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NEWS, VIEWS AND COMMENTS

Situs Inversus Totalis in Twins: A Brief Review and a Life History / Twin Research: Twin Studies of Trisomy 21; Monozygotic Twin Concordance for Bilateral Coronoid Hyperplasia; Prenatal Hormonal Effects in Mixed-Sex Non-Human Primate Litters; Insurance Mandates and Twinning After In Vitro Fertilization / News Reports: First Report of Identical Twin Puppies; Twins Sisters Turn 100; Remembering an Identical Twin Production Designer; New York City Marathon Quadruplets

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The presence of *situs inversus totalis* (full reversal of internal organs) in twins is briefly reviewed. Information gathered from 35-year-old monozygotic (MZ) female twin pair discordant for this condition is presented. This is followed by summaries of research on the frequency of trisomy 21 (Down syndrome) in twins, the first case of MZ twin concordance for bilateral coronoid hyperplasia, prenatal hormonal effects in mixed-sex non-human primate litters, and links between insurance mandates and twinning following in vitro fertilization. The final section of this article describes twin-related events reported in the news, namely, the first recorded birth of identical twin puppies; the 100th birthday celebration of a pair of fraternal female twins, the passing of an award-winning identical twin production designer, and the first running of the New York City Marathon by a set of quadruplets.

Situs Inversus Totalis in Twins: A Brief Review and a Life History

Situs inversus totalis is a rare condition involving dextrocardia (see below) and complete reversal of the internal organs (abdominal viscera). *Situs inversus partialis* involves the transposition of either the abdominal or thoracic viscera. *Situs inversus* is slightly more common in males than in females (Al-Jumaily et al., 2001). Situs anomalies occur in an estimated 0.001% to 0.01% of the general population (Akbulut et al., 2010).

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FIGURE 1

(Colour online) MZ twins discordant for *situs inversus totalis*. Tiffiny (left) is affected with the condition, while her twin sister Trissy is not. Photo credit: Dr. Nancy L. Segal

Given that about 25% of monozygotic (MZ) twins show opposite handedness, hair whorls and/or fingerprints, it is reasonable to assume that MZ twins are more likely than other individuals to show evidence of this condition. However, that is not the case — the reversals that some MZ twins typically show involve ectodermally derived traits (i.e., traits developed from the outermost cell layer of the developing embryo). The situation may differ for conjoined twins, some of whom do share some internal organs. In fact, it has been asserted that the incidence of *situs inversus* in conjoined twins (with and without cardiac fusion) is too high to be due to chance alone, and that *situs inversus totalis* may be a likely consequence of the twinning process (Layton, 1989). However, it is unlikely that conjoined twins would be complete mirror images of each other, due to the complex developmental events that give rise to them.

Situs inversus totalis occurs in about 6,000 to 8,000 live births (Supriya et al., 2013. It usually results from random developmental events, although a genetic effect has been suggested by its repeated presence in some families (Peeters & Devriendt, 2005; Silva et al., 2011; Abbasi, 2013). *Situs* inversus can occur with *dextrocardia* (base-to-apex axis of the heart points right) or *levocardia* (base-to-apex axis of the heart points left). *Situs inversus* with *dextrocardia* is really *situs inversus totalis* because the cardiac position, atrial chambers and abdominal viscera mirror the normal anatomy (Wilhelm & Holbert, 2016).

In October 2016, I was contacted by a 35-year old identical female twin who had been diagnosed as an infant with *situs inversus totalis* (SIT). Her twin sister showed no signs of the condition. I invited the twins to my laboratory for research activities, including comprehensive life history interviews. The twins' mother provided additional information during a birth history interview. The twins, Tiffiny (SIT) and her twin sister Trissy, are shown in Figure 1. Their monozygosity was confirmed by responses to a standard physical resemblance questionnaire.

The twins were born at 26 weeks' gestation to a 24-year-old mother and 23-year-old father. Their mother is of Filipino/Hawaiian background and their father is Caucasian, with Irish and French roots. The twins were the couples' last-born children of five, but their mother had experienced four miscarriages in between her successful pregnancies. The twin pregnancy was generally uneventful, although bedrest was required during the final 3 months. The twins were delivered by cesarean section and monitored in the neonatal intensive care unit of the Valley Presbyterian Hospital, in Van Nuys, California. Tiffiny weighed 2 pounds, 2 ounces at birth and was 13 inches long; Trissy weighed 2 pounds, 5 ounces and was 13.5 inches long. The twins were not discharged from the hospital until they were 2 months old.

