Twin Research and Human Genetics
Volume 18 ▌ Number 2 ▌ pp. 218–224 ▌ © The Author(s) 2015 ▌ doi:10.1017/thg.2015.6

NEWS, VIEWS AND COMMENTS

Insights From Twin Research: Conference at Royal Childrens Hospital, Melbourne, Australia / Twin Studies: Timing of Monozygotic Splitting and Commentary; Gestational Diabetes; ICOMBO'S Post-Partum Depression Study; Photographs of Conjoined Twins / Human Interest: Rare Quadruplets; Mistaken Identity on the Soccer Field; Prenatal Laser Surgery on Triplets; Twins Born to Prince and Princess of Monaco

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Highlights from a conference, 'Healthier Kids: Insights From Twin Research', held in Melbourne, Australia on December 5, 2014, are summarized. In addition to informative and exciting presentations and discussions of recent findings, three key themes emerged: (1) results from twin research have important implications for non-twins, (2) researchers from diverse disciplines should be encouraged to participate actively in twin research, and (3) investigators, twins and families need to work more collaboratively. Next, papers and studies concerning the biological bases of monozygotic (MZ) twinning, gestational diabetes and post-partum depression are reviewed. Finally, general interest reports of rare quadruplets, mistaken identity, prenatal laser surgery and a royal twin birth are provided.

■ **Keywords:** twin design, Melbourne twin conference, zygotic splitting

Insights From Twin Research: Conference at Royal Childrens Hospital, Melbourne, Australia

The modern, beautifully appointed Royal Childrens Hospital of Melbourne was the venue for the December 5, 2014 conference, 'Healthier Kids: Insights From Twin Research'. Located within the hospital is the Murdoch Childrens Research Institute (MCRI), a cutting edge center that conducts studies of infant, child and adolescent behaviors and medical conditions. The center was established in 1986 as the Murdoch Institute, supported by Dame Elisabeth Murdoch, her family and other prominent individuals. The

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FIGURE 1
(Colour online) DZ female and MZ male twin pairs from the same family. Photo by Dr Nancy L. Segal.

https://doi.org/10.1017/thg.2015.6 Published online by Cambridge University Press

conference was sponsored by the MCRI, Australian Twin Registry (ATR), Royal Children's Hospital of Melbourne, the University of Melbourne and the Royal Women's Hospital of Melbourne.

A primary goal of the conference was to highlight the extraordinary power of twin research designs for understanding the origins and development of human physical, behavioral and medical traits. However, the conference was unique in also inviting twins and parents of twins to provide input into the research process; for example, to identify areas needing attention and explain how research relationships can be facilitated among investigators, twins and families. Thus, a second primary goal was to enhance community involvement in twin studies. A session that brought researchers, twin pairs and parents together was a valuable addition that other conferences should follow. A photograph of young twins who attended the conference with their parents appears in Figure 1.

The conference began with introductory remarks by Dr John Hopper of the ATR, followed by comments from Kathryn North of the MCRI. The first scientific session, chaired by Dr Jeff Craig from the MCRI, included papers on the obstetrician's role in research, the neonatal genome, twin placentas and pregnancy, the life history of Chang and Eng, and fetal therapy in twins. The second scientific session, chaired by Dr Hopper, covered twin modeling and twin perspectives on epilepsy, language and literacy, bone health, dental characteristics and eye disease. Posters were available for viewing during the lunch hour. This was followed by a keynote address by Dr Nancy L. Segal from California State University, Fullerton, titled, 'Twins Raised Apart: The Science Behind the Stories'.

The afternoon session included a Forum and Discussion on what twins need from researchers, sponsored by the Raising Children Network and moderated by Dr Mark Umstad. The second part of the afternoon was organized into two simultaneously held sessions, one on Adolescence and the other on selected topics for Twins and Families. The Adolescence session, chaired by Dr Marc Seal, included papers on brain imaging and genetics, eating disorders, stability of DNA methylation, genomic studies and clinical trials. The session for Twins and Families (in which I participated) consisted of presentations on raising twins; the health of IVF multiples; the genetics of singing, language and speech; the individuality-twinship balance; and multiple birth challenges.

It is impossible to summarize the many findings and issues that were presented and discussed. However, key themes were (1) the significance of twin research findings for the general public, (2) the importance of involving clinicians and other medical specialists in twin research, and (3) the need to solidify ties between researchers and twins. Throughout the conference, the goal of more closely addressing challenges facing families with twins and other multiples was emphasized.

