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NEWS, VIEWS AND COMMENTS

Introductory Remarks

The scientific and popular appeal of twins and twin research guarantees a rich source of material for this column. I am grateful to Mike Miller for all the information he has provided on new discoveries. developments and resources that have become available during his tenure as contributor to this column. He has dispensed this knowledge with professional acumen and with good humor, setting a fine example for those who follow.

Behavioral aspects of intergenerational human cloning: twin-based perspective

The 1996 cloning of Dolly the lamb from a cell of an adult donor changed the prospect of adult human cloning from uncertainty to real possibility. Debates surrounding medical benefits and behavioral liabilities associated with adult human cloning were thus revitalized in many academic circles. Jurimetrics: Journal of Law, Science and Technology1 devoted space to comments from attorneys, physicians, ethicists and others following the 1997 National Bioethics Advisory Commission (NBAC) Report.² As a contributor to that special issue I had the opportunity to study the Report in detail. Commission members raised issues related to the revision of personal identities, interpersonal dynamics and family resemblances, but without benefit of the extensive psychological literature on experiential aspects of twinning, and twin studies of human behavioral

The following, adapted and reprinted in part from my 1999 book, *Entwined Lives*, and my 1997 article in *Juri*metrics,⁴ draws on the comprehensive body of twin-based findings and insights that are so crucial to informed discussion of human cloning's behavioral implications. It continues the cloning thread begun by Mike Miller in the December 1998 issue of Twin tical twinning results from sexual Research⁵ in which he summarized reproduction. It should be noted, how-

questions and concerns raised by President Clinton (who commissioned the NBAC Report) and Ian Wilmut, the Scottish researcher who cloned Dolly. Mike concluded humorously by noting that the wellknown domestic expert, Martha Stewart, volunteered herself as the first human to be cloned. He speculated that 'this may be a joke of her own, or maybe she truly wishes to have a second Martha to hang hand-made Christmas ornaments while she serves the cranberry steamed pudding'. In the autumn of 1997 I was especially amused by a front page photograph in a local Princeton, New Jersey newspaper showing five replicas of university president Harold T. Shapiro, Head of the NBAC and an identical twin himself.

The prospect of human cloning has been both a focus of fun and jest, and a source of alarm and fear. Fortunately it has also inspired some well reasoned discussion by scientists and others, as, for example, in Remaking Eden⁷ by Princeton University geneticist Dr Lee Silver, and in a paper by ISTS president Dr Elizabeth M Bryan.⁸ In my own reading of the issues I have been aware of insensitivity to important distinctions between clones and twins. I therefore begin with a closer look at how both have been defined and understood in science and the media.

Are twins clones? Are clones twins?

The assumed equivalence of twins and clones was evident in the NBAC's Report and has characterized most discussions of adult human cloning. I believe that these terms are not equivalent, and that identical (monozygotic or MZ) twins are clones, but clones are not identical twins. A clone has been defined as 'a precise copy of a molecule, cell, or individual plant or animal'. Identical human twins fit this definition since they form from the division of a single fertilized egg within the first two weeks after conception. (It could be objected that cloning results from asexual reproduction, while idenever, that human identical twins arise from a sexually produced zygote which then divides or clones itself.) In contrast, intergenerational clones (IGCs) are not identical twins because identical twins originate at the same time, they share intrauterine environments, and they are born at the same time, sharing familial and cultural events.

Note that I coined the term 'intergenerational clones' (IGCs) to convey the idea that adult human clones would be members of different cohorts. In an e-mail conversation with Dr Lee Silver. he suggested instead that the clonetwin distinction rests on semantics. His online dictionary offered two definitions of twins: i) one of two offspring born at the same birth, ii) one of two identical or similar people, animals or things. Adult human cloning would vield individuals whose relatedness would be consistent with the second definition, but not the first. Aside from the failure of clones to meet the three criteria listed above, identical twins, but not clones, may be subject to the vagaries of the prenatal environment (eg delayed zygotic splitting or fetal transfusion). I therefore believe that the twin-clone distinction goes beyond semantics, and prefer the term 'intergenerational clone' to 'delayed genetic twin' (which was used in the NBAC Report) because it allows for environmental events uniquely affecting the development of identical twins.

