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The Acardiac Anomaly
New Case Reports and Current Status

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Two cases of holoacardius are presented. Both had a normal 46,XX female karyotype, identical to that of their respective cotwin. Data are presented supporting the concept that the placental vascular anastomoses are the primary agents in the formation of an acardiac. Cytogenetics, epidemiology and other theories of pathogenesis are discussed.

Key words: Holoacardius, Twin placenta, Placental anastomoses, Acardiac's karyotype, Pathogenesis, Omphalocele, Cardiac development, Twinning

The acardiac anomaly is a phenomenon of abnormal development that is unique to the twinning process. These monsters, which usually totally lack a heart, have been reported since the 15th century and have prompted much interest, particularly as to their pathogenesis [24]. In humans, they are only seen in monozygotic twin pregnancies, since the necessary vascular anastomoses to the cotwin occur only in monochorionic placentas. Much debate has ensued as to whether this malformation is the result of primary failure of cardiac development, due to a genetic abnormality, or whether it is secondary to passive perfusion and reversal of circulation.

This report presents two additional cases of female holoacardiacs with complete chromosomal analysis and considers aspects of pathogenesis.

CASE REPORTS

Case 1

This 2200 g acardiac was delivered as the second of twins by cesarean section, done for breech presentation in a primigravida. Twins were not suspected and neither radiographs nor ultrasonography had been performed. The pregnancy was without other complications. Twin A, a female, was normal at birth, weighed 2750 g and had no cardiac or other problems in the perinatal period.

Pathology—Placenta. This diamnionic, monochorionic twin placenta had two umbilical cords, each with three vessels, which were inserted eccentrically. It possessed large artery-to-artery and vein-to-vein anastomoses. No other vascular connections were identified. Amnion nodosum was present on the amnion of the acardiac. The villous tissue was unremarkable.

Fetus. The acardiac fetus weighed 2200 g, measured 22 cm crown–rump, and had normal external female genitalia (Fig. 1a). It was extremely edematous and was amorphous at the cranial end, except for a small amount of hair and a small oral opening. No eyes or ears were identified. There were a large omphalocele and only four toes on each foot. Internally, the abdominal cavity was quite small. Two umbilical arteries were present, however: the left was smaller with intimal proliferation observed microscopically. These arteries led into an aorta which anastomosed near the caudal end with a vein connecting to the large umbilical vein. No remnant of heart, lungs, liver or pancreas could be identified. Irregular loops of small bowel, filled with green detritus, were present in the omphalocele and abdominal cavity. The intestine had no proximal connection and became atretic 1 cm from the ileocecal valve. The colon was filled with mucoid material and had a small appendix. The normal-appearing kidneys were the largest abdominal organs (4 g) and had small ureters which led into a small, empty bladder. No urethra was identified, but there was no evidence of dilatation of the urinary system. A single unremarkable adrenal gland was located between the two kidneys. The internal genital system was normal female except for the presence of a bicornuate uterus. Multiple ova could be identified on section of ovary. A well-formed vertebral column and a spinal cord were present.

Roentgenograms revealed normal lumbar and sacral vertebrae and leg bones, except for the absence of patellae and hypoplasia of tarsal bones (Fig. 1b). The pelvic bones were also hypoplastic. The thoracic cage was small with six pairs of malformed ribs. The thoracic vertebrae were reduced in size and occasionally fused. No arm bones or scapulae were present, and the only cranial bone found was a triangular fragment at the base.

Cytogenetics. Blood samples were grown in short-term lymphocyte culture while skin fragments were explanted into Leighton tubes and processed by fibrous tissue culture techniques [3, 5]. Cells in both cases were harvested after one hour of terminal colcemid exposure, hypotonic swelling with KCl and fixation with acetic acid/methanol. Giemsa banding was undertaken with trypsin [34] and karyotyping performed following the 1971 Paris Convention [26]. Both the host and acardiac in this case had a normal 46,XX karyotype. Common polymorphisms were identical in both twins.

