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Twins. Part 1. The Conception, Development, and Delivery of Twins

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Twins have occupied a prominent place in human imagination and mythology since ancient times. Greek mythology enshrined the twins Castor and Pollux in the heavens as the two stars of the constellation Gemini. Ancient Rome was said to have been founded by twins, Romulus and Remus, raised in the wild by a wolf. The establishment of several North American Indian tribes, such as the Hurons and Iroquois, is also ascribed to twins. Although deified in myths, twins have elicited ambivalent and opposite reactions among human communities. In *Twins and Supertwins*, Amram Scheinfeld, former member of the Genetic and Evolution Seminar of the University Seminars, Columbia University, New York, noted that the birth of twins was sometimes taken to be a bad omen, and one or both twins were killed or allowed to die through neglect.[1] But T.O. Oruene noted that groups such as the Yoruba tribe of Nigeria, who at one time practiced infanticide, today regard twins as special children invested with magical powers.[2]

Twins also occupy a special place in modern science. For example, genetically identical twins provide researchers with a kind of natural laboratory to explore the role that heredity and environment may play in the development of various medical and behavioral problems. In the first part of this essay, we'll discuss the unique biology of conceiving and giving birth to twins. Part two of this essay will focus on the use of twins in medical and behavioral research.

There are two biologically distinct types of twins, monozygotic (MZ) and dizygotic (DZ). MZ twins are genetically identical. They arise from a single fertilized egg (zygote) that splits in two during an early stage of development. These identical twins are always of the same sex. DZ, or fraternal, twins are no more alike genetically than any pair of siblings. They result from a more or less simultaneous double ovulation from the same or opposite ovaries and subsequent fertilization by two different spermatozoa. DZ twins can be of the same or opposite sex.

DZ twin births are more frequent than MZ births. In the US and Europe, for example, Zdenek Hrubec and C. Dennis Robinette, National Academy of Sciences-National Research Council, Washington, DC, noted that 12 of every 1,000 births produce twins.[3] One-third of these are MZ births. Interestingly, the frequency of MZ twinning is constant throughout the world, occurring in about 4 per 1,000 births.[3] But the rate of DZ births is extremely variable. According to P.P.S. Nylander, University College Hospital, Ibadan, Nigeria, the incidence of DZ twinning is highest among the Yoruba, at approximately 50 per 1,000 births.[4] Eiji Inouye, Institute of Brain Research, University of Tokyo,

reported that the lowest rate of DZ twinning occurs in Japan at 4 per 1,000 births.[5]

While these figures reflect the incidence of twin *births*, the incidence of twin *conceptions* is thought to be higher. With the recent increased use of ultrasound examination, a technique in which ultrasonic waves are bounced off the fetus and viewed on a television screen, twin pregnancy can be detected as early as the seventh week of gestation. Recent reports of first-trimester ultrasound examinations indicate that far more twins are conceived than are ultimately born. This phenomenon is known as the "vanishing twin." That is, one of the twin embryos is lost during the first trimester of pregnancy. Harris J. Finberg and Jason C. Birnholz, Harvard University Medical School, Peter Bent Brigham Hospital and Boston Hospital for Women, Boston, Massachusetts, examined 19 women with first trimester bleeding. In 14 they found double sacs indicating a twin pregnancy. Ten of these 14 pregnancies resulted in single births.[6] The actual incidence of vanishing twins is difficult to estimate because first-trimester ultrasound examinations are not routine. However, in a review of nine studies on vanishing twins, Helain J. Landy and colleagues, Northwestern University Medical School and Center for Multiple Births, Chicago, Illinois, found "disappearance" rates ranging from 0 to 78 percent.[7]