The twins' mother, Coralee, and her husband learned of Tiffiny's SIT when she was 2 weeks old. Physicians informed them that there was 'good news' and 'bad news' — the good news was that the twins were very rare and complete mirror images of each other; the bad news was that their lungs and other organs were not well developed due to their prematurity. However, both twins survived and are currently healthy.

Coralee cannot recall exactly how it was determined that one of her twins had SIT. Most likely, it was discovered

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during the infant's early medical check-up when the doctor listened to her heart with a stethoscope. Coralee does recall that when Tiffiny was 2 years old she contracted pneumonia and had to return to the doctor for a follow-up x-ray. The technician, who was unaware of her SIT, was completely perplexed by the images he saw because they appeared in reverse. Coralee also explained that when Tiffiny is attached in standard fashion to an EKG monitor her readings appear in reverse — in her case, the electrodes need to be placed in the opposite position.

The family has no known history of *situs inversus totalis*. There are no twins in the family, with the exception of some very distant cousins whose zygosity is uncertain.

Tiffiny and Trissy are typical MZ twins in most ways. Tiffiny is 62.5 inches tall, just 0.25 inches shorter than her sister, and their weight is identical at 140 pounds. Both twins are married and both twins have children — Tiffiny has one infant son and Trissy has three children, two boys aged 4 and 13, and a daughter aged 7. Tiffiny experienced one miscarriage prior to conceiving her son, but her doctor assured her that having SIT should not interfere with her ability to have a family. Tiffiny is completely healthy and has never had any health problems possibly linked to SIT. However, she plans to start wearing a bracelet with information about her condition in the event of a medical emergency.

Tiffiny indicated that both twins are right-handed, but also that both of them do some things with their left hand. Therefore, it was of interest to see how these twins performed on a behavioral assessment of their handedness, using the 14 items from the Crovitz-Zener Handedness Questionnaire (Crovitz & Zener, 1962). Most right-handers score between 14–30, while most left-handers score between 41–70. The twins scored 21 (Tiffiny) and 17 (Trissy), so both were well within the right-handed range. Interestingly, when the twins worked at a bank, they observed that when Tiffiny counted bills she held them in her left hand and moved them to her right hand (as is typical of right-handers), whereas Trissy performed this task in reverse.

Tiffiny is currently a registered nurse, having obtained a B.S. degree at Indiana State University in Terre Haute, Indiana. Trissy attended community college and is a full-time parent. The twins share interests in singing and drawing, although they claim to have different levels of talent in these areas. They also share a very close social relationship with one another.

Several case reports of MZ twins with SIT (Uchenna et al., 2012; Supriya et al., 2013) are available in the literature. However, I am unaware of any recent systematic twin studies of *situs inversus totalis*.

Twin Research

Twin Studies of Trisomy 21

Most prior twin studies of trisomy 21 (Down syndrome) have assessed the frequency of the condition by means of extrapolated numbers, based on older data. A particular strength of a new study from the University of California, San Francisco is that researchers analyzed data from the California Prenatal Screening Program, gathered between July 1995 and December 2012 (Sparks et al., 2016).

Among the 77,279 pregnancies, 182 (0.2%) had at least one fetus affected with trisomy 21. Organizing the data by zygosity and maternal age showed: (1) a lower than expected incidence of trisomy 21 among the MZ twin pregnancies of women aged 25 to 45 years, and (2) a lower than expected incidence among the dizygotic (DZ) twin pregnancies of women aged 25 to 45 years (although the incidence was not as low as that found for the MZ twin mothers). The ratio of observed-to-expected incidences ranged from 20.4% (ages 25–29 years) to 21.0% (ages 40–45 years) for the MZ twin mothers and from 41.6% (ages 25–29 years) to 60.3% (ages 40–45 years) for the DZ twin mothers. However, an exception occurred among women aged 35 to 39 years who had delivered DZ twins, whose ratio of observed-to-expected incidence was 89.5%.

A lower than expected incidence of trisomy 21 among twins has been reported previously, especially among MZ twins. It may be that the added stress of a multiple birth combined with a genetic anomaly leads to spontaneous abortion, such that many cases go undetected (see Segal, 2000). However, the researchers also noted that incomplete ascertainment and estimated (as compared with confirmed) zygosity of the twins may have affected the findings.