There are clearly variations on the three twinship features, such as prenatal death of one twin or separate rearing of twins from early infancy. These events do not, however, interfere with the multiple birth status of the individuals in question because these events follow natural twinning processes. IGCs are not characterized by any of the three criteria listed above, so while they do generate novel 'twin-like' relationships I do not believe that they can be classified as twins. The hypothetical situation of cloning a child to serve as a blood marrow donor for a terminally ill child would not create 'identical twins of different ages' as the NBAC's Report suggested, but would



create individuals who are genetically marriages between men and women the same. with children from former unions

Twins' social relationships

Most psychological twin studies demonstrate greater social closeness and affiliation between MZ twins than between fraternal (dizygotic or DZ twins). Social closeness does not, however, imply loss of individuality, and most identical twins enjoy their relationship and the emotional support, trust and understanding it uniquely affords. Some reunited MZ twins were concerned about loss of individuality prior to meeting their genetically identical twin, but admitted this concern proved groundless following reunion.

Individuation may be problematic for some identical twins, especially at adolescence when individuals may confront challenges to their identity and selfhood. Most identical twins emerge unscathed from these challenges. Unfortunately, a minority of identical twins with more severe personal identity struggles may offer the false impression that identical twins necessarily suffer individuation problems and/or are over-represented in clinical populations.

Fear of IGCs' diminished autonomy raised in the Commission's Report could be interpreted to suggest that reared apart twins might be better off never meeting, or (even more extreme) that identical twins should routinely be reared apart, but empirical observation reveals this is *not* the case. There are many recognized benefits associated with identical twinship, such as enduring companionship, sharing and assistance. The experiences of identical twins, both reared apart and together, offer a stringent test of the concern that identical genes might imply loss of a sense of selfhood. This does not occur among the majority of identical twins (who are naturally born in the same generation) where it might be more likely to occur than between IGCs born in different generations.

New family relationships

The nature and quality of family relationships generated by IGCs is unknown because this particular human kinship has never existed. Complex novel relationships have, however, been created through assisted reproductive technology (ART), and by

with children from former unions (blended families). Two investigations have found that adoptive parents and parents conceiving children through ART expressed greater warmth and emotional involvement with children, as well as greater satisfaction with parenting roles, relative to birth parents. Children conceived by ART did not differ from naturally conceived children in emotions, behavior, or quality of family relations. 12,13 These findings may reflect these parents' greater investment in and commitment to having children, although sample sizes were small and parental group differences might lessen as the young children in the study age. In the case of blended families, children may be required to adapt to new practices, and to altered relationships with parents and siblings, situations that can prove stressful. 14 Nevertheless, these childrens' outcomes depend on the quality of family functioning, as well as on their age and sex. Difficulties associated with this living arrangement come largely from changes in caretakers and caretaking routines, a situation that would not characterize IGCs.

In sum, the nature and quality of social relations between IGCs, and between IGCs and other family members remain speculative. Rejection of human cloning on the basis of uncertainty of outcomes does not seem defensible, although positive social outcomes among other unusual kinships may not offer sufficient justification for implementing cloning procedures.

Twin research on human behavioral traits

'Even identical twins... have different likes and dislikes, and can have very different talents.'

This statement in the Commission's Report (p. 33) warrants consideration with reference to twin research findings. It also seems somewhat contradictory to the thrust of arguments presented against human cloning.

Identical twins are less behaviorally alike than most people think. At the same time identical twins are more alike than any other pair of relatives. The greater similarity of identical twins reared apart vs fraternal twins reared together is compelling evidence that shared genes influence personality sim-

ilarity. One of the most surprising findings emerging from the behavioral genetic literature in the past decade is that shared environments do not conpersonality tribute to similarity between relatives living together. 15 This finding is somewhat counterintuitive, but tells us that common genes are responsible for personality similarity between relatives, and that environmental influences affecting personality development are those that individuals experience apart from their families.

The statement that identical twins are 'distinctly different' requires qualification. In the first place, identical twins do show personality similarity, as indicated by their average 0.50 correlation for most measured traits, but some individual identical pairs can be more alike than others. Psychologists studying infant twins observed that 'In each of these [four] identical pairs the personalities merged into a single picture... This merger could not be ascribed to similar appearance, for there was no difficulty in recording other identical looking pairs who exhibited some clear-cut differences.' An additional important point is that there is no evidence that personality similarity implies lack individuality.