Case 2

This 950 g acardiac was born prematurely as the second of twins. The normal female twin (850 g) was stillborn first, and was externally without malformations. No autopsy permit was obtained.

Pathology—Placenta. The diamnionic, monochorionic placenta weighed 380 g and had large superficial artery-to-artery and vein-to-vein anastomoses. No other placental anomalies were present. The cord of the acardiac showed two vessels and was inserted marginally.

Fetus. The acardiac weighed 950 g and possessed two lower extremities and remnants of arms. Scalp hair was present at the cranial pole (Fig. 2). The specimen was extremely edematous. An umbilical cord with only a right umbilical artery was attached to a defect in the central portion of the ventral wall, although there was no true omphalocele. Internally, a fused kidney, hemorrhagic adrenal gland and irregular portions of colon and small bowel were present. The uterus was bicornuate with well-formed ovaries containing normal ova as observed microscopically. There was good vertebral and spinal cord development.

Cytogenetics. Blood and skin fragments were cultured similarly to *Case 1*. Normal female karyotypes were found in both host and acardiac (Fig. 3). (These karyotypes have already been reported as an addendum to a previous communication [12]).

DISCUSSION

The pathogenesis of acardiac twins is still in dispute. Through evaluation of human and nonhuman cases, a reasonable hypothesis can be developed. Unquestionably, the presence of a particular form of anastomoses in the placenta, consisting of at least one artery-to-artery