FIGURE 2

(Colour online) MZ twins Stepha Heller (left) and Annetta Able (right), with Dr Nancy L. Segal (center). Photo courtesy: Dr Nancy L. Segal.

The conference attracted considerable media attention. Participants were guests on a number of Australian television (Seven National News, Channel 7 Sunrise program, Nine Afternoon News, National 9 News) and radio programs (ABC 774 Victoria Breakfast Show, ABC National Radio World Today lunchtime current affairs program, ABC Radio National evening show, ABC podcast and Radio 3AW). Newspaper and magazine coverage included the *Sydney Morning Herald*, *The Age, Herald Sun*, the *Australian*, the *Adelaide Advertiser* and *The Australian Women's Weekly* (in print February 2015).

Personal Twin-Related Highlights

Prior to the conference, my last visit to Melbourne was in 2004. At the time I spent five days living with identical twin Holocaust survivors, Annetta Able and Stepha Heller (originally from Czecholslovakia) and Stepha's husband, Robbie, who has since passed away. The purpose of my visit was to observe these twins in a natural setting and to tell their life story in a book, *Indivisible by Two: Lives of Extraordinary Twins* (Segal, 2005). The twins were 79 years of age at that time. Fortunately, I was able to invite them and Annetta's son, Danny, to the 2015 conference 11 years later and to meet them all again for a long dinner, during which

https://doi.org/10.1017/thg.2015.6 Published online by Cambridge University Press

time we exchanged many memories. The twins remain as delightful and as interesting as ever. I believe that at age 90 they are the oldest surviving twins from that unspeakable time in human history. The twins and I are pictured at the conference in Figure 2.

Another highlight was meeting a mother and her identical twin daughters, Olivia and Grace, who had participated in my ongoing study of young Chinese twins adopted together and apart. (This study is conducted from a distance by means of local testers, mailed questionnaires and online surveys.) Spending personal time with twins and their families is gratifying because it lends substance and meaning to the quantitative findings. Another wonderful moment was sharing television time with reared-apart female MZA twins who had participated in the Minnesota Study of Twins Reared Apart (MISTRA). These twins were the very last pair I had assessed before moving to California.

There was also a surprise visit from a reared-apart DZA twin who had also been part of the MISTRA. She had heard about the conference on the radio that morning. Lastly, I was delighted to meet the daughter and granddaughter of another reared-apart female MZA twin who had been assessed in Minnesota. We had never seen each other before, but clearly shared personal interests in twins and twin research.

Interest in twins and twin research is high. A conference similar to the December 2014 meeting is being planned for 2015 in Sydney.

Twin Studies

Timing of Monozygotic Splitting and Commentary

Conventional wisdom is that the placentation of MZ twins is dictated by the timing of zygotic division. In general, most professional and popular sources on multiple birth indicate that early splitting (within the first 3 or 4 days post-conception) is associated with two chorions and two amnions, splitting between days 5 and 8, is associated with one chorion and two amnions, and splitting between days 9 and 14 is associated with the rare presence of one chorion and one amnion. It is also widely noted that zygotic division occurring later leads to incomplete separation of the two zygotes, eventuating in conjoined twins. However, as has been discussed in the journal *Zygote* by the Spanish physician Herranz (2013), this sequence of events is theoretical — not proven — yet is viewed as factual because of its plausibility. He calls these MZ twinning events 'the model' and urges serious rethinking of what actually occurs.

Herranz presents a fascinating discussion of the older twin literature, tracing how MZ twinning events (which no one has actually witnessed), came to be regarded as scientific truth. He cites a 1922 paper by Corner, in which Corner introduces the idea of timing as possibly significant in the origins and placentation of MZ twins. However, Corner did not consider timing with regard to double chorion-double amnion (DC-DA) MZ twins, because DC-DZ twins were considered to be dizygotic (DZ) at that time. Subsequent to this work, but also in the 1920s, Siemens showed that some MZ twins could be of the DC-DA type, a discovery that required refinement of Corner's efforts. Then, in the early 1930s, von Verschuer suggested that early zygotic cleavage could produce DC-DA MZ twins. Following further developments, Corner authored a 1955 paper, addressing the different timing-outcome associations, while still acknowledging the theoretical nature of the MZ twinning model. Nevertheless, the model adopted a factual nature in the years that followed, despite the absence of hard evidence.

Herranz explains the transition from speculation to science by three factors: (1) Corner was a prestigious researcher with many noted achievements, (2) the model was logical, and (3) Corner's original diagram and adaptations gave the model reality.

