

NEWS, VIEWS AND COMMENTS

Highlights from the 15th International Congress of Twin Studies/Twin Research: Differentiating MZ Co-twins Via SNPs; Mistaken Infant Twin-Singleton Hospital Registration; Narcolepsy With Cataplexy; Hearing Loss and Language Learning/Media Mentions: Broadway Musical Recalls Conjoined Hilton Twins; High Fashion Pair; Twins Turn 102; Insights From a Conjoined Twin Survivor

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Highlights from the 15th International Congress of Twin Studies are presented. The congress was held November 16–19, 2014 in Budapest, Hungary. This report is followed by summaries of research addressing the differentiation of MZ co-twins by single nucleotide polymorphisms (SNPs), an unusual error in infant twin-singleton hospital registration, twins with childhood-onset narcolepsy with cataplexy, and the parenting effects of hearing loss in one co-twin. Media interest in twins covers a new Broadway musical based on the conjoined twins Violet and Daisy Hilton, male twins becoming famous in fashion, twins who turned 102 and unique insights from a conjoined twin survivor.

This article is dedicated to the memory of Elizabeth (Liz) Hamel, DZA twin who met her co-twin for the first time at age seventy-eight years. Liz and her co-twin, Ann Hunt, are listed in the 2015 Guinness Book of Records as the longest separated twins in the world.

Highlights from the 15th International Congress of Twin Studies

Budapest, Hungary was the site of the 15th International Congress of Twin Studies. The venue was the Danubius Flamenco Hotel. The Congress, held in conjunction with the 3rd Joint World Congress on Twin Pregnancy, is a biennial event. In addition to presentation of research findings, the meeting offered the important opportunity to honor the late Dr Louis Keith who passed away on July 6, 2014. Dr Keith's early efforts were largely responsible for the establishment

of the International Society for Twin Studies (ISTS) in 1974 and the international congresses that followed.

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There were many highlights of this meeting, so only a selected sampling can be provided here. The four-day congress opened with a ceremony that included remarks from the organizing committee: Giancarlo C. DiRenzo of Italy, Tim Spector of the United Kingdom, and Ruben Quintero of the United States. Introductions and overviews of Budapest were then presented by the doctors and identical twins, Adam and David Tárnoki and the Deputy Mayor of

Budapest, Dr Gábor Bagdy. Identical twins Lajos and Béla Barna then performed a duet of popular songs. Striking pictures of twins by the Hungarian photographer Imre Benkő were displayed throughout the auditorium. His impressive book, *Ikrek (Twins), 1982–2008*, published by the Hungarian Museum of Photography (2009; with a Foreword by Peter Baki and Dr Júlia Métneki), was available for sale and signing. Benkő's stunning achievements include the Bela



FIGURE 1

(Colour online) Deputy Mayor of Budapest, Dr. Gábor Bagdy. Photo: Nancy L. Segal.



FIGURE 2

(Colour online) Identical twin singers, Lajos (left) and Béla Barna. Photo: Nancy L. Segal.

Balazs Prize (1981), the Pulitzer Memorial Award (1991), recognized as the Meriton Artist of the Hungarian Republic (2004) and the Hungarian Photography Grand Prix Award (2009).

The opening night concluded with a lecture, 'Twins in History and Art', by Dr. Donatella Lippi, Professor of Medicine and History at the University of Florence, in Italy. Paintings of twin brothers in Greek mythology, Hypnos and Thanatos, and Castor and Pollux, were displayed and discussed. Twins were also depicted in the artistic works of Peter Paul Rubens and Paul Klee. Some productions showed conjoined twins, such as the famous conjoined pair, Chang and Eng. Professor Lippi noted that twins appear far more frequently in photographs than in paintings — perhaps a camera can more easily capture the fine details of twins' physical similarities and differences than a paintbrush.

A unique and fascinating session, 'Twin Studies in Central and Eastern Europe', was organized by the local hosts. The six papers were all presented by Hungarian investigators. The first paper by Adam Tárnoki noted that twin registries and/or festivals have been organized in the Czech Republic, Poland, Slovakia, and Croatia. However, there has been a general lack of ongoing twin research in Central and Eastern Europe, largely due to financial issues and the 'brain drain' following the Communist regime. A twin registry has been developed in Hungary after previous attempts in the 1970s. There are approximately 1,500 twin births occurring annually in Hungary. The second paper by David Tárnoki elaborated on the theme of twin registries, indicating that the current Hungarian registry has been growing since the mid-2000s. Twin studies in Hungary by Júlia Méteinek and Andrew Czeizel have spanned several areas, including congenital abnormalities and psy-

chosexual development. (Méteinek has published a stunning 2008 book on conjoined twins, *Egy vagy ketto? English: One or two?*) There have been some international research collaborations.

