absurd. Hence we are forced to the conclusion that after the end of each race the losing eggs die and a new group comes forward for the next competition. This conclusion is confirmed by the observation that the ovaries always contain large numbers of dying eggs. Nature, as we well know, is prodigally wasteful; it provides vast numbers of extra organisms to ensure the carrying on of its processes.

IF THE losing eggs all perish, how can we explain the fact that the probability of twins rises with women's advancing age? Probably the reason is that as the ovaries mature they produce larger and larger groups of new eggs before each ovulation, so that at the age of 40 the group of competing eggs is four times as large as at age 20. This may seem surprising, in view of the general impression that a woman is less fertile at 40 than at 20. Actually a study by Sten Wahlund of the Swedish Lapps, who do not practice birth control, showed that fertility in the sense of ability to conceive does not decline by age 40.

If the chance of getting two-egg twins quadruples with age, the chance of getting triplets should increase even more. This can be illustrated by the mathematics of a track meet. Other things being equal, if we quadruple the number of runners in a race, we quadruple the probability that two runners will finish in a tie. But the mathematical probability of a triple tie, which is very small to begin with, is multiplied 16 times when the number of runners is quadrupled. Thus if triplets always came from three separate eggs, a mother of 40 would have 16 times as great a chance of bearing triplets as a mother of 20. However, some triplets come from a single egg, the probability of which should not increase significantly with age, and some come from two eggs, where the probability only quadruples. The frequency of triplets can therefore be expected to increase somewhere between 4 and 16 times by age 40. The actual vital statistics from several countries show that the incidence of triplets is about 10 times greater in 40-year-old women than in 20-year-olds.

Is the tendency to bear twins or triplets inherited? We have no clear answer to this question; the figures are inter-

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preted variously in different quarters. They do appear to show, however, that the tendency to one-egg twins may be hereditary both on the father's and the mother's side and that a disposition to bear two-egg twins is determined by the mother's heredity.

SOME study, though not enough, has been given to the mechanism of multiple births in other animals. Some of our domestic animals, notably mares and cows, as a rule bear only one young at a time, and twin births are rather less common among them than among women. Sheep have twins and triplets fairly often. In pigs, rabbits, dogs and cats the birth of a litter of several young is the rule rather than the exception. Generally these multiple births come from separate eggs, but they must sometimes spring from a single egg, as evidenced by the occasional birth of a two-headed calf or other partly double animal. Some species of armadillos, the peculiar little scale-covered animals found in North and South America, bear one-egg multiplets as a general rule; they usually have from 4 to 12 young in a litter, all from a single egg. Occasionally a mother armadillo discharges two eggs at a time, as women do.

We may therefore say that one-egg twins and multiplets probably occur in all species, and that multiple births from separate eggs are very common, especially in small animals. We can distinguish three mechanisms for multiple births: 1) division of a single egg after fertilization; 2) division of the egg into two or more separate eggs before fertilization, and 3) the simultaneous discharge of two or more entirely independent eggs from different Graafian follicles. In animals that habitually bear several young at a time the multiple births must surely be under some form of hormonal control similar to that which governs single births in human beings.

This theory offers an explanation of some known facts which hitherto have been practically inexplicable. To some extent it has been substantiated by experimental findings, but the theory certainly needs further development and verification.

Goethe insisted: "Gray is all theory and green the rich tree of Life." No scientist would accept this pronouncement. The facts of everyday life are not *per se* interesting. What enthuses a scientist, guides his work and enables him to do what is expected of him is the development of theories to explain the facts. To him this is the most exciting part of his endeavor; the work of digging for the evidence to verify a theory is a more or less monotonous chore.

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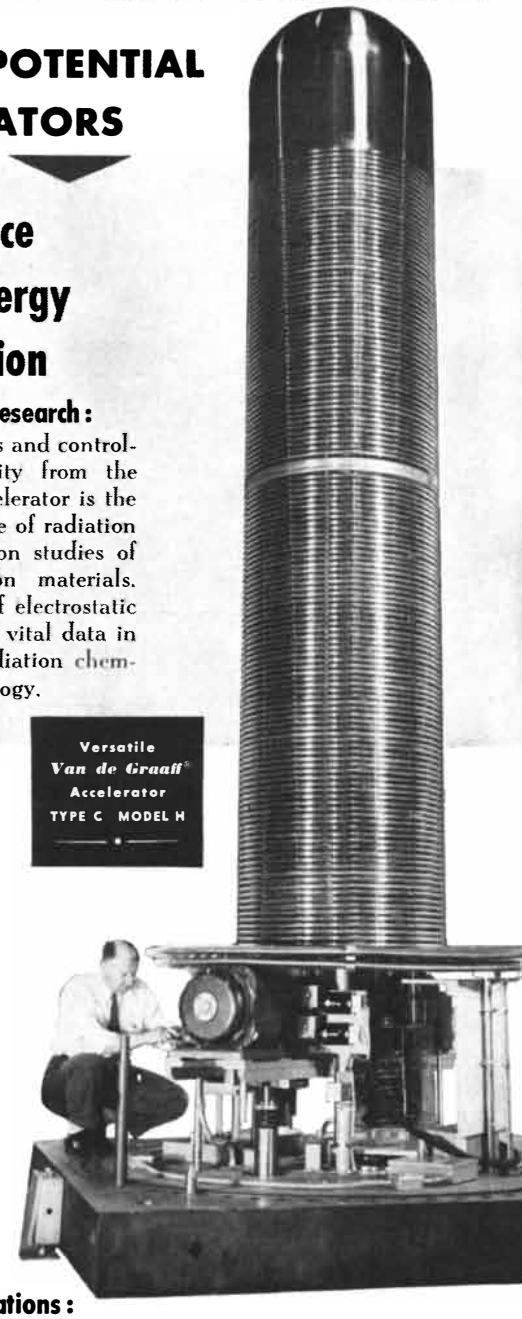
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