NEWS, VIEWS AND COMMENTS

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Identical and Fraternal: When Words Mislead

Monozygotic (MZ) twins are not precisely matched on any measured trait, yet reference to such pairs as 'identical' persists. Even as we document or celebrate MZ co-twins' striking behavioral and physical similarities, it is their departures from synchronous development that so often engage investigators and gratify families. Specifically, MZ co-twin differences may environmental identify factors involved in physical growth and disease predisposition, findings that inform human developmental processes in general. Co-twins' variation in birth weight or fussiness can help mothers and fathers distinguish between young twins, allowing the individuality of each child to shine through. In academic lectures and in after-school playgroups, researchers and parents are often pressed to explain that identical twins are not identical in every way, or perhaps in any way. Intraclass correlations, even for traits with high heritabilities such as height, brain waves and even fingerprints never reach 1.0.

Unlike MZ twins that occur following zygotic division during the first two gestational weeks, dizygotic (DZ) twins result from separate fertilization of two equips. These non-identical or 'fraternal' twins come in three varieties: male-male, female-female and male-female. DZ female same-sex twins (myself included) lack answers as to why 'fraternal', rather than 'soronal', has been the label of choice. Twins and many others regret the persistence of this inaccuracy, especially because the unique biological and psychological circumstances of the different DZ twin pairs are well known to investigators and families. In an earlier issue of Twin Research I surveyed evidence that DZ female twins with twin sisters face a significantly higher risk of breast cancer than MZ twins, female twins with twin brothers, and singletons.² Differences in opposite-sex co-twins' physical and social maturity have involved some parents in difficult deliberations over common vs separate classrooms or schools for their two children. It may be time to seriously rethink the familiar terms - 'identical' and 'fraternal' - and to consider if, and what, revisions may help achieve consistency with scientific understanding. Continued dialogue among members of the International Society for Twin Studies (ISTS) may yield a formal statement calling for accuracy and uniformity of reference to twin types in the psychological and medical literature, as well as in non-scientific contexts.

Dr Geoffrey Machin's (GM) essay expressing these concerns, forwarded to Twin Research Editor Nick Martin and to me, provided the impetus for this column. Excerpts from his piece are presented below, followed by my commentary (NS).

Word meanings

'Frater' is the Latin for 'brother' and its use for female-female or female-male DZ twins is objectionable because it is prejudicial and demeaning to females. The only 'fraternal' twins are malemale twins (whether MZ or DZ) and the male twin of a male-female pair (GM).

'Fraternal' means brotherly, so this term does not apply to females from DZ same-sex and opposite-sex pairs. 'Sororal' appears a natural choice for DZ same-sex female twins, but neither term seems adequate for members of male-female pairs. This difficulty might be circumvented with proper qualification when referring to these twins, eg fraternal, opposite-sex twin pair; sororal, opposite-sex co-twin. Current reference to all DZ twins as fraternal is not necessarily 'prejudicial' or 'demeaning' to female twins, it is simply wrong. (NS)

General misunderstandings

Parents are completely confused about the use of the word 'identical' instead of 'MZ' because they interpret the word literally to mean 'absolutely identical in every detail'. This is the sense in which we all use the word in other contexts, and it is therefore true to state that there are no such entities as 'identical' twins. (GM)

Confusion surrounding the term 'identical' extends beyond parents to students, non-twin researchers, the public and twins themselves. One of my students recently protested that MZ twins with whom she was acquainted expressed some obvious behavioral differences. Twins' close friends and relatives are especially sensitive to co-twins' subtle differences, emphasizing these features to distinguish between them. Consequently, parental misdiagnosis of MZ twins as DZ is considerably more frequent than the reverse. Several years ago, I determined that mothers ranked fifth in accuracy among six methods of determining zygosity.³ The methods in order of most to least accurate (as determined by agreement with serological classification) were investigator's impression, dermatoglyphic analysis (total ridge count), physical resemblance questionnaire, dermatoglyphic analysis (discriminant function analysis, based on total ridge count and pattern type), parents' opinions and physicians' diagnoses as told to parents.