Herranz's paper will be informative and thought provoking for all twin researchers, regardless of specialization. Perhaps it will encourage investigators to question other twin-related 'facts' that have been uncritically accepted. In fact, Herranz proposes a theory of MZ twinning that was seriously challenged by the German researcher Denker (2013) in a later issue of *Zygote*. It may be time to reevaluate what we know about MZ twinning and how we know it.

I wish to thank Dr Roger Short of the University of Melbourne, in Australia, for bringing Herranz's (2013) paper to my attention.

Gestational Diabetes

Gestation diabetes mellitus (GDM) affects approximately 6–7% of pregnant women. The ideal cut-off for the glucose tolerance test is 130–140 mg/dl. However, the ideal cut-off level for women pregnant with twins has been uncertain because the usual physiological changes associated with pregnancy may be increased. In an effort to fill this void, a researcher from the Maternal Fetal Medicine Associates in New York City, and colleagues, studied 475 women pregnant with twins (Rebarber, Dolin, Fields, Saltzman, Klauser, Gupta & Fox, 2014). These participants were mostly not obese and Caucasian. Approximately half were of advanced age (mean = 34.1 years, $SD = 4.3$) and most had conceived their multiples via assisted reproductive technology (ART).

The study procedure consisted of a 1-hour glucose challenge test (GCT) with a 50-g non-fasting oral glucose load between 24–28 weeks gestation. Women whose GCT levels

https://doi.org/10.1017/thg.2015.6 Published online by Cambridge University Press

equaled or exceeded 130 mg/dl underwent a 3-hour 100-g oral glucose tolerance test (OGTT). Diabetes was diagnosed if two of four key values from this second test were abnormal. It was determined that a cut-off value equal to or greater than 135 mg/dl on the 1 hour, 50-g test was best. This value yielded 100% sensitivity and a 28.6% test positive rate.

ICOMBO'S Post-Partum Depression Study

Results from ICOMBO's (International Council of Multiple Birth Organisations) study of post-partum mood disorder (PPMD) are now available. The study, conducted between March 12 and August 1, 2014, included 5,207 mothers of multiples from 18 countries. Inventories were available in English, French and Czech. The majority of respondents (94.1%) had twins, while the remainder had triplets or more. Zygosity was assessed by asking parents if twins were identical or fraternal. Most multiple birth children (60.6%) were DZ, with the remainder being MZ and a small percentage unclassifiable. In the event of any misclassification it is likely that some MZ twins were judged to be DZ, partly because approximately one-third of MZ twin pairs have two placentas (see Ooki et al., 2004).

The study yielded a large number of findings so only a selected sampling will be presented here. Nearly one-third (31.5%) of the participants were affected by PPMD, the largest percentage (33.8%) diagnosed when their children were less than 6 months old. A family history of depression was indicated by over half (50.3%) of those affected. In a little over half the cases (57%) the diagnosis of PPMD was made by a family physician, with the remainder made by an obstetrician/gynecologist, psychiatrist or other health professional. A small percentage of women (3.4%) required hospitalization as part of their treatment. Most parents (94%) were able to care for their babies, yet problems with attachment, holding and playing were indicated. Contributing factors to PPMD were the stress of caring for more than one infant (81.8%), delivery complications (44.7%), financial difficulties (39.2%), marital problems (38.8%) and stress from caring for ill babies (23%).

The percentage of women affected with PPMD in the ICOMBO study (31.5%) exceeded the percentage (10–15% in the first year), as reported across 17 states by the Center for Disease Control (Brett, 2008). This discrepancy could reflect the volunteer nature of the ICOMBO sample. ICOMBO also noted that an important issue not addressed by their study was breastfeeding and its relation to PPMD. Clearly, PPMD is a significant condition that requires more focused medical attention to multiple birth mothers. Given that birth complications are generally higher for MZ than DZ twins, it would be valuable to have DNA testing performed on the twins to explore possible PPMD-zygosity associations. Additional information about the PPMD study and ICOMBO can be found at the ICOMBO website: http://icombo.org or by contacting chair@icombo.org.