The third paper by P. Maurovich-Horvat discussed the heritability of coronary plaque morphology. He described a fascinating case of reared-apart MZ twins discordant for coronary plaque — the lighter twin had greater coronary plaque than the co-twin, most likely associated with smoking behavior. The fourth paper by A. Kovács described the first study on the inheritance of left ventricular malformation. Based on 22 MZ and 29 DZ twin pairs, it was concluded that genetic effects explain 94% of the variance. Additional studies will be needed to confirm this finding. The fifth paper by A. Pári and colleagues examined twinship from a sociological perspective, that is, experiential aspects of twinning. Among the findings were that females are more likely to utilize the advantages of twinship than males. The expected rank ordering of twin types regarding the significance of twinship (MZf, MZm, DZf, DZm, DZOS) was partly confirmed. The sixth paper by L. Littvay presented a comprehensive and informative overview of exciting future plans for the Hungarian Twin Registry. Littvay and his colleagues have gained access to identifying information for all Hungarian twins, and they will start by surveying those between the ages of 18 and 35 years. They plan to conduct surveys by cell phone apps to facilitate data collection.

A favorite session at ISTS congresses has been the Bulmer symposium on new developments in the biology of twinning. This session, hosted by N. Lambalk (Netherlands) and C. Derom (Belgium), included eight papers on MZ twinning mechanisms, chorionicity, endocrinology,



FIGURE 3

(Colour online) Hungarian twin registry investigators and local hosts, left to right: Adam Tárnoki, Levi Littvay and David Tárnoki. Photo: Nancy L. Segal.

twinning rates, genetic counseling, and GWAS studies. Selected findings are summarized here.

B. Reversade (Singapore) described a Jordanian family with 17 MZ twin pairs born within five generations. An allele in the ELA gene shared among family members and expressed within the inner cell mass is suspected of promoting MZ twinning. J. Craig (Australia) presented a case of naturally conceived monochorionic DZ twins. Their origin may be the fusion of trophoblasts, leading to a shared placenta and possible transfusion syndrome. T. L. Cutler (Australia) stressed the importance of helping parents understand zygosity and chorionicity. C. Derom (Belgium) presented data showing that MZ twins conceived via assisted reproduction have a higher ratio of single versus double chorions, compared with MZ twins conceived naturally or via ovarian stimulation. E. A. M. Kuiper (Netherlands) found elevated estrogen and progesterone concentrations among mothers of twins, relative to mothers of non-twins. Interestingly, at birth the twins showed lower concentrations of these hormones. T. Nielsen (Norway) emphasized the importance of considering past twinning rates in studies of current twinning rates. P.J.G. Zwijnenburg (Netherlands) noted the importance of including zygosity, heritability estimates, and specific phenotypes in genetic counseling with twins. C. Stern (UK) described biological mechanisms regulating MZ twinning. H. Mbarek (Netherlands) described

the first GWAS study for DZ twinning. Some suggestive SNPs associated with DZ twinning were found.

Other conference highlights included keynote lectures on Mendelian randomization (G. Davey-Smith, UK), latest developments in twin research (D. Boomsma, Netherlands), ultrasound and Doppler during the first trimester of pregnancy (G. Rizzo, Italy) and the microbiome (D. Ehrlich, France). A film, *Twin Sisters*, by Norwegian director Mona Friis Bertheussen, followed the lives of young reared apart Chinese twins, Mia and Alexandra. Pre-congress sessions on epigenetics, twin pregnancy and national multiple birth organizations were held on Sunday, November 16. A boat trip on the Danube River was memorable, especially the view of the Parliament.

It was announced that the entire collection of the society's journal, as it evolved from *Acta Geneticae Medicae et Gemellologiae* (AGMG, 1952–1998) to *Twin Research* (1998–2004) and finally to *Twin Research and Human Genetics* (2004 to the present), has been digitized. The series is now available online from Cambridge University Press (<http://journals.cambridge.org/action/displayJournal?jid=AMG>). In conclusion, the 16th International Congress of Twin Studies will take place in Madrid, Spain in October 2017. A one-day session on twin studies will be linked to the annual meeting of the Behavior Genetics Association, to be held in Brisbane, Australia in June 2016.