There is little understanding of the fact that co-twin differences in hand preference, body size and/or susceptibility to certain diseases does not discount the possibility of one-egg twinning. During a home research visit, a mother of MZ female twins very similar in appearance explained that her twins could not be 'identical' Note that the misperception that 'identical' twins are identical in every way is paralleled by another unfortunate term: 'mirror-image twin'. It is a common misunderstanding that some MZ twins are nearly complete physical opposites. The truth is that some MZ twins vary in the number and/or degree of the physical reversals they express, showing mirror-imaging effects in selected traits. (NS)

Sources of MZ co-twin difference

Genetic There are prenatal genetic, epigenetic and environmental effects on development that ensure that MZ twins are never 'identical'.4 Genetic discordances include: the most phenotypically discordant MZ twins who are the pump and acardiac twins of reversed arterial perfusion; these twins are always monochorionic (MC) and therefore always MZ. About 50% of acardiac twins have abnormal chromosomes, whereas the corresponding pump twins are usually normal. Heterokaryotypia is well known in MZ twins. Striking examples include cases where a 46,XY zygote maintains a 46,XY cell line, but there is also a 45,X cell line (as a result of postzygotic mitotic non-disjunction/anaphase lag). The resulting Turner-UIIrich twin has female gonads and internal and external genitalia, but is MZ to the male twin. MZ twins who are concordant for trisomy may be quite discordant for the phenotypic severity of that trisomy. Female MZ twins can show such different degrees of X chromosome inactivation that one has an X-linked genetic disease (such as Duchenne muscular dystrophy) whereas the other is guite normal. MZ twin males with X-linked mental retardation may show different expansions of trinucleotide repeats, resulting in different phenotypic severity.6 (GM)

A compelling case of MZ twin discordance for Turner Syndrome (XO) concerned a set of Italian triplets.⁷ One member of the male set was affected, but because she retained a Y chromosome in some cells she was expected to grow taller than other children with the condition, but not as tall as her brothers. A recent report from a hospital in Amsterdam described two MZ twin pregnancies in which co-twins showed discordance for chromosomal anomalies (Pair A: 46,XY and 47,XY + 21/46,XY; Pair B: 45,X/46,XY and 45,X).⁸ Consistent with the theme of the present paper, the title of this report was "Identical" Twins with Discordant Karyotypes'.

As indicated above, variations in X-inactivation patterns (lyonization) in MZ female twins is a source of difference that may not be fully appreciated.9 Only two of the Dionne quintuplets of Canada expressed X-linked color blindness, although all five MZ sisters carried the relevant allele.10 Despite the fact that MZ twins, whether concordant or discordant for physical conditions, tend to attract medical attention, there has never been a documented case of MZ female twin similarity for a major X-linked disorder.¹¹ The possibility that mutations in mitochondria may be associated with MZ co-twin differences also requires a closer look. Mitochondrial mutations have been found in the cells of some Alzheimer disease patients, a condition in which twins show 67-78% concordance.12,13 This possibility was also raised by an MZ male pair discordant for adrenoleukodystrophy (paralysis and sensory loss).14 Lastly, variation of a new mutation in the myelin protein zero (PO) in MZ twins with a demyelinating neuropathy is of interest.15 The twins' expressions of their disorder, consisting of delayed motor milestones and numbress of the limbs, differed. Proposed explanations included:

- somatic mutation prior to zygotic splitting, leading to mosaicism and different 'mutant loads' between the twins, or
- (2) unidentified external factors affecting PO gene expression.

Note that Dr Machin indicated that twins who are monochorionic are always MZ. A 1981 report urges cautious review of what twin researchers have come to regard as 'rules'.¹⁶ This case involved a normal male twin and a malformed female fetus produced by fertilization of the mature ovum and a polar body – most striking, however, was the presence of a single chorion. It was reasoned that the proximity of an egg and the first polar body during and after fertilization might have allowed implantation of the twins within a common trophoblast (tissue forming the wall of the blastocyst), leading to non-identical twins and one chorion. (NS).

