Resumen por el autor, Leslie B. Arey.

Fusión coriónica y gemelización aumentada en el oviducto humano.

Los datos que poseemos hasta el presente indican que la relación de los gemelos monocoriónicos y la de los dicoriónicos es unas quince veces mayor en el oviducto que en el útero. Los estados ilustrativos indican que esta desproporción de los ejemplares monocoriónicos resulta en parte de la fusión secundaria de los sacos coriónicos de los individuos dizigóticos. Por esta causa, en el caso del hombre, el término monocoriónico no debe usarse siempre para expresar el origen a expensas de un solo óvulo. Un factor todavía mas potente parece ser el aumento actual del impulso productor de gemelos. Su causa puede referirse más claramente a la inflamación tubal y sus resultados. Los mismos retardamientos y cesación del desarrollo que producen y siguen a la implantación tubal son responsables, respectivamente, de la gemelización excesiva y la malformación de los ejemplares obtenidos del oviducto.

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CHORIONIC FUSION AND AUGMENTED TWINNING IN THE HUMAN TUBE¹

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FOUR FIGURES

INTRODUCTION

Monozygotic twins of the higher mammals are necessarily monochorial. It is likewise customary to accept a common chorion as proof that mammalian twins are identical or homologous, that is, monozygotic in origin. This, however, need not be an infallible criterion. One of the armadillos, *Dasypos villosus*, has usually two monochorial young at birth; Fernandez ('15) has shown that these embryos at first occupy individual chorionic vesicles which then progressively fuse until they appear as one (3.5-cm. stage). Fusion of twin chorions among ungulates is apparently common; Lillie ('17) has proved beyond doubt that only rarely does such union fail in twin cattle and that it also occurs in the sheep and hog. There are no other data known to me. Lillie expresses the following opinion (p. 400): "A number of mammalian groups could be at once excluded from consideration because the conditions of placentation are such as to prohibit chorionic fusion; in mammalian groups such as primates and many rodents in which the ovum becomes embedded in the uterine mucosa, there is, of course, an insuperable bar to early chorionic fusion." Nevertheless, in the human tube at least—and here, except spatially, the conditions of implantation are essentially identical with those in the uterus (Mall, '15)—indications of chorionic fusion occur. This truth became apparent during an analysis of the data accompanying the recorded cases of tubal twin pregnancy ('22 a). The supporting evidence will now be presented.

¹ Contribution no. 92.

STATISTICAL EVIDENCE OF CHORIONIC FUSION

First, the subject is best approached statistically. A rigid examination of the literature has revealed forty cases of tubal twins that appear authentic ('22 a); in addition there are eight cases which may be termed probable or presumptive. Among the positive list thirty-one specimens are recorded as having a common chorion, although apparently four more should be included, whereas in three only was it double.² In the probable group there are six definite statements; four of the six cases have double chorions.³ Combining both sets, the ratio becomes 33 (or possibly 37) : 7. To the list of double-ovum twins must be added those that develop bilaterally, one in each tube. There appear to be less than a dozen proved cases.⁴ Hence the total records show that monochorial specimens occur twice as frequently as the dichorial cases.⁵ Since, however, viable (uterine) identical twins are but one-seventh as frequent as the ordinary fraternal type, it follows that tubal monochorial twins are some fifteen times more common than might be expected if the tube were no more favorable than the uterus as a seat for twin production.

² In one of the three the evidence is not unequivocal for doubleness.

³ This relatively high ratio of doubleness is explained largely by the fact that duplicity itself was one of the determining factors utilized in rejecting several inadequately established cases from the positive group.

⁴ McDonald and Krieger ('13) collected the recorded cases of bilateral tubal pregnancy. They listed twenty-five proved cases, including both twin and successive specimens. Only in nine instances were both fetuses present and of the same age; in eight cases they were of different ages (including two with one member a mummy and one a lithopedion); two specimens had a fetus in one tube paired with a clot and villi in the other; in two cases there were clots with villi in both tubes. Twenty-seven additional cases were listed as 'probable but not proved'; as a matter of fact, in none of these instances was there positive anatomical evidence of bilateral gestation, either twin or successive; sixteen combined a fetus in one tube with a hematoma without villi in the other, while eleven were represented by hematomata in both tubes.

⁵ In this computation that group of dichorial cases which combine a simultaneous tubal and uterine pregnancy was, of course, ignored, for it belongs properly to neither category. Furthermore, comparable tubal conditions which allow one member of such pairs to descend uninterruptedly doubtless subtract a proportionate number from the monozygotic tubal specimens.

In view of these numerical relations, the preponderance of monochorial tubal twins seems to offer *prima facie* evidence of some modifying factor or factors. What these are will next demand consideration.