The Commission's Report states (p. 67) that 'observers cannot help but imbue identical bodies with some expectation that identical persons occupy those bodies since body and personality remain intertwined in human intuition', which also deserves reappraisal. Research shows that parents' treatment of identical twins does not create behavioral similarities; rather, parental treatment is a response or reaction to twins' similar behaviors. Investigators have shown that parents of the most similar looking identical twins rated them *least alike* in behavior, relative to parents of other twins. 17 This suggests that parents may be sensitive to subtle differences in twins' behaviors that are not apparent to strangers, but also shows there is no necessary connection between similarity in physical attributes and similarity in behavioral traits. It has been pointed out that if more 'look-alike' identical twins receive more similar treatment than less 'look-alike' identical twins, this should not lead to more similar behavior because treatment does not affect biological functions underlying personality. 18 Furthermore, even when



parents misjudge twin type, their personality ratings of twins are consistent with true twin type. In other words, identical twins perceived to be fraternal are generally perceived to be as alike in personality as identical twins in general. Identical twins can, theresome perceived developmental differences.19

The greater average personality similarity of identical twins, relative to other individuals, suggests that the personalities of some pairs of IGCs would also be alike, although perfect correspondence would not expected. It seems to me that the key question is not whether the personalities of IGCs would be alike or not, but whether those who are alike might experience undue emotional or psychological distress because of it. There is no compelling evidence that identical twins who are more alike in personality than others are especially distressed; in fact every year thousands of identical twins gather at national and international conventions to celebrate their twinship and their likenesses. These findings may dispel some concerns not necessarily procedure.²⁰ raised over human cloning, but again justify

Nature via nurture or nurture via nature?

The statement that 'the extent to which human beings are shapers and creators of their personal and collective futures continues to be important and contested' (p. 48) should be addressed in light of what twin studies reveal about human behavioral development. Active-gene environment correlation, the concept that individuals seek out people, places and events compatible with their genetically-based abilities and interests, may explain the behavioral parallels between identical twins reared in separate environments. No one endorses the idea of a 'gene for rock climbing' or a 'gene for divorce', but both of these behaviors may be associated with genetically influenced risktaking tendencies or aggressive personality styles.

The old *nature* vs *nurture* debate was refashioned as the *nature-nurture* debate in the 1950s and 1960s, emphasizing that both sources of influence are involved. Bouchard et al later refined

this concept as nature via nurture to convey the idea that genetic factors are expressed 'by influencing the character, selection, and impact of experiences during development'. 21 More recently, Bouchard asserted that children's characteristics appear to drive their parents' fore, be behaviorally similar despite rearing practices, recommending 'nurture via nature' as another appropriate term for the melding of genes and experience in behavioral development.²² His more recent formulation captures the concept of reactive-gene environment correlation, the idea that parental treatment is largely guided by children's genetically influenced temperaments and talents.

The foregoing does not suggest that genetic influence on behavior denies or diminishes the free will of the individual who chooses to act or not to act. IGCs would enter different generations with different standards, values and opportunities, so differences in behavioral expression are expected. (IGCs may also differ in behavior due to errors in cell replication, despite their identical genes.) Identical twins reared apart, while part of the same generation, find themselves in different environments (sometimes in different cultures), yet they often end up being very similar in behavior. It is possible (even expected) that IGCs would also show some behavioral similarities, freely chosen and compatible with genetically influenced tendencies. Concern that human cloning reduces free will does not seem to follow from what is known about identical twins.

Comment

More informed discussion of behavioral issues can proceed once relevant data have been assembled. approach would be to systematically gather information on identical twins' own perceptions of their similarity and their views on how similarities affect their happiness, well-being and life choices. Another approach would focus on naturally occurring human models that mimic essential aspects of IGCs. For example, it should be possible to study similarity and social relations between same-sex siblings, 23 and between parents and children²⁴ who look and/or behave very much alike, but who differ in age. No doubt, dialogue and discussion will continue and it is my hope that behavioral issues will

move beyond speculation to rely increasingly on empirical evidence.