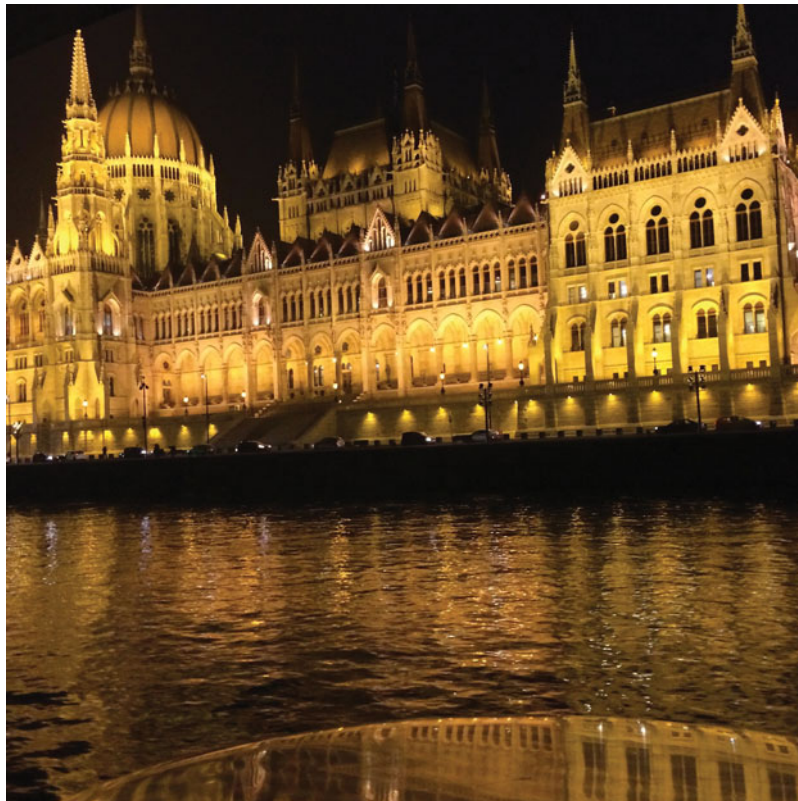


FIGURE 4

(Colour online) The Hungarian Parliament building, Budapest. Photo: Nancy L. Segal.

Twin Research

Differentiating MZ Co-Twins Via SNPs

Having a genetically identical (MZ) twin has medical advantages, such as access to a perfect donor in the event of organ transplantation or blood transfusion. Until now, a related, but problematic, issue was that paternity, criminality and other forensic situations involving twins could not be resolved because DNA at the scene matched two individuals, not one. However, Weber-Lehmann and colleagues (2014) at Eurofins Genomics Campus in Ebersberg, Germany have created a test that can distinguish MZ co-twins via DNA analysis. The procedure will be used for the first time in a Boston rape case involving identical twins, Dwayne and Dwight McNair, pending the judge's approval. Dwayne is the defendant (Bidgood, 2014).

The investigators developed a test based on whole genome sequencing and the identification of unusual de novo mutations. Participants included an adult male identical twin pair and the wife and child of one of the twins. The laboratory team was kept unaware of which twin was the child's father to avoid biased assessment. DNA was obtained from blood samples of the mother and child, and from blood, buccal mucosa and sperm samples of the twins. First, the twins' zygosity and parent-child paternity were confirmed by standard methods. (At this stage either of the twins could have been identified as the father.) Then, DNA from the twins' sperm sample and the child's blood was used to identify inherited germline/somatic mutations that occurred after the twinning event. Such mutations would only be present in the father and child. Ultimately, five SNPs were detected in the father and son, but not in the uncle (father's identical co-twin).

This is a ground-breaking study with important findings: (1) Rare mutations can arise soon after the blastocyst divides to create MZ twins; (2) These rare mutations can be transmitted into somatic tissue and the germline; (3) Legal cases involving MZ twins' paternity, criminality and other issues can now be resolved; (4) The fact that MZ co-twins are not strictly biologically interchangeable is underlined.

Mistaken Infant Twin-Singleton Hospital Registration

Many twins are born prematurely, sometimes requiring treatment in neonatal intensive care units (NICU). Deliveries under such circumstances can be chaotic, leading to errors in infant identification. A recent case at the Baruch Padeh Medical Center in Poria, Tiberias, Israel is exemplary in this regard (Kushir et al., 2014). Twins born at 24 weeks were admitted to the NICU and received life support. A midwife entered Twin 1's data into the hospital's informa-

tion system, but was called away for an emergency while entering Twin 2's data, leaving it incomplete. Twin 1 was issued a permanent ID number, whereas Twin 2 was issued a temporary ID number. It was determined that when the midwife returned she mistakenly added a third (virtual) baby to the system thinking that the incomplete data belonged to Twin 1. The data from Twin 2 and the virtual baby were merged, such that clinical orders for Twin 2 carried the ID number for the virtual infant. The error was detected when the neonatologist noticed that the permanent ID number of a clinical order was at odds with the demographic details of Twin 2 — the ID number belonged to the virtual twin. Failure to detect the error could have led to delays in treatment or administration of the wrong treatment. Data for each infant are entered on separate screens, increasing the chances for error.