ANATOMICAL EVIDENCE OF CHORIONIC FUSION

The readiest explanation of the foregoing numerical disproportion is that separate ova have fused to produce pseudomonochorial twins. With this hypothesis in mind, the descriptions of all recorded cases of unilateral tubal twins were examined to ascertain if there is evidence of chorionic fusion in man. Briefly, such evidence does exist, as the following selected cases exemplify.

First in the series is Young's ('11) specimen, which comprises a tube with two dilatations; one represents a ruptured chorionic sac with its embryo still inside; the other sac was unruptured, entirely distinct from the first, and contained a twin embryo. Amann's ('08) case is apparently in the same category, and the clinical histories and anatomical descriptions recorded by Ferroni ('03), Saniter ('05), and Shauta ('05) make it probable that these also should be included. There is more doubt in the cases of Fenger ('91) and Salin ('95); they may be successive pregnancies. Figure 1 is a diagram of this preliminary condition based upon Young's specimen. Whether these particular ova ever would have fused had development continued or whether they were too far separated is unimportant; they typify the primary relation.

The next stage in fusion is illustrated by a tubal pregnancy described by Mall ('15) and Meyer ('20), listed in the Carnegie collection as no. 825 (fig. 2). Externally the tube bore a single swelling the size of a walnut, but section revealed two well-preserved chorionic vesicles, lying at about the same transverse level in the tube and flattened on the surfaces of mutual contact. The opposed chorionic faces had the appearance of a thin septum (Mall, pl. 9, figs. 4 and 5; Meyer, fig. 1), which proved to be double, partially separated by villi. Actual embryos and amnia had disappeared.

Pulcher ('05) has described a fusion still more advanced; it is a stage just prior to complete union (fig. 3). At the middle of the tube was a tumor the size of a fist. Its interior was divided by a thin translucent septum into two chambers, each of which contained a well-preserved 2-cm. embryo. Both umbilical cords were inserted near the center of the common septum. This partition was studied microscopically by sections; it is said to consist of a double layer of amnion. Nevertheless, since the umbilical cords pass to the septum, it must funda-

Figs. 1 to 4 Stages illustrating secondary chorionic fusion between dizygotic tubal embryos. Fig. 1, Young's specimen; fig. 2, Mall's specimen; fig. 3, Pulcher's specimen; fig. 4, Costa's specimen.

mentally represent a former double chorionic wall which had thinned and degenerated until it was no longer recognizable as such to the investigator.⁶ During the growth of these ova, the nutritional mechanism necessarily became progressively incompetent. Under these conditions, the embryos should be underdeveloped; in accordance with this expectation, we find the

⁶ Possibly the amnion was a constituent as well; each chamber is said to be lined with a 'smooth glistening membrane.' As this was the author's inaugural thesis, he presumably studied the specimen with care, although he failed properly to interpret the septum or the significance of the insertion of both umbilical cords in it.

menstrual histories indicating fetuses of twelve to fourteen weeks, when in reality they measure but 2 cm., which corresponds to seven weeks' normal development. It was a fortunate chance that the umbilical cords were inserted in the abutting chorionic walls; otherwise the specimen would have passed (as Pulcher believed) for twins with a common chorion and double amnion.

The final step in fusion is furnished by Costa ('07). Externally, the tube exhibited two dilatations, well separated and apparently distinct; internally, a neck-like constriction partially divided two communicating compartments, each of which contained a fetus, 5 and 5.3 cm., respectively (fig. 4). It is, of course, possible to interpret this as a single gestation sac secondarily constricted, but as it is a normal specimen, preceded by graded stages, fusion is more logical. The chances are greatly against the coincidence of single-ovum twins being so significantly spaced within a doubly dilated tube and chorion.⁷

Absolute proof of chorionic fusion waits upon the finding of male and female fetuses inside a common sac. Eventually such specimens may be confidently expected, especially since it is now possible to recognize sex in embryos as small as 15 mm. (Spaulding, '20).

In supplemental support of the principle of chorionic fusion, it is significant that two fetuses may occupy one gestation sac even when the history and anatomical relations point clearly to successive, rather than simultaneous pregnancies. Hence fusion, or inclusion, is certain. An illustrative case is that of Henricius and Kolster ('99), who attended a woman during two successive pregnancies without delivery on either occasion; at autopsy the left tube proved to be a single sac which contained a recent full-term fetus and a mass of fetal bones. A similar case is recorded by Racoviceanu and Bogdanovici ('04); the patient twice went to term without delivery; the right tube was a sac which contained a small, shrunken, but well-preserved fetus and an old lithopedion.

