CONGENITAL MALFORMATIONS IN ONE OF MONOZYGOTIC TWINS

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The purpose of this communication is to describe two cases of gross foetal abnormality and to discuss the influence of intra-uterine environment on the development of congenital abnormalities when the contribution of inherited or genetic factors is made known by the co-existence of a genetically similar but normal twin. The anomalies will not be discussed in detail, but some explanation of the mechanism of their occurrence will be attempted, since, even if this proves incorrect, it may stimulate useful reconsideration of the problems presented by congenital malformations which now assume such a great importance in practice.

Like Twins and Factors Influencing Inheritance

If the outcome of intra-uterine development is determined solely by genetic inheritance, monozygotic or like twins should be completely indistinguishable from one another at birth. Right and left asymmetry with a mirror image difference often does exist, but this is not a valid difference and need not be discussed now. It is widely admitted, however, that even like twins may differ in size at birth. Moreover, Schatz (quoted by Newman, Freeman, and Holzinger, 1937) found that at about the middle period of pregnancy the size difference in monozygotic twins was greater than at term and, on the average, much greater than for dizygotic or unlike twins. The careful survey of the literature on twin pregnancies with one twin blighted made by Kindred (1944) is also relevant. Here one twin dies, usually between the third and the fifth month, and is retained in utero until the birth of its living partner at, or near, term. This condition has a roughly similar incidence in both monozygotic and dizygotic twins. The occurrence of this condition must suggest that the development of twins, even when they are derived from the division of the same fertilized ovum and possess an identical genetic inheritance, can be very significantly influenced by differences in the environment they establish for themselves in the maternal uterus. Joined or Siamese twins and double monsters are often closely identical (Szendi, 1939). Parasitic twins and teratomata, if it is insisted that these latter arise from cells laid aside so early in development, are both examples of much greater inequality of growth and even of organ differentiation. Here, however, division of the initial cell mass between the two individuals is relatively late, and may be unequal, and the juxtaposition of the growing tissues and the organizers of the two individuals may disturb development. These more extreme abnormalities are, therefore, unsuitable material for a study on genetically similar material of the role of environmental differences in utero and especially for the study of the effect of nutritional differences.

Despite the value of the study of like and unlike twins in the assessment of the relative contribution of the environment and of heredity in post-natal life in health (Newman, Freeman, and Holzinger, 1937, and Newman, 1942) and in disease (Kallmann and Reisner, 1943), twins have been little studied for data on the relative importance of environment and heredity in intra-uterine development. The Mateer embryo of the pre-somite period (Streeter, 1920) showed a normal embryo and probably also an abnormal and yet monozygotic twin. Such cases are of interest, but have not been discussed in this connexion. Macklin (1936) collected from the literature cases of malformation in twins. The records rarely indicated the nature of these twins. She found, however, that twins of like sex were concentrated in the group where both twins were malformed. Where but one twin was malformed, the twins were presumably binovular (dizygotic), because they were as often of different sex as ordinary siblings. She argued that this was good evidence that malformations were not determined by environmental causes, but were due to inherited defects of the genetic inheritance. To-day there is convincing evidence that some congenital malformations can, and do, arise from environmental causes, such as rubella. It is not necessary to think that even identical abnormalities always have the same causes. Environmental causes may create copies (phenocopies) of conditions which are more often determined by genetic factors (Goldschmidt, 1938). Information on any environmental conditions which may operate in this way is most desirable.

The probable nature of this environmental disturbance must be considered. Studies of the occurrence of malformation when the maternal diet is deficient, and where it is presumed in consequence that embryonic nutrition is also deficient, provide some evidence in animals, but no satisfactory
evidence that in man nutritional requirements can determine malformations. The blighting or death of one ovum of a monozygotic pregnancy is probably to be regarded as the result of unequal sharing of nutrient. The deficiency usually leads to death and, if abnormalities are present in the dead and blighted ovum, it will very likely be impossible to establish this months later from its macerated or papyraceous remains. The uterus otherwise must present a very similar environment to both twins and such maternal influences as general nutrition, infection, and toxoaemia should affect two genetically similar embryos equally.

Criteria for Diagnosis of Monozygotic Twins
It is necessary to decide on what basis a diagnosis of monozygotic or like twins can be made. Diagnosis by the study of the foetal membranes has fallen into some disrepute among those who study twins in late post-natal life. A casual examination of these membranes is useless and they must be properly examined grossly and microscopically and with adequate tissue sections. Very rarely monozygotic twins are enclosed in a common amnion; usually they are separated only by the walls of their amniotic cavities and the chorion should continue as a common membrane around both. In dizygotic twins there are four membranes between the foetuses, two amniotic and two chorionic layers (dichorionic placentae), and, though the two placentae may appear fused, there is no continuous layer of chorion from one placenta to the other. Some confusion has been caused because some workers have failed to recognize that a fairly high proportion, probably about 30 per cent., of monozygotic or like twins are born in dichorial placentae. In these cases the ovum cleavage has occurred early; the separated cells are not enclosed in a common membrane and each forms its own chorion.