Epigenetic Among the epigenetic effects are the observation that MZ twins are usually (though not always) discordant for major malformations. (GM)

It is also the case that major congenital malformations occur more often in twins than in non-twins across all anatomical regions. An excellent review paper, based on international data, is available.¹⁷ This survey does not, however, record the frequency of MZ twin discordance for each defect. (NS)

Environmental Prenatal and perinatal events include all the effects of monochorionicity on fetal growth and development. No one would deny that the donor and recipient of twin transfusion are MZ, but nobody could say that they resemble each other closely. And twin transfusion occurs in at least 10% of MC twins! It is notable that first-born twins of HIV-positive mothers are more likely to acquire HIV in the birth canal transit than are secondborn.¹⁸ (GM)

It is a common misperception among many professionals and members of the public that a shared intrauterine environment enhances twin similarity. This reasoning was inappropriately applied in a 1997 study in which it was argued that twins' prenatal circumstances have overestimated genetic influence on IQ.¹⁹ Preenvironments may affect natal intellectual development, but they do not increase co-twins' intellectual resemblance. Intrauterine processes (eg fetal transfusion syndrome, fetal crowding, and delayed zygotic division) are instead associated with MZ co-twin differences. In August 2000 I attended the annual Twins Days Festival, in Twinsburg, Ohio, where I encountered a rare, striking case of developmental discordance in 17-year-old MZ female twins. One twin showed normal, physical growth, whilst her co-twin had experienced deficient blood circulation during gestation, causing congenital gangrene and failure of the right leg to grow. A sonogram at 13 weeks revealed nothing remarkable, but it is suspected that some time later a blood clot lodged in the upper thigh, denying blood to that region. According to the twins' mother, twin-to-twin transfusion may have been the source of the blood clot. Her physician also informed her that congenital gangrene is extremely rare - he was aware of only approximately 85 such cases (including twins and non-twins) in the world-wide medical literature when the girls were born in 1983. The affected twin has been fitted with an artificial limb and engages successfully in various sports activities including first base position in softball. It is worth noting that the zygosity of these twins has never been determined scientifically. Their mother always believed they were DZ, due to her ease in telling them apart and because DZ twins occur in her family. There is room for disagreement, however, because the twins' striking physical resemblance (as judged by me) is clearly consistent with MZ twinning. DNA analysis is planned.

Bronson Price's (1950) classic paper may remain the best reminder of the varied influences to which MZ twin fetuses are uniquely subject. It is somewhat of a marvel that MZ twins are as alike as they are, on average, given their inauspicious beginnings.

Note that Cesarean-delivered firstborn twins and vaginally delivered second-born twins are at equal risk of contracting HIV infection from infected mothers.¹⁸ (NS)

Spectrum of MZ co-twin differences

Whereas these examples of discordance may be thought to be unusual, extreme, not representing the 'norm', I believe that they are the tip of an iceberg of many prenatal events that affect MZ twin development, making them considerably less than 'identical'. In varying degrees, often in rather subtle ways, they differentially affect development of all MZ twins. (GM)

Researchers recognize that DZ twins, like full siblings, are situated along a spectrum of genetic relatedness with some pairs sharing higher proportions of trait-relevant alleles

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than others. Parallel conceptualization of MZ twinning might anchor pairs as a function of relative within-pair similarity, with reference to genetic, epigenetic and/or environmental influences. It is no longer possible to recognize only two types of twins, MZ and DZ – twins may be better thought of as comprising two very broad categories each including numerous variants.

Appreciation of MZ co-twin differences associated with major traumas or unusual prenatal events is probably more widespread than the fact that many pairs express subtle, but significant, physical and behavioral differences. A current research interest among evolutionary psychologists is fluctuating asymmetry (FA), defined as departure from perfect body symmetry.20 Increased FA, as indexed by greater side-to-side differences in wrist circumference, facial width and other anthropometric measures, is believed to reflect greater developmental instability, linked to stressful biological and environmental events. Individuals with greater FA are judged less physically attractive and have fewer sexual partners (traits associated with reproductive fitness) than their more symmetrical counterparts. This work does, however, leave unanswered the extent to which reproductive fitness may be genetically influenced and the extent to which FA may be a valid marker for fitness. MZ co-twins offer an ideal solution to this question. A recent twin study found that lower FA twins were judged more attractive than their relatively higher FA co-twins.²¹ Further efforts, however, are required to determine if lower FA co-twins are more successful across various life history domains. However, the key point in the context of the present discussion is that the body symmetries and asymmetries of co-twins are not perfectly ΜZ matched. This research evidence supports the impressions of countless parents commenting on the slightly different head shapes, head sizes and other physical features of their MZ twin children. (NS)