Maternal inheritance of the tendency to produce DZ twins is generally supported by the research literature. However, there are conflicting reports concerning whether or not women are genetically predisposed to MZ twin births or whether there is a paternal genetic contribution to twinning. The work of P. Parisi and colleagues, School of Medicine, First University of Rome and the Gregor Mendel Institute for Medical Genetics and Twin Studies, Rome, supports both of these possibilities. They found the incidence of twinning to be much higher than average among maternal relatives of both MZ and DZ twins, and also significantly elevated among paternal relatives of DZ twins.[8]

But the stable frequency of MZ twin births around the world suggests that it is a "random" event.[3] Although the precise mechanism for MZ twinning is unknown, M.G. Bulmer, lecturer in biomathematics, University of Oxford, England, notes that one suggestion is that it results from a retardation of the zygote's growth, usually within 10 days of conception.[9]

In MZ twinning, the timing of the single zygote's cleavage into two separate zygotes can be determined by the type of placenta and membrane structure found at birth. The placenta establishes a vascular connection between the mother and fetus through the umbilical cord. Two membranes contiguous with the placenta surround the embryo—the outer chorion and the inner amnion. Each forms at different stages in the developmental process. Doubling of the placenta, chorion, *and* amnion indicates that the zygote split sometime between the first and fifth days after conception. Gerald Corney, Medical Research Council (MRC) Human Biochemical Genetics Unit, Galton Laboratory, University College London, reported that 20 to 30 percent of MZ twins fall into this category.[10] A single placenta and chorion, but double amnion, indicate that the separation took place between the 6th and 9th days. The majority of MZ twins show these features. A single placenta, chorion, *and* amnion indicate that the cleavage occurred between the 9th and 10th days following conception. Ian MacGillivray, University of Aberdeen, Scot-

land, reported that single-amnion twins occur in only three percent of MZ pregnancies.[11] Further delay in cleavage results in conjoined or Siamese twins, which occur in about 1 of every 400 MZ births.[9]

The case for a hereditary factor is stronger for DZ twinning than for MZ twinning. Several investigators have discovered an association between the conception of DZ twins and maternal height and weight. According to Grace Wyshak, Harvard University Medical School, mothers of DZ twins are relatively taller and heavier than mothers of either singletons or MZ twins.[12] These differences in height and weight, which are strongly influenced by genetics, suggest a genetic influence in DZ twinning.

But Wyshak's finding can also suggest the involvement of a nutritional factor.[12] That is, better fed and, therefore, heavier women may have an increased chance of conceiving DZ twins. D.M. Campbell and colleagues, University of Aberdeen, and Robert Gordon's Institute of Technology, Aberdeen, tested this nutritional hypothesis.[13] They compared mothers of various weights and from different social classes who gave birth to twins. The researchers found no difference in the incidence of twinning between the social classes. Instead, the data support a genetic tendency for taller and heavier women to produce DZ twins.[13]

Hormonal differences between mothers of DZ twins and those who bear singletons also indicate a genetic predisposition for DZ twinning. In a 1964 paper, Samuel Milham, then of New York State Department of Health, Albany, suggested that mothers of DZ twins may have increased levels of pituitary gonadotropic hormones.[14] Pituitary gonadotropins, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), are responsible for ovulation, that is, the maturation and release of the egg from the ovarian follicle. Thus, higher gonadotropin levels may increase the chance of multiple ovulation and result in a higher incidence of DZ twinning. In fact, physicians induce ovulation in some women who have difficulty conceiving by artificially increasing their gonadotropin levels. Most of the recent headline cases of quadruplet and higher-multiple births refer to women under such treatment.