⁷ Mall ('15) has described rare cases of degenerating ova without embryos which assume an hour-glass shape during dissolution. This process has no relation to Costa's specimen.

In passing, it should be mentioned that the amnia of twins also join readily. Twelve cases in the twin series specifically mention this point; in eight specimens the amnion was single.

AUGMENTED TWINNING IN THE TUBE

Although chorionic fusion may be invoked satisfactorily to reduce in part the preponderance of monochorial tubal twins, it is pertinent to inquire if the relative frequency of monochorial tubal twins may not be largely explained by an excessive production of monozygotic twins rather than by the fusion of the chorionic sacs of dizygotic individuals. In order to return an answer, it is necessary to consider both the cause of twinning and of tubal implantation.

Stockard ('21) has been able convincingly to reduce the primary cause of all non-hereditary abnormal development, including true (monozygotic) twinning, to a single factor—developmental inhibition or arrest; the exact type of deformity that results depends solely on the precise moment when the interruption occurs. Thus, twin formation results from a slowing of the developmental rate at the time of gastrulation, which in mammals corresponds to the period of the primitive streak. Such an arrest allows other potential embryonic axes on the blastoderm to assert themselves, whereas in normal development they are dominated and suppressed by the chief axis. Direct experimentation on fishes refers the cause of arrest to retarded oxidations. Occasional twinning in the chick and the customary quadruplet formation in the Texas armadillo lend strong support to this view. Both are subject to arrest and reduced oxygen supply—the chick by a lowering of the temperature when laid, the armadillo blastocyst by a quiescent period of several weeks in the uterus before it becomes implanted.

The direct application of this fundamental concept to abnormalities and twinning in the human tube follows logically when once the conditions attending tubal implantation are known. Mall ('15) studied the extensive Carnegie collection of embryos, in which many clinical histories accompany the specimens. He concluded that tubal pregnancy is associated with

preceding inflammatory changes, usually of long standing. It appears that such inflammatory disturbances may continue over long periods during which the inflammation is constantly too severe to permit the germinal products to unite or maintain development; later, however, the condition may abate sufficiently so that the ovum can develop, at least for a time, although it is still incapable of reaching the uterus.⁸ Incidentally, it seems probable that if tubal pregnancy had not occurred in these cases when it did, the tube might soon have healed sufficiently to allow ordinary uterine gestation to proceed. The ovum fails to gain its normal destination in the uterus because of the impairment of the ciliated cells, as well as by kinkings of the tube through adhesions, by becoming trapped in epithelial diverticula of inflammatory origin or through adherent mucosal folds. "In short any change which delays the ovum in its progress will favor tubal pregnancy." An ovum taken up by the mucous membrane at the outer end of the tube may be delayed by the impaired ciliated cells until it is too large to pass the narrow end of the tube; it may wander into blind pockets or diverticula; more commonly still it is transported to the middle of the tube, where inflammation and follicular salpingitis are most common, and there become stranded because the ciliated cells can carry it no farther. Any of these delays, therefore, to which may be added the rarer hazards afforded by blind tubes, pocketed and double tubes, or delays due to migration from the opposite ovary, are the effective primary factors conditioning tubal implantation.

When the normal progress of the ovum is blocked in one of the ways designated it may then attack the tubal wall; in the meantime, however, it has attained a later stage of development than is customary at implantation. If, therefore, such delayed implantation and the establishment of tardy or inadequate oxygen relations (see below) should cause a developmental slowing at the critical moment for twinning, two embryonic axes would assert themselves as in the fish, chick, and armadillo, and mono-chorial twins result. This outline of events becomes a natural

⁸ In another publication ('22 b) I have shown that this sterile period averages nearly six years.

inference when Stockard's discovery is applied to the known condition of the tube and ovum in tubal pregnancy. It helps account rationally for the preponderance of single-ovum twin pregnancies in the tube, which, by its greater susceptibility to prolonged and slowly clearing chronic inflammation, further explains why the uterus bears relatively fewer monozygotic twins.

The theory of Stockard is further supported in its human application by the demonstrable frequency of faulty implantation in tubal cases and its relation to malformation of the parts. Mall failed to find a typical decidua here, and hence its function in checking hemorrhage by forming a dam between the tips of the villi and the eroded mucosa is foregone. There result numerous hemorrhages which form old clots between the villi. "Even the best of specimens frequently show such extensive hemorrhages around the chorion and such marked degeneration of the villi that it is a wonder that the ovum continues to grow normally." Checks, permanent or temporary, while the chorion is struggling to overcome natural deficiencies in its nidus are sufficient to account both for excessive twinning, if the delay prior to implantation be not sufficient, and for the observed double frequency of anomalies in these specimens over the uterine group.⁹

Mall held that the primary causative factor of these pathological embryos is faulty implantation which prevents an adequate transfer of nutriment. Stockard agrees with the primary factor, but from his experimentation is forced to attribute the proximal cause to inadequate oxygenation.