Comments

MZ twins absolutely need to know that they are MZ, because of the (crucial) implications for concordance/discordance for QTL disor-

 \mbox{ders}^{22} and for transplantation. $\mbox{}^1$ The declaration of twin rights states that knowledge of zygosity is a birthright.²³ Let us therefore use the correct zygosity terminology. Twins and their parents are perfectly capable of understanding what zygosity means, and that MZ simply means derived from one zygote without any implication whatsoever that the twins will be 'identical' in the accepted sense of that word. To use the words 'identical' and 'fraternal' is probably more detrimental than not telling twins or their parents anything about zygosity. Let us tell them the precise truth as we know it. I think it is likely that the majority of twins and their parents throughout the world today are confused and misled because of imprecise terminology, as a result of which their zygosity is actually completelv unknown to them. The blame for this lamentable state of affairs can be laid squarely on the word 'identical'.

Not only should appropriate terminology be used in this professional journal of twin research, but we should also bend our energies to make sure that all other publications, whether professional or lay, use the correct terminology. In particular, the whole community (I nearly said fraternity) of twins and their parents should be encouraged to understand that we don't really mean 'identical' when we say 'identical', so let's not say it. (GM)

Given that knowledge of zygosity is important for twins, parents, educators, psychologists, physicians, attorneys and others concerned with twins' welfare and development, it is time to work toward mandatory zygosity testing for every same-sex twin pair. Newborn infants are routinely weighed, measured and screened for phenylketonuria (PKU), a procedure vital to their well-being and care, so a similar argument is justifiable for accurately classifying same-sex twins. Costs of DNA analysis are diminishing rapidly as technology improves, and because multiples still represent a minority of births costs to medical facilities would not be excessive. A temporary alternative would be to have zygosity diagnosis covered by health insurance plans, but this would still deny the procedure to families lacking such resources.

There are precedents for changing outdated or inappropriate scientific

terms and the case of 'selective mutism' (SM) is exemplary. (Twin studies of selective mutism were reviewed in an earlier issue of Twin Research.²⁴) SM is the failure to speak in some situations despite adequate speech skills in other social contexts. It affects approximately one in 1000 school children and occurs twice as often in girls as in boys.¹ It is regarded as a social anxiety disorder, not a language disorder. SM was first reported in 1877 by the German physician, Kussmaul who called it 'Asphasia Voluntaria', or voluntary mutism.²⁵ The name changed to 'elective mutism' in 1934 when, Tramer, a British physician, tried to convey the concept that children spoke to certain people, not to others. The disorder was labelled as such in both DSM-III and DSM-IIIR. Families with SM members objected that 'elective' mutism falsely implied a preference or deliberate decision by the affected person not to speak. Mutual efforts by researchers and relatives of SM individuals were ultimately responsible for changing the name to 'selective mutism', the term used in DSM-IV.

It is important to listen to individuals for whom terms matter. MZ twin, Scot Hollenbeck, is an Olympic and Paralympic wheelchair racer. (Disabled athletes participate in the Paralympic Games held two weeks after the able-bodied Olympic Games, in the same venue.) Scot was injured in an automobile accident at age 14 years, an event leaving him paralysed from the waist down. He and his twin brother, Sean, allowed me to feature their moving story in a chapter on twins' athletic skills.¹ In reviewing an early version of the text, Scot commented that it was crucial to distinguish between the Paralympic Games (a competition for disabled athletes) and the Special Olympics (a competition for mentally handicapped athletes, in which twins have also participated): 'There is great public confusion between [them]'. Again, it is important to listen to individuals with greatest knowledge of the terms in question.