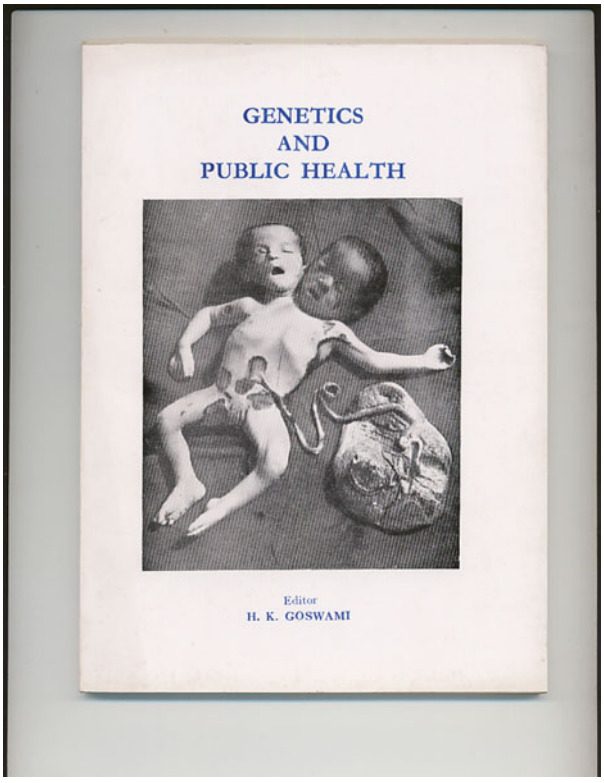

FIGURE 3

(Colour online) Dicephalic parapagus conjoined twins. Photo courtesy: Dr Hit Kishore Goswami.

Photographs of Conjoined Twins

Pictures of conjoined twins are informative with respect to their unique anatomy. The photographs reproduced in Figures 3 and 4 were provided by Dr Hit Kishore Goswami, retired and visiting Professor of Botany and Genetics, in Bhopal, India. The original photographs appear in a 1983 scientific proceedings, *Genetics and Public Health.*

Human Interest

Rare Quadruplets

Female quadruplets, Indie, Esme, Scarlett, and Evangeline, were born in August 2014 to Ashley and Tyson Gardner of Pleasant Grove, Utah (Wood, 2014). These multiples are rare because they are composed of two MZ twin pairs; note that this particular set yields four DZ twin pairs and a total

https://doi.org/10.1017/thg.2015.6 Published online by Cambridge University Press

FIGURE 4

Thoracopagus conjoined twins. Photo courtesy: Dr Hit Kishore Goswami.

of four triplets sets, based on combinations. The babies were conceived via in vitro fertilization. The quads were born 12 weeks premature, but their delivery was uneventful, with each newborn weighing approximately two pounds. The quadruplets and their family will be featured in an upcoming television series on TLC, scheduled to air in late 2015.

Mistaken Identity on the Soccer Field

An unusual, but understandable, referee error occurred in April 2014 during a soccer match between the amateur Italian teams SSD Castellano (ninth level) and GS Alviano (Daley, 2014). Identical twin Michele Rossi (number 7) was removed from the field by referee Cirillo for a foul that his co-twin, Matteo (number 9), had committed. The error occurred in the 27th minute of the game. Matteo, a striker, had put his team Castellano up 2 to 1, but fouled, leading to an argument between the two teams. It was during this commotion that the referee dismissed the wrong twin. The sporting judge, Marco Brusco, claimed that the error affected the game's outcome and recommended that the match be replayed.

Prenatal Laser Surgery on Triplets

A British woman, Laura Slinger, and her partner Martyn Halliwell, were expecting triplets that they had conceived naturally. The triplets were all female and two of them, Eilah and Elsie, were MZ twins; the third triplet was named Erin. Unfortunately, twin-to-twin transfusion syndrome was detected 17 weeks into the pregnancy, necessitating prenatal laser surgery. Such surgery to separate the blood supply between the MZ co-twins is not without risks, both during and subsequent to the operation. Even the third triplet who was not involved would be at risk if the procedure triggered an infection or early labor. However, no complications occurred and the triplets were born safely at the Liverpool Women's Hospital in October 2014, in England. Their weights were two pounds (Elsie), two pounds, twelve ounces (Erin) and three pounds, one ounce (Eilah). The babies were eventually transferred to Burnley General Hospital for monitoring and to be closer to home.

Twins Born to Prince and Princess of Monaco

Royal twins, Jacques and Gabrielle, were born on December 10, 2014, to Prince Albert and his wife, Princess Charlene of Monaco. They were born in the Princess Grace Hospital, named after the actress Grace Kelly, who was Prince Albert's mother. Forty-two cannon were sounded 2 hours after the birth, which is double the number for single births. Jacques and Gabriella are the first royal twins of Monaco and the second royal pair in the United Kingdom; the first pair was born to King James I and his wife, Joan Beaufort, in 1430.

Jacques is the future prince of Monaco. Had both twins been male, the firstborn twin would have had this role. Gabriella was born 2 minutes ahead of her brother, but the country's laws of succession recognize the firstborn son.

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