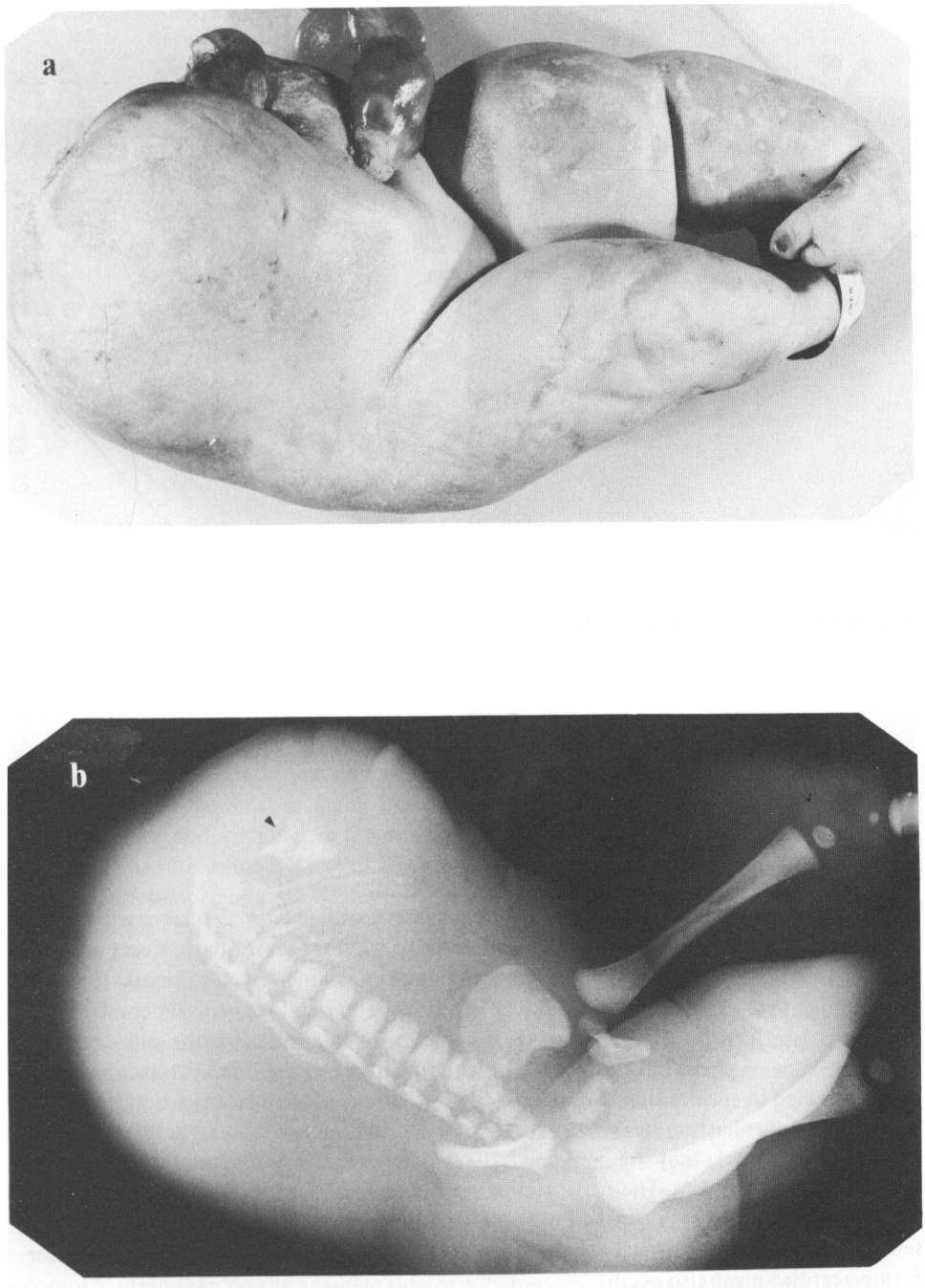

Fig. 1. Acardiac Case 1. (a) Well-formed lower extremities and omphalocele. (b) Radiograph showing relatively well-formed spinal column, pelvis, and legs. A triangular fragment (arrow) is the only remnant of skull. Massive edema of soft tissues is prominent.

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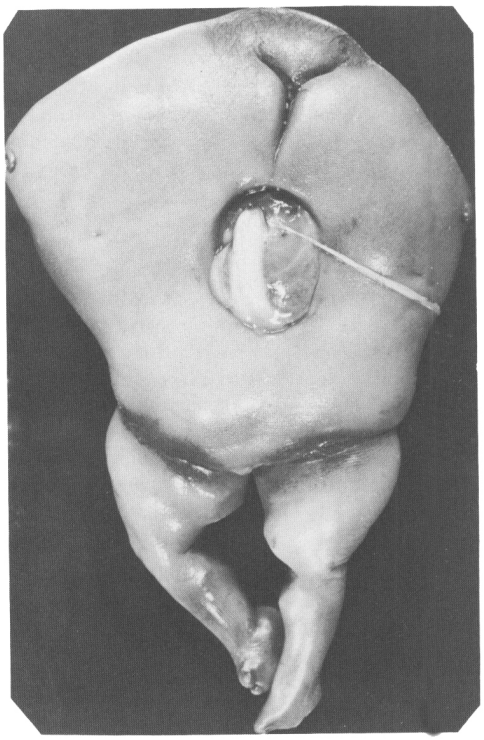

Fig. 2. Acardiac Case 2. Note well-formed lower extremities, facial cleft, and a small amount of hair at the cranial pole. No true omphalocele is present.

and one vein-to-vein connection, allows the parasitic acardiac twin to survive with a reversed circulation. Much controversy exists, however, as to whether these anastomoses are primary agents in the genesis of these monsters or whether they are merely coincidental findings.

Although several anatomic variations of artery-to-artery and vein-to-vein connections have been described [4, 21, 40], the factor common to all acardiacs is the existence of this particular type of placental anastomoses. It should also be noted that acardiacs have only been described in species that show vascular anastomoses of the placentas between twins. In humans, such anastomoses occur with rare exception only in monozygotic, monochorionic pregnancies. In cattle they are common between dizygotic twins and are the event commonly leading to freemartinism. The particular combination of an artery-to-artery and vein-to-vein anastomosis is the most unusual form these vascular communications take [7], and thus sets the stage for the potential acardiac development [17]. Reversal of circulation in the future acardiac must also occur.