Kushir and colleagues advise implementation of a system that assigns a permanent ID number to each newborn as soon as possible to avoid merging or updating patient demography. They also recommend the use of a Radio Frequency Identification (RFID) system that has been shown to reduce cost, increase patient safety, and improve medical services. RFID is a wireless non-contact system that uses radio-frequency electromagnetic fields to transfer data from a tag on a person or object for purposes of identification and tracking. The RFID system triggers an alarm if an infant has incomplete registration when transferred to the delivery room or to the NICU. As I indicated in my book, *Someone Else's Twin* (Segal, 2011), such devices can also help ensure that mothers receive the right baby at discharge.

Narcolepsy With Cataplexy

A rare case report of a young MZ female twin affected by narcolepsy with cataplexy is informative for two reasons: The patient had a healthy co-twin and the condition appeared in childhood (Ito et al., 2014). Thus, the co-twin discordance enabled the researchers to speculate on the presence of symptoms in one twin and the absence of symptoms in the other twin. This case also allowed the researchers to consider the implications of the young age of onset for diagnosis and treatment. Note that narcolepsy with cataplexy typically develops during the teenage years.

Narcolepsy is a sleep disorder involving daytime sleepiness and atypical wake-sleep cycles. Cataplexy involves sudden temporary loss of voluntary muscle function associated with emotional arousal; for example, anger or pleasure. The two conditions were observed in one member of a 7-year-old MZ female twin pair, although the symptoms

appeared at age 5; the condition was misdiagnosed initially. The twins' monozygosity was indicated by the presence of a single chorion. The twins differed considerably in weight, but not in height. These measures in the affected and unaffected co-twin were 121.1 cm and 33.2 kg, and 127 cm and 26 kg, respectively. Interestingly, the twins showed the same level of appetite. A Wechsler IQ test completed by the affected twin revealed an IQ score of 121, a verbal IQ score of 109 and a performance IQ score of 129. According to Ito et al., the verbal and performance IQ score difference was significant, as were the differences among the separate subtests. It was suggested that these scores reflected impairment of the orexin system, possibly explaining her cognitive performance. (Orexin neurons, which project from the hypothalamus to different brain regions, affect feeding, the wake-sleep cycle, metabolism and higher cognitive functioning.) Unfortunately, an IQ test was not administered to the unaffected co-twin.

The authors noted that the affected co-twin fell from her bed on two occasions at the age of 10 months, bruising her head. This was the only environmental difference detected between the twins that might have explained their discordance. Narcolepsy has a genetic component, although MZ twin concordance (5/16 pairs) is low. It was also noted that the condition was not diagnosed in the patient for two years, given its rarity in young individuals. The investigators urged more careful assessment of young children referred for excessive sleepiness.

Hearing Loss and Language Learning

A new study by Maria V. Kondaurova and colleagues in the Department of Otolaryngology at Indiana University

demonstrated that hearing loss in one twin affected the caregiver's speech to the other twin (Kondaurova et al., 2014). The study involved three pairs of twins: male-female twins, age 15.8 months, both with normal hearing; male-male twins, age 11.8 months, one with normal hearing and one with a hearing aid; and male-female twins, age 14.8 months, in which the hearing-impaired male twin had a cochlear implant. Mothers were recorded playing with their infants during three sessions over a one-year period. It was observed that speech directed toward the twins concordant for normal hearing was of lower pitch, showed more variable pitch and showed a greater range of pitch compared with speech directed toward the twins in the other pairs. In addition, speech directed to normal-hearing co-twins included more syllables, showed a faster rate and had longer utterances than that directed toward twins in the pairs with a hearing impaired twin. The investigators concluded that pediatric hearing loss in one co-twin affects parental speech to both co-twins. Analyses of vowel space and individually directed speech are planned for the future.

This case study is provocative, although more definitive conclusions must await additional study using larger samples. It is also unclear if the male-male pair was MZ or DZ; perhaps parents react in kind to MZ twins despite their hearing differences. This study has only been published as a 2014 conference abstract, making it difficult to judge the method and interpretation. However, it does call attention to the importance of parental interactions with unaffected twins across medical conditions. In particular, it recalls Bryan's (1983) observation that healthy twins can be disadvantaged to some degree, given parental investment in caring for their affected co-twins.