Monozygotic (MZ) and dizygotic (DZ) would be accurate and appropriate as exclusive labels for the two types of twins. These terms capture twins' different biological origins, avoid the misimpression that MZ twins are exactly alike and are familiar to researchers everywhere. Early reference to uniovular and biovular twins might have also fulfilled these goals,²⁶ whereas Merriman's (1924) use of 'duplicates' and 'fraternals' would not have.²⁷

In conclusion, while emphasizing that MZ twins are not strictly identical, the striking behavioral and physical similarities they display should not be unappreciated. It can be argued that MZ co-twin resemblance is less impressive than their resemblance compared with other pairs of relatives. It remains fascinating that, despite the many factors working to carve out differences between them, MZ twins remain as behaviorally alike and as socially close as they are. (NS)

Biology of Twinning and Twin Biology

Genes for multiple birth

researchers New Zealand have recently identified a specific genetic factor associated with multiple birth.² Mutations in the gene GDF9B, located on the X chromosome, appear to affect twinning tendencies in sheep - a single copy of the allele enhances fertility, while two copies preclude fertility. This research is exciting for several reasons. It is the first time that a gene has been known to affect egg production directly, rather than via the pituitary gland. Furthermore, the same gene is present in mice, rats and humans, opening new avenues toward overcoming infertility. Additional scientific details about this study, conducted by scientists at AgResearch, are available.29

The work originated with a New Zealand ewe whose striking fertility changed her from an ordinary farm animal destined for slaughter to a valued research subject selected for science. I was reminded of a case in which an apparently infertile Friesian cow, inseminated with Charolais semen and placed near a Simmental bull, delivered superfecundated twins – the cow was scheduled for slaughter just prior to conception.³⁰

Weight loss

A vast body of human and non-human studies support genetic influence on the regulation of relative body weight.³¹ A unique analysis, targeted to genetic influence on the manage-

ment of body weight in obese female twins will, no doubt, become a significant addition to this literature, Fourteen pairs of MZ female twins, with an age range of 24-48 years, a mean body mass index (BMI) of 34.2 ± 7.8 weight and of 93.9 ± 21.2 kg, were recruited through newspaper advertising. The venue for the study was Charles University, in Prague, although the study involved investigators from both the Czech Republic and the United States. Patients remained in an inpatient hospital unit for 40 days during which time their dietary regimen and exercise program were carefully monitored. Subjects lost an average of 8.8 ± 1.9 kg of weight and 6.5 ± 2.3 kg of body fat. More interesting, co-twin correlations for changes in body weight ($r_i = 0.85$, P < 0.001) and changes in body fat $(r_1 = 0.99)$, P < 0.0001) were highly significant. Genetic factors, therefore, appear to be implicated in these measures. This study poses a striking parallel to one in which pairs of MZ male twins showed similar weight gains in response to overfeeding.

Ultrasound techniques

Fetal transfusion can lead to marked body size differences between affected MZ co-twins. The larger twin is at increased risk for heart damage, especially on the right side. In contrast, the smaller twin does not show heart damage, but may experience anemia. University of Pennsylvania researchers recently used fetal echocardiographical techniques to examine 39 twin pairs at 16-32 weeks gestation.³⁴ They demonstrated that in 59% of the cases, the larger co-twin did, in fact, show an enlarged heart. The current goal is to develop procedures to allow earlier detection of difficulties, given that fetal hearts are completely formed by 8 weeks.

Sports Prodigies, Internet Operators, Hard Legalities, Criminal Lives and the Twins Days Festival

Twins in Sports

Great MZ twin atheletes offer insights into the origins of athletic skill without diminishing the thrill of performance. The Olympic Games were two **(1)** 341 weeks away at the time of writing, so it was worth visiting the lives of some outstanding pairs.

Morgan and Paul Hamm, from Waukesha, Wisconsin have distinguished themselves as the first twins selected for the United States men's Olympic gymnastics team. (A pair of brothers competed together in 1956).³⁵ Paul ranked second in the selection process, while Morgan was selected by a committee to fill one of the last two positions on the six-member team. In addition to their athletic prowess, the twins exemplify the generous spirit characteristic of most MZ twins who train and compete together: 'We want to motivate each other. We want the other one to do well ... If I made it and he didn't, I'm sure he'd be happy for me, but we want to do this together'.