Differences in blood levels of FSH correlate with the variable rates of DZ twinning between the ethnic groups mentioned earlier. For example, Nylander reported that, *on each day* of the menstrual cycle, FSH levels are higher in Yoruba mothers of DZ twins than in Yoruba mothers of singletons.[4] This finding is unusual because FSH levels peak just before ovulation, although they are also high at the early stage of the menstrual cycle when the follicle begins rapid growth. In a multi-institutional study comparing US women who have had two sets of DZ twins with mothers of singletons, Nicholas G. Martin and colleagues, Medical College of Virginia, Richmond, found higher FSH levels in the DZ mothers in this early phase of the menstrual cycle.[15] In Japanese women, who have a very low rate of DZ twinning, Hiroaki Soma and colleagues, Tokyo Medical College, found low FSH levels in *all* stages of the menstrual cycle compared with mothers of singletons in both the US and Nigeria.[16]

Differences in hormone levels may also explain why older women are more likely to bear twins than younger women. The incidence of DZ twinning is highest in women between the ages of 35 and 39.[17] However, if a woman is a twin herself, or the sibling of twins, the tendency to produce twins remains high even until age 44.[17] Pituitary gonadotro-

pins, particularly FSH, are reported by Francisco I. Reyes and coworkers, University of Manitoba, Canada, to be present in greater quantities in older women.[18]

Another factor that predisposes women to produce DZ twins is parity, or the number of live children born. For example, Gordon Allen, Division of Biometry, National Institutes of Mental Health, Rockville, Maryland, analyzed data from 50,000 pregnancies. After correcting for the increase in twinning that is associated with age, he found that the frequency of twinning rises with the number of children born.[19] This finding may be related to an enlargement of the anterior pituitary with successive pregnancies, in addition to this gland's natural enlargement with age.[20] The anterior pituitary produces the gonadotropic hormones responsible for ovulation. Thus, the effect of more frequent twin conceptions with an increasing number of pregnancies might be explained as a fertility phenomenon. But R.G. Record and colleagues, University of Birmingham, England, found results of more direct tests for greater fertility in twin-prone women to be negative.[21]

Compared to a single pregnancy, certain physiological changes associated with multiple pregnancy can confuse an early diagnosis. For example, as early as the first trimester, twin pregnancy is characterized by a weight gain larger than that expected for a single pregnancy.[11] In a single pregnancy, such weight gain could be mistaken for an early sign of pre-eclampsia. Pre-eclampsia is a condition in which the maternal diastolic blood pressure increases to 90 mm Hg or higher after the 26th week of gestation. More will be said about pre-eclampsia later.

Certain maternal blood-composition values are also different between twin and singleton pregnancies. According to Chester Martin, Catholic University, Radboud Hospital, Nijmegen, the Netherlands, twin pregnancy is characterized by a 50 percent greater increase in blood plasma volume compared with a single pregnancy.[22] This is a necessary physiological adaptation to the transport of nutrients to two fetuses, and it may cause anemia, a common problem in multiple pregnancies. An increased alpha-fetoprotein (AFP) value is also not unusual in twin pregnancy.[11] However, in a single pregnancy, elevated AFP may indicate neural-tube defects or malformation of structures related to the central nervous system of the fetus. J.P. Neilson and colleagues, Queen Mother's Hospital, Glasgow, Scotland, recommend ultrasound examinations to investigate the possibility of fetal abnormalities in all cases of elevated AFP.[23]

Ultrasound examination is frequently recommended as a tool for the early diagnosis of multiple pregnancy. By using ultrasound, a multiple pregnancy can be diagnosed as early as the first seven to eight weeks of gestation. By the 7th week, gestational sacs can be seen, and by the end of the 12th week, fetal heads are visible.

According to Joseph G. Schenker and colleagues, Hadassah University Hospital and the Hebrew University, Hadassah Medical School, Jerusalem, a reliable clinical diagnosis of multiple pregnancies can be made only in the latter part of the second trimester.[24] The uterus in a multiple pregnancy, as measured from the top of the uterus to the pubic bone, is larger than expected for gestational age. But a significant size difference is not noticeable before about 12 weeks.[25] Other clinical signs of multiple pregnancy include detection by the mother of increased fetal activity and a larger than normal accumulation of amniotic fluid, a condition, according to Ralph C. Benson, Oregon Health Sci-

ences University, Portland, that is 10 times more common in multiple than single pregnancies.[26] Palpation of the abdomen may also reveal a head that is small in relation to the expected size of a single fetus. Twin pregnancy is also indicated when two separate fetal heartbeats are found, with different rates and at separate points.[25] Fetal heartbeats can be heard as early as the fifth month of gestation by placing a specially adapted stethoscope on the mother's abdomen.

