equilibrium network of their immune system (*22*), leading to autoimmunity or neoplasia, is intriguing but experimentally undetermined.

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11. The BrdU concentration in the conditioned medium was calculated as (disintegrations per minute of ^3H in 100 μl of conditioned medium divided by the disintegrations per minute of ^3H in 100 μl of 65 μ*M* BrdU) × 65 μ*M*. In this study the precise calculation was (630/183,800) × 65 μ*M* = 0.22 μ*M* BrdU.
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Genetic Studies of an Acardiac Monster: Evidence of Polar Body Twinning in Man

Abstract. *Two maternally derived chromosome sets and both maternal histocompatibility antigen haplotypes were identified in the tissues of a malformed triploid acardiac twin that developed within the same chorion as its normal twin. These findings indicate that the twins arose as a result of independent fertilizations, by two different spermatozoa, of a normal haploid ovum and its diploid first-meiotic-division polar body.*

Since the middle of the 19th century, twins have been categorized as either monozygotic or dizygotic. Monozygotic or "identical" twins arise from division of a single fertilized ovum and possess identical sets of nuclear genes. Dizygotic or "fraternal" twins are the products of simultaneous fertilizations, by different spermatozoa, of two independently released ova and are genetically no more alike than full sibs (*1*). Other types of twins may result from superfecundation (fertilization of ova by separate fathers during the same menstrual cycle), superfetation (sequential conceptions during successive menstrual cycles), fertilizations of separate ova from the same corpus luteum, or simultaneous fertilization of meiotic products of the same primary oocyte, such as an ovum and its first or second polar body (*2*). Evidence for the last mechanism emerged from the following case.

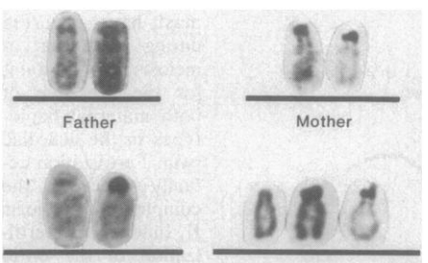

Fig. 1. Photograph of chromosomes 13 stained to show NOR heteromorphisms in the parents and twins. There is no visible silver staining at the NOR of either paternal chromosome 13, whereas there is positive NOR staining on both maternal chromosomes 13. Twin A has one chromosome 13 with positive staining and one without staining, as expected. In the cells of the triploid acardiac twin, two of the three chromosomes 13 show positive NOR staining, indicating that they are maternal in origin.

A 22-year-old primiparous black female gave birth to a normal male and his grossly malformed twin. Dissection of the malformed twin revealed holoacardius amorphus, an aberration of normal development that is found only in the twinning process (*3*). The twin placenta was monochorionic and diamniotic, with extensive vascular anastomoses between the small region supplying the acardius and the much larger region supporting the normal twin. All previously reported cases of human acardia have involved one member of a monochorionic twin pair, the single chorion being considered proof of monozygosity (*4*).

Lymphocytes from both parents and the normal twin, and skin and gut fibroblasts from the acardius, were grown by standard cell culture techniques (*5*). Chromosomes were studied after trypsin-Giemsa banding (*6*). The parents were cytogenetically normal, and the unaffected twin had a normal male (XY) karyotype. The acardiac twin had an essentially triploid XXX karyotype (*7*). Such sex discordance, remarkable in the presence of a single chorion, implied that the twins were derived from separate conceptional events involving different spermatozoa (*8*).

Additional genetic marker studies were performed to determine the parental origin of the extra haploid chromosome set in the triploid acardiac twin.

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Although cytogenetic marker studies with QFQ and C banding techniques gave results consistent with a diploid contribution from the mother, the parental mating types were such that none of these markers provided conclusive evidence of a maternal source (*9*). However, metaphase chromosome staining with ammoniacal silver revealed informative heteromorphisms of the nucleolar organizer region (NOR) in the secondary constrictions of group D and group G chromosomes (*10*). Counterstaining with quinacrine mustard dihydrochloride permitted unequivocal chromosome identification; NOR-stained chromosomes 13 of both parents and twins (Fig. 1) demonstrated that the acardiac twin received two of its three chromosomes 13 from its mother. The other group D and group G chromosomes also evidenced NOR staining consistent with a double maternal contribution to the acardiac twin.

Histocompatibility antigen (HLA) types A and B on the leukocytes of the parents and the normal twin and on fibroblasts from the acardiac twin were identified by the standard Amos-modified microcytotoxicity technique (*11*). Identification of the HLA haplotypes was confirmed by absorption of specific antiserums with fibroblasts from the acardiac twin and by retesting on known positive cells (*12*). The normal twin inherited HLA specificities A2 and B12 from his father and Aw23 and B7 from his mother. Fibroblasts from the acardius contained three distinct A locus specificities, Aw23, A3, and Aw31, and two B locus specificities, B7 and B17. Because Aw23 and A3 were present only on the mother's cells, the acardiac twin clearly inherited both maternal HLA haplotypes and a single haplotype from the father. Moreover, the fact that the father contributed different HLA haplotypes to the twins further confirms their genesis from different spermatozoa (*13*).