Note: the first source cited above referred to the Hamm twins as 'fraternal', no doubt because the twins believe this to be the case. The second source described them as 'cast members off the set of a Doublemint commercial', yet noted that one twin (Morgan) has a slight curve in the bridge of his nose. Given the rare blend of physical, intellectual and personality traits underlying élite athleticism, it is likely that the twins are MZ. The single photograph accompanying the written material on them is, unfortunately, inconclusive. Uncertainty surrounding their true zygosity is illustrative of a point made above, namely the need to perform diagnostic procedures on all twins soon after their birth. Knowing their true twin, type could significantly color viewers' judgments of their respective achievements in the Olympic games.

Aree and Naree Song Wongluekiet, from Bangkok, are only 14 years old, but they are ascending the ranks of élite female golfers.³⁷ The twins are currently second and third, respectively, in the national junior girls' ranking. Their sports career began at age seven as a way to spend more time with their father. He allowed them to play, challenging them to become the best in the world. They appear to be fulfilling this formidable goal.

Twins Online

MZ twins, Ali and Hadi Partovi, arrived in the United States from Iran at age 12.³⁸ Both twins received first

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and master's degrees from Harvard University in computer science, hoping for careers in a new technological field. Following graduation, they headed to Silicon Valley, CA where they have had numerous opportunities to apply their individual and joint talents. Their resumés include several examples of unusually cooperative business ventures. When Hadi headed Microsoft's Internet Explorer division he was denied admission to a Netscape meeting on browsers - so Ali attended in his place. When Hadi was offered a position at LinkExchange, he was not yet ready to leave Microsoft so Ali took the position instead, relying on his twin brother to complete a series of programming tasks.

The twins had attempted to enroll in different classes while at Harvard, but they found it too difficult to differ. They realized that their preferences and abilities were quite similar, leading them to careers that afforded the right level of excitement and challenge. It is likely that clever use of their twinship will continue, given their association with different, but closely located companies.

Separating conjoined twins

A British judge recently ruled that 2-week-old conjoined female twins should be surgically separated to save the life of one twin.³⁹ The twins, who are joined at the lower abdomen, share a heart and lungs. Neither twin would survive without medical intervention. yet the twins' parents are strongly opposed to sacrificing one daughter to allow the other to live. A solicitor acting on behalf of the families appealed against the decision.⁴⁰ A group in Italy offered the family free housing and medical treatment for the twins.⁴¹ A recent Court of Appeal Decision to Separate the twins was announced. The family decided not to appeal, saying they did their best for their children.42

These differing opinions underline the anguish families feel when confronted with such difficult decisions. Earlier prenatal detection and management of conjoined twins means that these dilemmas may be more frequent in the future. Assisting mothers and fathers in making informed choices remains a significant responsibility for members of the medical and psychological community. Discussion of the complexities posed by such cases is planned for the 2001 meeting of the ISTS in London.

The Krays

There is an incredible little volume documenting the activities and life histories of 12 twin pairs notorious for their criminal lives.⁴³ One such pair, Ronnie and Reggie Kray, were born to a poor family in a working-class London district. Teenage delinguency (which included various weapons) continued into the adult years, but a series of unlawful businesses (managed by members of the Kray gang) were added in adulthood. Their matched appearance made it easy to deceive police officers. The Krays became well known in London society following purchase of a club they named the 'Double R', an establishment that attracted individuals with wealth and celebrity.

One night Reggie murdered a man when his incompetence and disloyalty became clear. The ensuing 'trial of the century' produced 30-year sentences for each twin and a ten-year sentence for their older brother, Charles, who acted as an accomplice. Ronnie Kray died in Broadmoor mental hospital in 1995 after serving 26 years. It was recently announced that Reggie Kray would be released from prison, given that he had only a few years left to live. (He had been in jail for over 30 years.) However, he passed away on 1st October 2000 at age 66, suffering from terminal bladder cancer.4

Twins Days Festival

The 25th annual Twins Days Festival was held on 4-6 August 2000 in Twinsburg, Ohio. This event attracts several thousand twin pairs of all ages for participation in look-alike contests, games, research, celebration and more. I attended the festival for the first time this year and thoroughly enjoyed myself. Watching the twins move in tandem, chatting with parents eager for information and renewing relationships with twins from the past were priceless moments. I urge twin researchers to set aside part of one summer to witness this extraordinary gathering. It will remind you of why working with twins is exciting, informative and fun.

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