It has been shown in experimental animals that proper folding of the cardiac tube depends on normal blood flows and pressures [30]. Thus, the eventual absence of a heart in the acardiac monsters, either total or partial, stems from subsequent developmental arrest or even degeneration in the abnormal circulatory environment [39]. Schatz [32] felt that the circulatory reversal was caused by obstruction to flow, possibly from an omphalocele [32]. A reversal of flow, however, only requires the slightly earlier initiation or a more powerful circulation of one twin. Moreover, not all acardiacs possess omphaloceles. Some

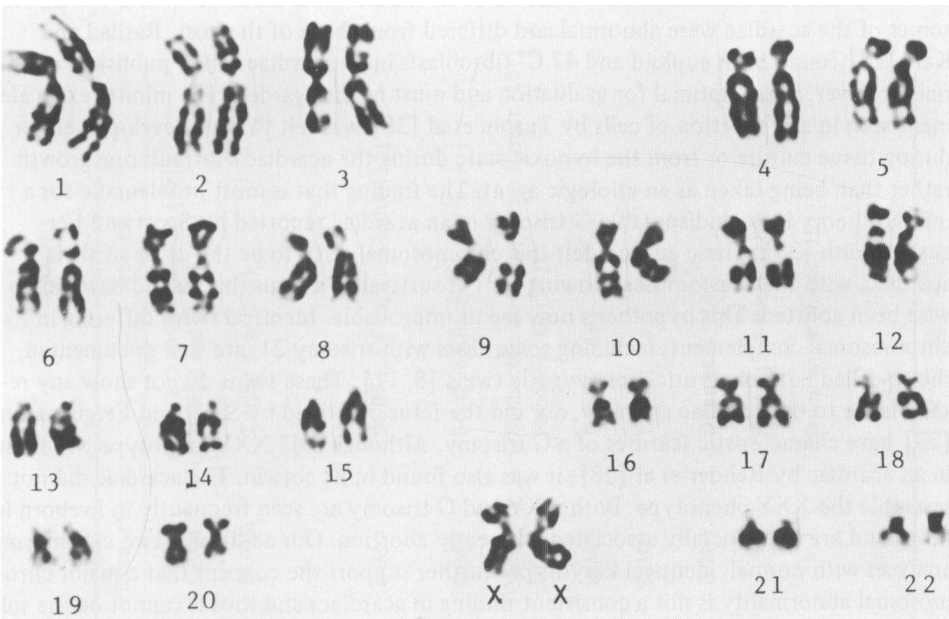

Fig. 3. Case 2, Giemsa-banded karyotype 46,XX.

environmental abnormality of a potential acardiac, including other abnormalities of placentation, could lead to delay or slight deficits of its development. This has been suggested for other malformations found to be discordant between monozygotic twins [22, 25], and acardia is certainly the most severe of these.

The remaining abnormalities in the acardiac are the direct consequences of its passive circulation. The blood flowing to this fetus is most certainly at a much lower oxygen tension and pressure, being the waste of the other twin, and it may well not be able to support full normal development. The case of Svedja [37] of a single fetus pseudo-amorphus with major acardiac abnormalities supports this concept. In acquiring the initial flow from the umbilical artery, the lower portion of the body of the acardiac tends to be the better developed region. The exact form and complement of organs which develop (or fail to degenerate) is quite variable and again is probably dependent on timing of the initial reversal and degree of perfusion. Unfortunately, studies actually measuring parameters of the blood flow, as could have been done at cesarean section in *Case 1*, have never been performed.

The multiple variations of acardiacs are well described in the many published reports compiled by Frutiger [16] and James [19]. We believe that attempts at dividing them into various categories based on form of development [20] serve no useful purpose, as the principal etiology is similar for all. Normal appearing kidneys are often seen, but in the presence of the low perfusion they may fail to function. Oligohydramnios with amnion nodosum is often seen on the acardiac side of a diamnionic placenta. Massive edema attesting to circulatory stagnation is virtually always present, and the acardiac may actually weigh more than its twin although it is certainly less well developed [1].