Triploidy can be dispermic (haploid ovum and two spermatozoa), diplospermic (haploid ovum and one diploid spermatozoon) (*13*), or digynic (double-nucleated ovum, diploid giant ovum, or diploid first polar body and one spermatozoon) (*14*). The coincidence of twinning and monochorionic placentation in our case supports the likelihood that an ovum and its first polar body were fertilized (Fig. 2). The first polar body, formed during meiosis I at the time of ovulation, contains a diploid chromosome complement. Thus, independent fertilization of an ovum and its diploid first polar body, before further cytokinesis, could result in unlike-sexed twins, one of which would be triploid. The proximity of an ovum and its first polar body in the perivitelline space within the zona pellucida, during and after fertilization and in transit down the fallopian tube (*15*), could permit the implantation and subsequent development of the twins as distinct inner cell masses within a common trophoblast, leading to nonidentical twins within a single chorion. We doubt, but cannot exclude, the mechanism of secondary fusion of separate diploid and triploid embryos with resorption of the adjoining chorions; such a breakdown of adjacent membranes with establishment of vascular anastomoses regularly accompanies dizygotic twinning in the marmoset and is occasionally seen in other mammals (*16*).

Evidence supporting the possibility of polar body twinning includes electron microscopic documentation of sperm penetration into polar bodies (*17*). In addition, there are reports of chimeric individuals, with two genetically distinct cell lines, who seem to have arisen from independent fertilization of an ovum and one of the polar bodies by different spermatozoa with subsequent fusion to form a single individual (*18*), not unlike induced mouse chimeras (*19*). The present case suggests that polar body fertilization can lead to separate twins as well as chimeric individuals.

Our findings provide evidence of polar body twinning in man. Furthermore, the placentation and discordant sex of this twin pair demonstrate that, although monochorionic twins may always be monovular, they are not necessarily monozygotic, and they do not invariably arise after implantation, as previously thought. Whether polar body twinning can result in two normal twins remains to be determined, but the use of pericentromeric genetic markers should facilitate their detection.

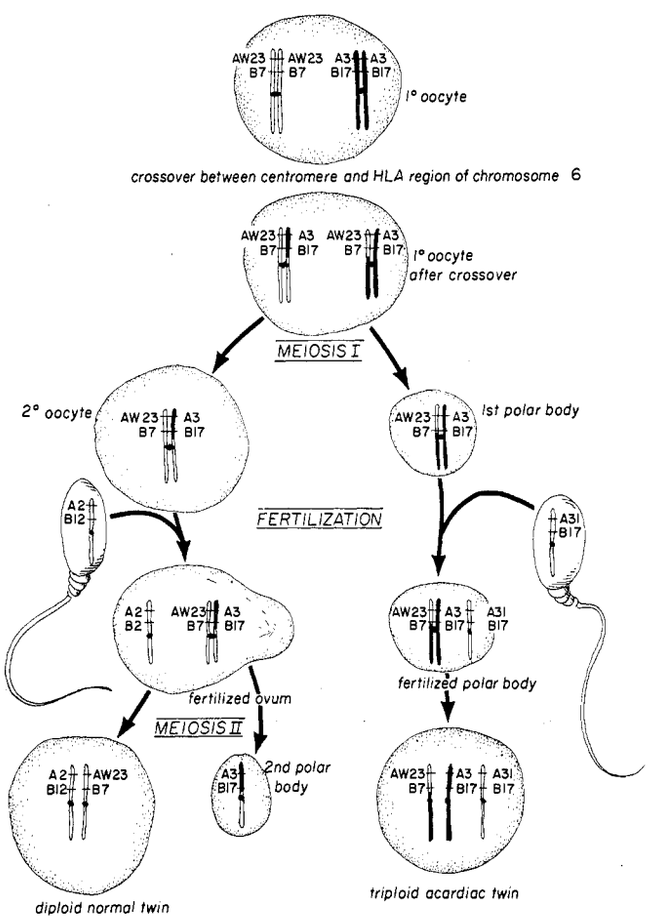

Fig. 2. Schema illustrating proposed origin of findings in parents and twins. The HLA haplotypes are shown on the short arm of chromosome 6, during maternal meiosis. A crossover must have occurred during prophase of meiosis I to account for the presence of both maternal haplotypes in the acardiac twin. Fertilization actually precedes the completion of meiosis II. Independent fertilization of the ootid and its diploid first polar body by different spermatozoa (one X-bearing and one Y-bearing) would result in a diploid male twin and a triploid XXX twin.