A related issue is the rare occurrence of MZ twins *discordant* for trisomy 21. These pairs are estimated to occur in only 1/385,000 diagnosed cases. It has been suggested that mitotic nondisjunction followed by twinning might explain the discordance observed in these rare MZ twin pairs (Choi et al., 2013).

Monozygotic Twin Concordance for Mandibular Coronoid Hyperplasia

Researchers in the United Kingdom have reported the first case of mandibular coronoid hyperplasia (MCH) in a pair of 16-year-old MZ female twins of Afro-Caribbean origin (Khandavilli et al., 2016). MCH is a rare condition that involves a gradual reduction in the opening of the mouth. Explanations for its occurrence are uncertain, but increased activity of the temporalis (a large muscle associated with raising the lower jaw), hormonal effects, trauma, and various familial causes have been proposed. The condition can

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be present in unilateral or bilateral forms; the twins in question showed the bilateral form.

The twins experienced limited opening of the mouth and crowding of the teeth, complaints responsible for their referral to Birmingham's University Hospital. The physicians were able to rule out trauma, childhood illnesses, and family histories as underlying factors. The twins showed a similar skeletal-dental relationship, although some structural differences were noted. Surgical correction (bilateral coronoidectomy, i.e, bone projection removal) was a treatment option offered to them, but the twins preferred to undergo orthodontic intervention. This case is of particular interest because it suggests that genetic factors may be implicated in MCH. The researchers also cited a case of non-twin siblings concordant for the condition, noting that their resemblance was more consistent with environmental factors. However, sibling resemblance does *not* dismiss the role of genetic effects.

Prenatal Hormonal Effects in Mixed-Sex Non-Human Primate Litters

There has been ongoing interest in the effects of prenatal androgen exposure on the physical and behavioral development of human females. These studies were prompted by findings that female mice, rats and gerbils show increased aggressivity if situated between two males in utero. Another compelling finding is that female twin cattle become infertile if sharing the womb with a male co-twin. At the human level, a natural experimental design to test such hormonal effects is the study of opposite-sex twins. Research to date had been mixed — for example, increased sensation-seeking and elevated spatial skills have been observed among females with twin brothers, compared to females with twin sisters — however, these differences could conceivably be explained by social contacts between the male-female co-twins. Some studies, but not all, have reported somewhat delayed menarche in females with twin brothers (see Segal, in press).

A recent study to enter this research arena examined the effects of prenatal androgen exposure on females from seven primate species (Bradley et al., 2016). Behavioral and life history data were gathered from long-term captive breeding records and compared between the members of all-female litters and mixed-sex litters. Measures of reproductive success included female survival, reproductive success, timing of puberty and behavioral variation (aggression, scent-marking, sexual behavior). None of these measures were found to differ across the same-sex female and mixed-sex litters. In addition, there was no evidence of *CYP19A1* gene duplication, a mechanism thought to aromatize (convert) the male hormone testosterone into the female hormone estradiol.

The researchers concluded that the absence of masculinizing effects on females from mixed-sex litters has implications for why some species produce multiple litters, while others do not. The results may also inform the field of animal husbandry in that prenatal hormonal effects can affect the fertility of some commercial species. The researchers did cite some human male-female twin studies showing evidence of male hormonal influences on female co-twins as though the question was settled, but they did not mention findings that are slight or mixed. Many unanswered questions remain.

Mandated Insurance and Twinning After In Vitro Fertilization

The average cost of an in vitro fertilization (IVF) cycle in the United States is $12,400. Most insurance companies do not cover this cost, although eight states do have mandated insurance coverage for this procedure. It has been suggested that elective single embryo transfer may be a more frequent choice in states with a mandated insurance policy, given the risks of a multiple pregnancy. Studies have found conflicting findings regarding comparative multiple birth rates in states with and without mandated insurance, including reduction or no difference. Researchers at Duke University in North Carolina have argued that these inconsistent results come from failure to control for baseline patient characteristics, as well as to consider patient-level data.

Provost et al. (2016), using information from the Assisted Reproductive Technology Clinic Outcomes Reporting System (2007–20l1), found that the multiple birth rate was lower in mandated states (29.0%) compared with non-mandated states (32.8%). After controlling for participant age, this relationship remained statistically significant among women younger than 35 years who underwent embryo transfer on day 5. The rate of 5-day embryo transfer was also higher in mandated states. It was concluded that mandated insurance is associated with a reduction in multiple birth conceptions, due to single embryo transfer.