Early diagnosis is essential because complications are more common in twin pregnancies than in those producing single babies. One of the most common problems is pre-eclampsia. Pre-eclampsia is associated with a higher risk of perinatal mortality, that is, death around the time of birth, and of fetal growth retardation. A study by Xavier De Muylder and colleagues, Hôpital Notre-Dame, Montreal, Canada, examined 220 twin deliveries for the years 1969 to 1974. They found a threefold increase in the incidence of pre-eclampsia compared with singleton pregnancies.[27]

In general, twins are more likely than singletons to die around the time of birth. For example, Milada Zahalkova, National Health Institute, Cernopolni, Czechoslovakia, estimates that twins are 11 times more at risk of perinatal death than singletons.[28] Premature birth accounts for much of this increased risk of perinatal mortality for twins. Luigi Gedda and colleagues, Gregor Mendel Institute for Medical Genetics and Twin Studies, reported the time of gestation for twins to be about 20 days shorter than for singletons.[29] In a 1982 study, F. Puissant and F. Leroy, St. Pierre Hospital, Free University, Brussels, Belgium, found that death in twins born between 29 and 38 weeks of gestation was usually due to respiratory distress and cerebral hemorrhage associated with low birthweight.[30] And 50 percent of stillborn twins delivered after 38 weeks were already decomposed or macerated, indicating that death occurred several days before delivery. Death may have been prevented by artificial termination of the pregnancy at 38 weeks.[30] More will be said about the causes of premature delivery later.

Perinatal mortality in twins is also associated with birth order. In a study of 575 twin deliveries, Puissant and Leroy found the mortality rate for second-born twins to be about 1.4 times that of first-born twins.[31] The second baby is primarily at risk of oxygen deficiency due either to a premature separation of the placenta from the uterus after the birth of the first baby or from reduced placental circulation. The longer the interval between births, therefore, the greater is the threat of oxygen deficiency if a problem exists.

This interval is affected by the position of the second fetus in the womb. Second-born twins are frequently oriented in a breech or transverse position,[31] rather than the normal cephalic presentation in which the head enters the birth canal first. Consequently, the second-born twin faces the possibility of a more traumatic birth.

In addition to their increased risk of perinatal mortality, twins are more likely than singletons to suffer congenital malformation.[31] But this risk is limited *only* to same-sex twins who are most likely MZ. Peter M. Layde and colleagues, Centers for Disease Control and Georgia Mental Health Institute, Atlanta, examined the association between birth defects and same-sex twins.[32] They found that these twins have about a 50 percent greater chance of congenital malformation, including gastrointestinal defects, genital anomalies, and neural-tube defects. Same-sex twins also had an increased incidence of cardiovascular

malformation when compared to singletons.[32] A similar study by J. Burn, Institute of Child Health, London, and Corney found the risk of cardiovascular malformation in MZ twins to be approximately twice that of both DZ twins and singletons.[33]

About 90 percent of monochorional twins (twins sharing a single chorion) have some sort of vascular connection between the parts of the placenta supplying each fetus.[9] This can lead to the so-called "transfusion syndrome" in which one twin transfuses blood to the other through the vascular connection. Frank Falkner, University of Michigan, Ann Arbor, and Charles H. Hendricks, University of North Carolina, Chapel Hill, suggest that one-third of all monochorional twins may be affected.[34] As a result of this transfusion, the donor twin is small and anemic while the recipient is large and has an excessive amount of blood. Bulmer, in his frequently cited book *The Biology of Twinning in Man*, suggests that the transfusion syndrome is the main cause of increased mortality in monochorional twins.[9] These twins also run a risk of neonatal death due to cardiovascular complications.