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3. The acardiac twin was 12 cm long and weighed 322 g. Except for a patch of hair, its cranial end was amorphous and edematous. There were a large omphalocele, absent upper and malformed lower limbs, and total absence of heart, lungs, liver, and kidneys. An ectopic urogenital anlage had failed to differentiate sufficiently for histologic sex determination. C. Kaplan, K. Benirschke, *Acta Genet. Med. Gemellol.* **28**, 51 (1979); K. Benirschke, V. Des Roches Harper, *Teratology* **15**, 311 (1977); J. S. Deacon, G. A. Machin, J. M. E. Martin, S. Nicholson, D. C. Nwankwo, R. Wintemute, *Am. J. Med. Genet.* **5**, 85 (1980).
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8. Data on ten acardiac fetuses include four cases in which the acardiac twin was aneuploid (trisomic or monosomic for a single chromosome) and the other twin was chromosomally normal (*3*). Identical twins differing in chromosome complement for a single chromosome can readily be explained by postzygotic nondisjunctional events. Because several of the acardiac twins had normal chromosomes, aneuploidy cannot be the only etiology. K. Benirschke postulated that acardia might arise from fertilization of a polar body, but was unable to confirm his hypothesis, by demonstration of sex discordance, in a sex chromatin survey of six preserved pathologic specimens [*Obstet. Gynecol.* **14**, 72 (1959)]. Many different primary abnormalities of early embryogenesis could result in acardia. If the defect occurs in a twin pregnancy, a reversal of blood flow through placental vascular anastomoses may sustain the development of the defective embryo, but also induce the morphogenetic defects associated with acardia. Thus all acardiacs, regardless of their karyotypes, would have a similar phenotype, varying with the degree of perfusion by the normal twin. In the present case, the cytoplasmic deficiency of the polar body, the presence of triploidy or the tetrasomy 15 may have contributed to the primary defect in embryogenesis.
9. The morphology and staining characteristics of the stalks, satellites, and centromeres of specific human chromosomes are heteromorphic. The heteromorphisms are inherited as Mendelian traits and are characteristic for a particular chromosome in an individual. P. A. Jacobs, *Prog. Med. Genet.* **2**, 251 (1977); V. D. Markovic, R. G. Worton, J. M. Berg, *Hum. Genet.* **41**, 181 (1978).
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Novel Single-Pass Exchange of Circulating Uridine in Rat Liver

Abstract. *Evidence is presented that the liver effects an essentially complete degradation of plasma uridine in a single pass and replaces it largely from hepatic pools of acid-soluble uridine nucleotides. The concentration of uridine in the hepatic vein of the rat was essentially the same as that in the arterial circulation and portal vein. However, the isolated perfused rat liver degraded more than 90 percent of infused [5-^{3}H]uridine in a single passage. Similar results were found in vivo when tracer amounts of [^{3}H]uridine and [^{14}C]uridine were infused into the portal vein of an intact rat. Furthermore, less than 2 percent of the infused uridine entered the acid-soluble nucleotide pools of the liver after 30 minutes of infusion. Intraperitoneal injection of [^{3}H]orotate allowed selective labeling of liver (and kidney) pyrimidines. After 3 hours, the specific activity of uridine in the hepatic vein was more than three times that in the arterial circulation. This unusual exchange, which is not saturated even at uridine concentrations as high as 50 μM, contributes to the rapid turnover of plasma uridine and explains its inefficient utilization in peripheral tissues.*

The rapid turnover of plasma uridine suggests that this circulating nucleoside may have a role in the metabolism of pyrimidines by various tissues (*1*, *2*). Defining the location and quantitative significance of this process has recently become possible by the use of new techniques in high-performance liquid chromatography. Studies with phosphonacetyl aspartic acid (PALA) and pyrazofurin, potent inhibitors of the synthesis de novo of pyrimidines, indicate that selective depletion of ribonucleotide pools occurs in some tumors, but that the pools are essentially unaffected in normal tissues and insensitive tumors (*3*, *4*). These observations suggest that circulating pools of pyrimidines could rescue depleted tissues. The source of these pools has not yet been clearly established, but preliminary clinical studies showed that they are relatively unaffected by high doses of PALA (*5*). The liver provides preformed purines to other tissues through the vascular system (*6*), and a similar process has been suggested for pyrimidines (*7*). We therefore undertook a quantitative analysis of the uptake and metabolism of uridine by the liver.

A very rapid turnover [half-time ($t_{1/2}$) ~ 3 minutes] of plasma uridine (1 to 2 μ*M*) has been observed in rats (*2*) and dogs (*8*). In rat plasma, cytidine concentrations are somewhat higher (3 to 5 μ*M*), and the turnover is less rapid ($t_{1/2}$ ~ 25 minutes). Since the liver is the primary location of enzymes responsible for uridine catabolism, the fate of [5-^{3}H]uridine perfused through an isolated rat liver was examined. During a 30-minute period, the radioactivity associated with uridine in the circulating medium decreased with an apparent $t_{1/2}$ of 4.8 minutes; total clearance in a single pass in this apparatus would give a $t_{1/2}$ of 4.9 minutes (Table 1). Thus the liver is extremely efficient at extracting and degrading uridine. Yet in fed, intact rats the concentration of uridine in plasma leaving the liver in the hepatic vein (mean ± standard deviation = 1.32 ± 0.45 μ*M*, *N* = 24) was, if anything, slightly higher than the concentration in portal (1.03 ± 0.3 μ*M*, *N* = 11) or arterial (1.06 ± 0.2 μ*M*, *N* = 21) blood.

To obtain data on the turnover of

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