Although the foregoing scheme is favored by the authors, other hypotheses of acardiac formation have been proposed. In efforts to further support these hypotheses, various cytogenetic studies have been undertaken. The first was done to confirm like-sex [6]. Subsequent chromosomal analyses of a number of human and bovine acardiacs have yielded some challenging results. The published karyotypic data on acardiacs, including the present

two cases, are summarized in the Table. To be noted are those instances where the chromosomes of the acardiac were abnormal and differed from those of the host. Rashad and Kerr [27] found both euploid and 47 C^+ fibroblasts in an acardiac. Their published material, however, is not optimal for evaluation and must be disregarded. The minute extra element seen in a proportion of cells by Turpin et al [38] was felt to have developed either during tissue culture or from the hypoxic state during the acardiac's intrauterine growth rather than being taken as an etiologic agent. The finding that is most problematic for a unified theory is the indisputable G trisomy in an acardiac reported by Scott and Ferguson-Smith [33]. These authors felt this chromosomal error to be the cause of their acardiac, with the anastomoses allowing for the survival of a fetus that would have otherwise been aborted. This hypothesis now seems improbable. Identical twins differing in chromosomal complement, including some cases with trisomy 21, are well documented, the so-called heterokaryotic monozygotic twins [8, 11]. These twins do not show any resemblance to the acardiac anomaly, nor did the fetus described by Scott and Ferguson-Smith [33] have characteristic features of a G trisomy. Although a 47,XXY karyotype was found in an acardiac by Rehder et al [28], it was also found in its cotwin. The acardiac did not resemble the XXY phenotype. Both XXY and G trisomy are seen frequently in liveborn infants, and are not generally associated with early abortion. Our additional two chromosomal analyses with normal, identical karyotypes further support the concept that a major chromosomal abnormality is not a consistent finding in acardiacs and thus it cannot be the sole etiology.

The chromosomal studies on animal acardiacs have dispelled the possibility that unequal splitting of an embryo can be the only mechanism leading to such anomalies [20]. In the case of Dunn et al [16], the sex of the bovine acardiac differed from that of its cotwin. His findings are not of a form explainable by nondisjunction; moreover, dizygotic twinning is the most common type in this species.

A major argument against the hypothesis of the primacy of placental anastomosis is the concept of a primary defect of cardiac development, due to an unknown cause. This has been raised most prominently by Severn and Holyoke [35], who feel that acardiacs result from the failure of the primordial cardiac tubes to fuse. Thus, both the heart and its derivatives, including lung, liver and thyroid, should be absent. This overlooks the fact that rudimentary hearts (hemiacardiac), as well as liver, lung and pancreas, have all been described in one specimen or another which otherwise was characteristic of the usual acardiac anomaly [13, 16, 36]. In *Case 1* here described we found bile-stained material in portions of the gastrointestinal tract thus attesting to the presence of a focus of hepatocytes not identified, or the degeneration of previously existing liver tissue. Those tissues that are usually absent must be more susceptible to developmental arrest or degeneration in the acardiac environment than the ones that are usually identified at autopsy.

Many acardiacs show a single umbilical artery, but it is doubtful that there is any difference in etiology between acardiacs with one or two arteries, as others have suggested [21], or if this is of itself an etiologic moment. A single umbilical artery stage is normal in early embryos [23]. The subsequent development of one or two arteries may vary much like the spectrum of other anomalies, which are quite similar in these two classes of acardiacs. Interestingly, in the first case the right vessel was smaller and showed partial fibrous obliteration, probably representing a transitional form to a one-artery cord, the end stage. Clinically, atrophy and aplasia of an umbilical artery are similar and there is no qualitative difference in the two types [2]. The abnormality leading to acardia may more commonly exist with situations leading to single umbilical artery, but not invariably so.