SUMMARY

The available data indicate that the ratio of monochorial to dichorial tubal twins is about fifteen times greater in the tube than in the uterus.

Illustrative stages indicate that this disproportion of monochorial specimens results in part from the secondary fusion of

⁹ Mall ('17) studied the anomalies of 1000 embryos and records that tubal monsters are twice as common as those in the uterine group.

the chorionic sacs of dizygotic individuals. Hence for man the term 'monochorial' need not always connote a single-ovum origin.

A still more potent factor appears to be an actual augmentation of the twinning impulse. Its cause is most clearly referable to tubal inflammation and its sequelae. The same delays and arrests which cause and follow tubal implantation are respectively responsible for the excessive twinning and malformation of tubal specimens.

LITERATURE CITED

- AMANN 1908 Zwillingschwangerschaft in einer Tube. Zentr. f. Gynäk., Jahrg. 32, S. 798.
- AREY, L. B. 1922 a The complete data of tubal twin pregnancy. (In preparation.)
1922 b Tubal twins and tubal pregnancy. Surg., Gynec. and Obstet. (in press).
- COSTA, R. 1907 Intorno alla gravidanza tubarica gemellare di un lato. Annali di Ostet. et. Ginec., t. 29, pp. 185-212.
- FENGER, C. 1891 Tubal pregnancy with two ova in same fallopian tube. Jour. Amer. Med. Ass'n, vol. 16, p. 564.
- FERNANDEZ, M. 1915 Ueber einige Entwicklungsstadien des Peludo (*Dasypus villosus*) und ihre Beziehung zum Problem der spezifischen Polyembryonie des Genus *Tatusia*. Anat. Anz., Bd. 48, S. 305-327.
- FERRONI, E. 1903 Beitrag zum Studium der tubaren Zwillingschwangerschaften in derselben Tube. Zentr. f. Gynäk., Jahrg. 27, S. 275-281.
- HENRICIUS, G., UND KOLSTER, R. 1899 Zwei Früchte verschiedenen Schwangerschaftszeiten entstammend, in demselben Tubensack. Arch. f. Gynäk., Bd. 58, S. 95-102.
- LILLIE, F. R. 1917 The free-martin; a study of the action of sex hormones in the fetal life of cattle. Jour. Exp. Zool., vol. 23, pp. 371-453.
- MALL, F. P. 1915 On the fate of the human ovum in tubal pregnancy. Carneg. Inst. of Wash., Contr. to Embryology, vol. 1, no. 1.
1917 On the frequency of localized anomalies in human embryos and infants at birth. Am. Jour. Anat., vol. 22, pp. 49-72.
- MEYER, A. W. 1920 Hydatiform degeneration in tubal and uterine pregnancy. Carneg. Inst. of Wash., Contr. to Embryology, vol. 9, no. 40, pp. 325-364.
- MCDONALD, E., AND KRIEGER, W. A. 1913 Bilateral and multiple ectopic pregnancy. Jour. Amer. Med. Ass'n, vol. 60, pp. 1766-1769.
- PULCHER, J. 1905 Zwillingschwangerschaft in der Tube. Inaugural-Dissertation, Univ. zu Heidelberg. H. Dörr.
- RACOVICANU UND BOGDANOVICI 1904 Doppelte extra-uterine Schwangerschaft, uterine Schwangerschaft mit fötaler Retention. Zentr. f. Gynäk., Jahrg. 28, S. 1469-1470.

- SALIN, M. 1895 Fall af tubar tvillingsgraviditet. Förhandlingar vid Svenska Läkare-Sällskapet, sid. 180-184.
- SANITER, R. 1905 Tubare Zwillingschwangerschaft mit zwei Eiern verschiedener Grösse. Ztschr. f. Geburtsh. u. Gynäk., Bd. 55, S. 492-496.
- SCHAUTA, 1905 Tubare Zwillingschwangerschaft. Zentr. f. Gynäk., Jahrg. 29, S. 45-46.
- SPAULDING, M. H. 1920 The early recognition of sex from the external genitalia in human embryos 15 to 50 mm. long. Anat. Rec., vol. 18, p. 261.
- STOCKARD, C. R. 1921 Developmental rate and structural expression, etc. Am. Jour. Anat., vol. 28, pp. 115-278.
- YOUNG, H. C. T. 1911 Unilateral twin tubal pregnancy. Austral. Med. Gaz., vol. 30, pp. 736-739.