News Reports

First Report of Identical Twin Puppies (Hogenboom, 2016)

South African veterinarian Kurt de Cramer was delivering the litter of an Irish wolfhound who was in distress. During the course of a cesarean-section delivery he noticed an uncharacteristic bulging of her uterus. He made an incision and was shocked to discover two same-sex fetuses attached by umbilical cords to the same placenta. After delivering

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five additional puppies in the litter, he turned his attention back to the suspected identical twins. They did *not* appear exactly the same — white markings on their paws, chests and tails differed somewhat — but this did not rule out the possibility that they were monozygotic. For example, human identical twins can differ in height, weight, facial markings and other features due to differing prenatal events.

Analysis of DNA samples taken from the two puppies' blood at 2 weeks of age were consistent with monozygosity. DNA samples extracted from tissue at 6 weeks of age confirmed this result. In addition, the DNA profiles of the five other puppies differed from those of the suspected twins, but showed the expected level of similarity for littermates. The research team reported their findings as the first case of canine MZ twins — named Cullen and Romulus — but they did not dismiss the possibility that another such pair (or pairs) may have gone undetected in past deliveries. They pointed out that while the number of placentae would have been one less than the number of pups, the mothers often eat the placenta so the count would not have seemed unusual.

Twins Sisters Turn 100 Years of Age (Parker, 2016)

Twin sisters Phyllis Jones and Orene Crump celebrated their 100th birthday together on November 20, 2016. The twins, both widows, have been living together for the past 5 years in Stourport, Worcestershire in the United Kingdom. The twins appear to be dizygotic based on their different appearance in joint photographs taken over the years. They attribute their longevity to 'hard work and good food', but genes also play a role, especially at older ages (Hjelmborg et al., 2006). In fact, the twins had an older sister who passed away at age 92. It is believed that Phyllis and Irene are one of six British centenarian twin pairs.

Remembering an Identical Twin Production Designer (Grimes, 2016)

Most people have seen the film *The Wrong Man* (directed by Alfred Hitchcock), *Kramer vs. Kramer* (directed by Robert Benton), and *Heaven Can Wait* (directed by Warren Beatty), but they probably do not know that an identical twin production designer contributed significantly to these films' success. It was Paul Sylbert, who earned both an Oscar (for *Heaven Can Wait*) and an Oscar nomination (for *The Prince of Tides*), as well as a lifetime achievement award from the Art Directors Guild. Sylbert passed away on November 19, 2016, at age 88.

Film production for *Heaven Can Wait* was a collaborative effort between Sylbert and his twin brother, Richard. In fact, Richard Sylbert was a more noted film production designer than his brother, with film credits that include *Who's Afraid of Virginia Woolf* and *Chinatown*. Richard passed away in 2002 at the age of 73.

The Sylbert twins were born in Brooklyn, New York (McKinley, 2002). In addition to their fascination with film, both men were fly fishers and pipe smokers. They served together in the army and attended the Tyler School of Art at Temple University, in Philadelphia, where they studied painting. In 2004, Paul Sylbert began teaching in the school's film and media arts department (Grimes, 2016).

Quadruplet Marathon Runners

The 27-year-old Siemann quadruplets, composed of three sisters (Amanda, Maria and Jessica) and one brother (Brian), are believed to be the first quadruplers to compete in a New York City Marathon — they did so in November 6, 2016 (Pilon, 2016). The quadruplets were born in 1989, in Brooklyn, to Teresa Siemann (a nurse) and her husband John (who worked on Wall Street). The couple already had an older son, John Jr. The babies were delivered prematurely by 2 months, and weighed just nine pounds in total; there was no mention of fertility treatment. The quadruplets were healthy, although Brian suffered an injury to his spinal cord during his first few days in the neonatal intensive care unit and is confined to a wheelchair.

It was Brian's idea for the quadruplets to enter the marathon. Brian had been competing in Paralympic races, and his sisters had been running half marathons; running the full marathon, therefore, seemed to be a natural transition for both the sisters and their brother. Interestingly, the quads' parents did not especially encourage their children to engage in sport activities, but they all showed interest and promise in those areas, including their older son. Brian competed in the elite wheelchair competition, so he finished ahead of his sisters and would be there to welcome them as they crossed the finish line.

These fraternal multiples join a growing list of twins and triplets whose athletic talents took them to the 2016 Olympic Marathon in Rio de Janeiro, namely the identical German twins Lisa and Anna Hahner and the identical Estonian triplets Liina, Lily and Leila Luik.

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