Notes

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- Segal NL. Entwined Lives: Twins and What They Tell Us About Human Behavior. Dutton: New York, 1999.
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- 6 Dr Wilmut has recently indicated interest in adult human cloning, reasoning that it might help control serious diseases; see www.nandotimes.com, January 20, 1999.
- 7 Silver L. Remaking Eden: Cloning and Beyond in a Brave New World. New York: Avon Books, 1997.
- 8 Bryan EM. A spare or a individual? Cloning and the implications of monozygotic twinning. Human Reproduction (in press).
- 9 It is virtually impossible, but theoretically plausible for two non-twin children in a family to inherit the exact same gene complements from their parents. This event would replay the results of adult human cloning, yet no one would think of calling such siblings twins.
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- 19 Scarr S. Environmental bias in twin studies. In: Manosevitz M, Lindzey G, Thiessen DD (eds). *Behavioral Genetics: Method and Research*. Appleton-Century-Crofts: New York, 1996.
- 20 Repeated references to behavioral differences between identical twins was somewhat perplexing: if identical twins are assumed to be different then concern over cloning should be less intense. It is possible that inattention to findings supporting genetic influence on behavior reflects the legacy of environmentalist perspectives prevalent since the turn of the century. Behavioral-genetic research did not join the mainstream of psychology until the early 1980s.
- 21 Bouchard Jr TL, Lykken DT, McGue M, Segal NL, Tellegen A. Sources of human psychological differences: The Minnesota Study of Twins Reared Apart. *Science* 1990; **250**: 223–228. This formulation of the nature–nurture controversy captures the idea of activegene environment correlation.
- 22 Bouchard Jr TJ. The genetics of personality. In: Blum K, Noble EP (eds). Handbook of Psychiatric Genetics. CRC Press: Boca Raton, 1997.
- 23 It is theoretically possible for fraternal twins and full siblings to share 100% of their genes, although a realistic range is 25–75%; see Pakstis A, Scarr-Salapatek S, Elston RC, Siervogel R. Genetic contributions to morphological and behavioral similarities among sibs and dizygotic twins: Linkages and allelic differences. Soc Biol 1972; 19: 185–192.
- 24 The remarkable resemblance between Isabella Rossellini and her late mother, the actress Ingrid Bergman, in both appearance and in voice is well known.

Insights on twin pregnancy and delivery

The greater birth risks of twins than singletons are well known so information that may reduce these risks is welcome news. Dr Barbara Luke and colleagues at the University of Michigan Medical School in Ann Arbor recently explored relationships

between twins' fetal growth rates and birth weights and mothers' weight gain during the early, middle and late stages of pregnancy. Not surprisingly, mothers who gained the most weight (25 lb by 20 weeks, 41 lb by 28 weeks and 53 pounds by 36 weeks) delivered higher birth weight twins (2541 grams, on average) than mothers who gained correspondingly less. For example, women who gained only 5 lb by 20 weeks, 13 lb by 28 weeks and 25 lb by 36 weeks delivered twins weighing 2270 grams, on average. The most intriguing result from this study was that mothers' early weight gain affected fetal growth rates during the middle and late stages of pregnancy. Specifically, maternal weight gain by 28 weeks had the greatest impact on fetal growth and birth weight, although weight gain by 20 weeks also made a significant contribution. These findings urge increased attention to diet and nutrition among women with multiple pregnancies. The original report of this study appeared in the American Journal of Obstetrics and Gynecology 1998; 179: 1155-1161.

Information on the labor progress of multiple birth deliveries has been poorly documented, leaving physicians to rely on partograms established for non-twin pregnancies. (Partograms are labor curves tracing the timing and degree of cervical dilation during delivery.) A new study conducted by Dr Eyal Schiff and colleagues at the Tel Hashomer Hospital in Tel-Aviv shows that revision of existing charts is necessary for more successful management of twin deliveries. The progress of labor was closely monitored for 163 twin deliveries and 163 non-twin deliveries in which women were matched for parity and age. Measurements included the length of the first stage of labor (interval between 4 and 10 cm, or complete cervical dilation) and length of the second stage of labor (interval between complete dilation and delivery). Twin deliveries showed significantly shorter first stages of labor than singleton deliveries (3.0 \pm 1.5 hours vs 4.0 ± 2.6 hours), although this was true only for nulliparous twin mothers. Possible explanations for this difference include the lower birth weight of twin than non-twin infants and greater uterine contractibility (and hence efficiency) in twin deliveries. The original report of this study appeared in the *American Journal of Obstetrics and Gynecology* 1998; **179**: 1181–1185.