Low birth-weight is another complication of twin pregnancy. Twins are usually born about two pounds lighter than singletons. Premature delivery is the main cause of their low birth-weight. A frequent cause of premature delivery is the early rupture of the fetal membranes. MacGillivray noted that this occurs more frequently in MZ than in DZ twins[35] and is most likely related to the structure of the membranes. Remember that MZ twins usually share a single chorion, sometimes even the same amnion, while each DZ twin is enveloped in its own membranes.

Another factor that contributes to premature delivery is an acute and excessive accumulation of fluid in the amniotic sac. This problem is more common in MZ twins, especially when the twins are males. MacGillivray reported that male twins comprise a greater proportion of preterm MZ deliveries than do females.[35] Warren Newton and colleagues, Northwestern University Medical School, Prentice Women's Hospital, Chicago, confirmed MacGillivray's finding.[36] They suggest that male twins, whether MZ *or* DZ, are unique in this respect. Usually, pairs of male twins have a greater combined weight than female or opposite-sex pairs at any gestational age.

Gedda and colleagues, mentioned earlier, suggest another possible cause of preterm delivery. The early delivery of twins of either sex may be due to an abnormal stimulation of the uterus caused by the increased load of two fetuses.[29] A multiple pregnancy is also characterized

Table 1: A selected list of organizations that provide information on twins.

Australian Multiple Birth Association
P.O. Box 105, Coogee
New South Wales 2034
Australia

Center for Study of Multiple Birth
333 E. Superior St.
Suite 463-5
Chicago, IL 60611

International Society for Twin Studies
Gregor Mendel Institute
Piazza Galeno 5
00161 Rome
Italy

International Twins Association
114 N. Lafayette Drive
Muncie, IN 47303

National Organization of Mothers of Twins Clubs, Inc.
5402 Amberwood Lane
Rockville, MD 20853

Twinline
2131 University Ave.
Suite 204
Berkeley, CA 94704

by increased fetal movement, which might rupture the membranes. In addition, increased concentrations of protein-like substances that mimic the effect of oxytocin may be present in twin pregnancies.[29] Oxytocin is a hormone that stimulates uterine contractions.

Although twins have low birthweights due to premature delivery, they eventually catch up to the normal growth and weight standards for singletons. Ronald S. Wilson, University of Louisville, Kentucky, found that during the first three months, twins make a dramatic jump in weight, gaining as much as five pounds. Only by the time they are eight years old, however, do twins reach the normal weights expected for singletons.[37]

As a consequence of the many potential complications and risks, twin pregnancies are often a financial burden for the family. Prenatally, the mother may be hospitalized for a longer period of time in anticipation of early labor and delivery. Postnatally, the low birthweight infants often require intensive-care nurseries and long-term hospitalization. In a study of the social costs of twins, Emile Papiernik, INSERM, Clamart, France, concluded that a twin pregnancy may be 10 times more costly than a single pregnancy.[38]

Clearly, more research into the special problems associated with twin pregnancies is needed. Early diagnosis is also essential to prevent the complications that delivery poses to both the mother and her twins. Table 1 lists some of the organizations devoted to twins. One is the International Society for Twin Studies, which is supported by the Gregor Mendel Institute for Medical Genetics and Twin Studies. The society promotes twin research and cooperation between scientists and also organizes an international congress every three years.

The society also publishes a journal, *Acta Geneticae Medicae et Gemellologiae—Twin Research*. The term "gemellologiae" is derived from the Latin root "gemel" meaning twin. Data from ISI®'s *Journal Citation Reports*® (*JCR*™), volume 15 of *Science Citation Index*® (*SCI*®), 1983, confirm that this journal is cited by researchers in a variety of fields such as anthropology, biology, genetics, developmental psychology, obstetrics and gynecology, and psychiatry. In short, twin research is not only a multidisciplinary research area, but it also has wide impact. In part two of this essay, we'll review what researchers in the behavioral and medical sciences have learned in their studies of twins.

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