Media Mentions

Broadway Musical Recalls Conjoined Hilton Twins

The new Broadway musical *Side Show* opened to stunning reviews (Isherwood, 2014). It is based on the story of the real conjoined twins and 1930s vaudeville performers, Violet and Daisy Hilton. The original production played on Broadway in 1997, but did not attract a large audience and closed after only 3 months. I saw that production and thought it was excellent. I speculated that audience discomfort with a subject that, nevertheless, fascinated most people explained the play's failure (Segal, 2000). Seeing conjoined twins in the media places some distance between subjects and viewers that would diminish in live theater. It is, therefore, interesting to learn why the current production is considered a *New York Times* 'critics' pick'. Isherwood explains that the play touches on the universal desires of wanting to be like every-

one else (Violet) and being distinguished from the crowd (Daisy).

Daisy and Violet were joined in the pelvic region, allowing them to stand back to back (see Segal, 2000). As such they were pycopagus-conjoined twins — joined by a coccyx or sacrum, with two bodies duplicated normally (see Segal, 2000). They appeared as if a slightly angled mirror had been placed next to one individual. The twins, born in England in 1908, were abandoned by their mother. They were sold to 'Sir' as freaks for a production featuring an assortment of physically atypical individuals (e.g., a three-legged man). The twins were later noticed by a talent scout, who appreciated their beautiful voices and brought them the fame that at least one of them wanted (Isherwood, 2014). They passed away in 1969 (Keene, 2005).

High Fashion Pair

Four sets of siblings, including one twin pair, have been recognized as the ‘new band of fashion brothers’ (Ortved, 2014). The twins are Israeli-born Ariel and Shimon Ovadia, now 31 years of age, who grew up in Brooklyn, New York. They appear to be identical twins, based on inspection of photographs. In 2012, the twins were named one of the best new menswear designers in the United States. Their training comes from their work with *Magic Kids*, a line of children’s clothing owned and operated by their father. The twins’ chance meeting with clothing designer Ralph Lauren inspired them to pursue their interests and talents on a larger scale. One example of their innovation is the use of enamel for buttons on shirts. The twins’ creations were quickly noticed by members of the fashion world — they were finalists in the Vogue/CFDA (Council of Fashion Designers of America) Fashion Fund.

Twins Turn 102

Female twins Ruth Cox and Ruby Harris recently celebrated their 102nd birthday (Fox TV, 2014). The twins, who appear to be identical from photos, live apart. Ruby lives in Oswego Springs, Oregon and her twin sister Ruth lives on the opposite United States coast, but flew in for the party. The twins graduated from the University of Kansas School of Nursing in 1933. They attribute their longevity to avoidance of alcohol and cigarettes.

Human longevity has a modest but significant genetic component, estimated at 20–30% (Hjelmborg et al., 2006). Based on Danish, Finnish and Swedish twin cohorts born between 1870–1910, it was determined that genetic effects on the life span are minimal until age 60. Having an MZ co-twin survive to old age increases the chances that the other twin will also do so.

Insights from a Conjoined Twin Survivor

It is rare to hear the reflections of a survivor from an operation that sacrificed a conjoined identical twin sister (Downs, 2014). Gracie and Rosie Attard were born in Manchester in the United Kingdom in August 2000. Prior to their delivery, ultrasound scans revealed a conjoined twin pregnancy. The twins’ parents were devout Catholics and refused abortion. The twins, born via Cesarean section, shared their aorta, bladder and circulatory system. Gracie fared well, while Rosie did not; Gracie’s heart was pumping the blood that kept her sister alive. Physicians were convinced that both twins would die without surgical separation; however, they believed an operation would save Gracie, but not her sister. The Attards refused to allow such medical intervention, but were overruled by the courts. The twins were separated during a 20-hour operation and, as expected, Gracie lived and Rosie did not.

Gracie, now aged 14, has spoken publicly about her unique birth situation. She does not feel guilty over her sister’s death because it was not her decision. Still, she feels sadness at her loss and curiosity as to how similar she and her sister would have been had both lived. She gains strength from her twin’s memory during stressful times, such as when taking an examination.

The emotional significance of twin loss, either before or soon after birth, has been studied intensively by Woodward (2010). However, this type of loss may be unfamiliar to psychological and medical professionals outside the twin community. I would urge additional research and discussion of early loss from the twin survivors’ perspectives. Individuals wishing additional information on this topic may wish to read a very informative research article by Votteler and Lipsky (2005) that summarizes 10 conjoined twin cases, including physical, medical, and behavioral aspects.

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