Twins on and off Broadway

The 1997 Broadway musical Side Show revealed the personal and professional triumphs and defeats of Daisy and Violet Hilton, conjoined twins and 1930s vaudeville stars. The Hilton twins were pygopagus conjoined twins; they were joined in the pelvic region, allowing them to stand nearly back to back; it was as if a slightly angled mirror had been placed next to one individual. These twins, studied by psychologist Helen Koch in 1927, showed an intriguing catalogue of behavioral and physical similarities and differences. In fact, conjoined twins are proving to be surprisingly less alike than many people suppose. Their varied prenatal experiences, coupled with tendencies to differentiate psychologically, are most likely responsible.

Side Show opened to strong critical acclaim, promising a long run on New York's Great White Way, but this was not to be. 'What the audience won't watch' signalled news of the closure of Side Show after a brief run. Were audiences 'unwilling to see a musical about a subject they considered distasteful'? Did 'mass squeamishness over[ride] all the old barometers of good reviews'? I believe both suggestions by R Lyman in the New York Times of 4 January 1998 partly explain the show's collapse, reflecting the widespread view of conjoined twins as unnatural and troubling. Conjoined twins have fascinated people for years, but information on the printed page may offer a comfortable distance between readers and twins that live theater does not allow.

The Mütter Museum at the College of Physicians of Philadelphia maintains an extensive website with medical and historical facts about conjoined twins (http://zygote.swarthmore.edu/clcave4b.html).

The headline 'Double Play' in the *New York Times* Weekend Arts section of 8 January 1999 caught my attention. It announced the premiere on 19 January of Paula Vogel's newest comedy, *The*



Mineola Twins, starring actress Swoosie Kurtz. The play follows the lives of identical twin sisters, Myrna and Myra, from the Eisenhower presidency (1953-1961) to the Bush years (1989-1993). Kurtz plays the roles of both twins. This play is described as a funny tale of liberalism versus conservatism, and one that makes use of the good twin versus evil twin theme. This device has been common in literature and in theater arts for exploring opposing sides of issues, problems and events. It has also been applied to real life events, most notably in the 1996 case of California twins Sunny and Jeen Han. Jeen allegedly planned her twin sister's murder to assume her identity in order to erase her own checkered past. The good twin-evil twin distinction dissolved once we learned that Sunny had also been cited for credit card fraud.

It is unfortunate that the notion of good and evil twins persists beyond the fictional events for which it was probably intended. Most investigators studying twins are aware that identical twins' behavioral differences are often a matter of degree. To suggest that twins necessarily assume extremely contrasting roles vis-à-vis one another is misleading to twins and to their families.

The Mineola Twins opened on Broadway on 18 February 1999. For additional information see the following websites: www.nytoday.com/ scripts; www.playbill.com.

A little treasure could be found off Broadway last year. A young children's puppet show by the Netherland's Speeltheater, Nicky, Somewhere Else, told the life history of Nicky who became aware of his deceased twin Noël from a photograph. Ivan Gelder, the New York Times reviewer (14 May 1998) was impressed by the creativity and sensitivity with which this loss was presented. Research shows that loss of a twin is a devasting event to surviving twins. Most available studies have, however, involved adult participants so little is known about the immediate and long-term consequences of this loss in childhood.

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Growth disturbances in twins

Birth weight of twins is on average about 1000 g (30%) less than that of singletons. In addition, it often occurs that the difference in birth weight between the two of a pair is considerable. This latter phenomenon is ascribed to differential access to nutritional sources, which in turn has to do with differences in placental blood supply to each foetus and consequently with placental anatomy.