TABLE. Published Karyotypic Data on Acardiacs

Species	Donor	Acardius	Placenta*	Authors
1963 Man	Normal male	46,XY (4 fibroblasts)	DiMO	Richart and Benirschke [29]
1966 Man	Normal male 46,XY (lymphocyte)	46,XY (9 fibroblasts) 47,XY + C (38 fibroblasts)	DiMO	Rashad and Kerr [27]
1967 Man	Normal female 46,XX (27 lymphocytes) 47,XX + minute (1 lymphocyte) 46,XX (9 fibroblasts)	46,XX (27 fibroblasts) 47,XX + minute (4 cells)	MoMO	Turpin et al [38]
1973 Man	Normal male 46,XY (38 lymphocytes) 46,XY (40 fibroblasts)	46,XY (40 lymphocytes) 47,XY + G (50 fibroblasts)	DiMO	Scott and Ferguson-Smith [33]
Man	Normal male 46,XY (30 fibroblasts)	Failed	DiMO	Scott and Ferguson-Smith [33]
1977 Man	Premature male, died	46,XY (49 fibroblasts)	MoMO	Benirschke and Des Roches Harper [12]
1978 Man	Male, abortus 47,XXY (fibroblasts)	47,XXY (fibroblasts)	DiMO	Rehder et al [28]
1979 Man	Normal female 46,XX (13 fibroblasts)	46,XX (5 lymphoc., 24 fibrob.)	DiMO	Present case
1979 Man	Normal female 46,XX (15 lymphocytes)	46,XX (15 fibroblasts)	DiMO	Present case
1967 Cattle	Normal male 60,XY (373 lymphocytes)	60,XX (9 lymphoc., fibrob.) 61,XX + A (14 lymphoc., fibrob.)	DiMO	Dunn et al [14]
1969 Cattle	Normal female 60,XX (lymphocytes)	60,XX (fibroblasts)	?	Herzog and Rieck [18]
1972 Sheep	Normal male twins 70% 54,XY (lymphocytes) 18% 53,XY 12% <52,XY	33% 54XY (fibroblasts) 19% 53,XY 46% <52,XY	?	Dunn and Roberts [15]

*DiMO = Diamnionic, monochorionic; MoMO = Monoamnionic, monochorionic.

James [19] has extensively compiled published data on acardiacs, and recently commented on certain epidemiologic features. These include higher incidences of females, monoamnionic placentas, and higher multiple births in gestations with acardiacs (although statistical analyses of these are not given). We have also found a predominance of females in our own material (11 vs 7), but neither this figure nor James' material is as yet significant using a chi-square analysis, and validation of the implications will require more observations. Unfortunately, the exact placentation in acardiacs is often not recorded. Generally speaking, monoamnionic placentas do not have anastomoses more frequently than diamnionic ones. Perhaps they do provide a more opportune environment for acardiac development. The fact that higher multiple births may be more common is most interesting and supportive of our concepts. In this situation there are also more placental anomalies [9]. These could provide the right additional circumstances when the necessary anastomoses are present, since, as noted previously, an acardiac is not seen invariably with artery-to-artery and vein-to-vein linkage. Of parenthetic interest is the fact that no acardiacs have been reported in the fraternal twins of marmoset monkeys where these anastomoses are common, if not the rule [8]; however, it is expected that with some interest in this direction acardiacs may eventually be noted.

The prognosis for the normal twin is usually good if the pregnancy goes to term. Occasionally, the enlarged uterus may deliver prematurely. The donor twin may suffer cardiac failure from the need for perfusion of the acardiac. Hydramnios has been observed, and obstetrical complications may occur from the size or presentation of the acardiac [24, 31], sometimes necessitating cesarean section, as in our first case. Acardiacs are virtually never diagnosed until delivery. Hopefully with the help of radiology and ultrasonography, a case will be prenatally detected and physiologic measurements made in the acardiac at delivery.

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