Italian investigators¹ have recently elucidated the possible role of umbilical vein endothelial cells in the aetiology of growth discordancy in twin pregnancies. They collected endothelial cells from the umbilical cords of five singleton pregnancies and from five dichorionic twin pregnancies, one pair being growth discordant (a relatively large difference). It appeared that endothelial cells from the smaller twin of all pairs showed increased fluidity compared with the larger twin, and especially so in the growth-discordant pair. Endothelial cells from the larger twins were more similar to those of singletons. These results lead the authors to the conclusion that foetal-foetal transfusion may be a causal mechanism in the aetiology of growth discordancy.

Physiologically, twin-twin transfusion syndrome in monozygotic twins, as manifested in growth discordancy, may result in congenital endocardial fibroelastosis in the larger of two monozygotic twins. Endocardial fibroelastosis is a diffuse patchy thickening of the mural endocardium, particularly in the left ventricle, due to proliferation of collagenous and elastic tissue. Histopathologist EJ Lazda of the University of Wales² has recently furnished evidence for the role of growth discordancy in the aetiology of endocardial fibroelastosis in the larger

Can a Caesarean delivery in multiple pregnancies be avoided?

The delivery of twins is considered to be a high risk event. A Caesarean delivery is in itself a risk which, if not necessary, is better avoided since the foetus may suffer from the anaesthetic. Obstetricians at Northwestern University in Chicago³ have tried to describe the factors which contribute to the risk of a Caesarean delivery and which of them can be influenced by the obstetrician, ie those factor(s) which could reduce the risk. They analysed 134 twin gestations of which 25 were delivered by Caesarean section and 109 vaginally. The investigators found that a Caesarean section was more likely in case of nulliparity (the first pregnancy of a woman) and that the timing of the epidural administration of analgesia is associated with Caesarean delivery. This latter risk factor can be influenced by the doctor.

Genes and eating habits influence fat distribution over the body

The ratio between waist and hip measurements (WHR) is thought to indicate the way total body fat volume is distributed over the body. Too much fat is generally considered a risk factor for cardiovascular disease. But the pattern of fat storage over several parts of the body, as expressed in WHR, is also a risk-modifying condition: abdominal fat (waist) contributes more to CHD-risk than fat around the hips. Total body fat volume results from the type and quantity of food intake as well as from inborn, genetic conditions. The relative contribution of either of these two factors has recently been estimated by epidemiologists at the US universities of North Carolina and South Carolina. 4 The investigators measured WHR in 680 female twin pairs, aged between 31 and 90 years. The analyses, corrected for Quetelet index and age, revealed that between 36 and 61% of the variance in WHR could be attributed to genetic factors, whereas individual differences in waist circumference were heritable for about 77%. Central adiposity (excess of waist fat) appeared to be associated with lower education, increased alcohol intake, cigarette smoking and low physical activity.

Perinatal mortality among spontaneous and IVF multiples

Canadian obstetricians⁵ have recently tested their conjecture that multiple pregnancies which are the result of assisted reproductive techniques (ART) have a lower probability of



perinatal mortality than pregnancies resulting from spontaneous conception. In a sample of 72 multiple ART gestations (56 twins and 16 triplets) and 124 spontaneous gestations (108 twins and 16 triplets) they found that ART-twins (not triplets) have significantly lower perinatal mortality than spontaneous twins. This effect might, according to the investigators, be due to a higher frequency of monochorionic placentation in the spontaneous conceived group of multiples. Perinatal morbidity, gestational age at delivery, as well as birth weight did not differ between the two types of multiples.

The genetics of longevity

Every-day experience seems to be that long life runs in families because of a common genetic makeup. The truth of this compelling pre-scientific impression was tested by Swedish gerontologists⁶ looking at mortality rates and within-pair similarity for age of death in a sample of 3656 monozygotic and

6849 dizygotic same sex twin pairs. An extra, interesting methodological feature in the sample was that 130 twin pairs happened to be separated at birth and reared apart.

Neither among pairs of which both members died relatively young, nor among long-living pairs, had the differences in age at death a genetic component. Taking the whole sample, a maximum of about 30% of the variance in longevity had to be ascribed to non-shared environmental conditions. And this conclusion was confirmed in a smaller analysis of the reared-apart twins only. This result suggests that individual life style may have a more profound influence on life expectancy than is generally assumed.

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