It is important to decide if dichorionic, usually dizygotic, twins can come to possess a single chorion. Arey (1922) has suggested on insufficient evidence that occasionally the two separate chorionic cavities may become continuous with one another through the breakdown of the adjacent chorionic walls. If this occurs the retention of a partition formed by two thin and fused amniotic walls would seem somewhat unlikely and such twins would probably be described as monochorionic twins with a common amnion. It is highly improbable that those monozygotic twins of identical inheritance who possess a monochorionic placenta and two amnions will be mistaken for dizygotic twins of unlike inheritance, if the membranes are carefully studied. Additional support for a monozygotic origin may be provided by a study of the placental blood vessels. There is some agreement that in man readily demonstrable blood vessel anastomoses are associated only with monozygotic twins. Thus von Verschuer (1939) injected placenta and found thirty-two cases with circulatory anastomoses and these were all monozygotic twins on complete tests of resemblance. In one hundred cases there were two chorions and no anastomoses, and of these seventy-six were dizygotic and twenty-four were monozygotic after similar studies. It would seem that only some monozygotic twins possess such anastomoses and that in man, as opposed to cattle, unlike twins do not mix their blood.

The only alternative to such a study of foetal membranes is a meticulous comparison of blood groups, eye colour, iris pattern, hair and skin colour, form and texture, finger and palm prints, and general features. This is largely impossible in malformed infants, one or both of whom may die at birth. It prejudices the issue since only if there is close physical correlation will the diagnosis of monozygotic twinning be made. It was not employed in the cases to be described. Blood grouping is difficult in the newborn and could scarcely be useful when there are communications between the circulation of the two twins. Some comparisons might, however, give useful collaborative evidence of genetic identity in future cases.

Case 1. Mrs. A, a primipara aged 45 years, was admitted at twenty-five weeks with severe pre-eclamptic toxoaemia, oedema, urine loaded with albumen, and a blood pressure of 160/80. At thirty weeks spontaneous labour occurred and two stillborn female infants were delivered.

The placentae were fused, the partitions between the foetuses had been accidently torn in some places, but multiple sections of this and of the junction between the placentae of each foetus showed only amnion in the partition and the chorionic membrane was continuous from one placenta to the other. Several large blood channels (fig. 1) passed

FIG. 1.—The circulations of the twins communicate by blood vessels, one of which is clearly seen. (Case 1.)
from the circulation of one foetus to the other.

Foetus B. Intrapartum stillbirth. There was a history of maternal toxaemia, breech presentation, prolapse of the cord through the incompletely dilated os, and cessation of cord pulsation during attempts at replacement. In the foetus there was asphyxial petechial haemorrhage in the heart, lungs, thymus, and subserosal tissues, and gross congestion of all organs.

Prematurity was 30 weeks; weight 1,800 g. Crown to heel measurement, 41 cm. There was evidence of early intra-uterine maceration.

Foetus C. Intrapartum stillbirth. The congenital anomalies of the heart were persistent ostium atrio-ventriculare communis, with an incomplete septum primum and absence of the septum secundum, a single atrio-ventricular valve, and an incomplete interventricular septum; dextro-position of the aorta; hypoplasia of left ventricle; and slight coarctation of aorta (infantile type). There was congenital atresia of the oesophagus without tracheo-oesophageal communication (variant of Type I of Ladd, 1944). There was gross dilation of the vagina and dilation of the cervical canal and corpus uteri with a shelf-like diaphragm at the lower end of the vagina (fig. 2) and retrograde leakage of vaginal squamous epithelial debris into the peritoneal sac with extensive vernix peritonitis (fig. 3). Prematurity

30 weeks; weight 800 g. The crown to heel measurement was 33 cm.

In foetus C the cardiac anomalies are those which would arise from disturbances of those growth processes which are normally most active at the end of the fifth and beginning of the sixth week of embryonic life. The anlage of the septum primum has then appeared, the antero-superior and postero-inferior endocardial cushions between the future auricles and ventricles are present, the interventricular septum is incomplete, and the spiral subendocardial bulbar ridges have formed but have separated the aortic and pulmonary channels only in the distal part of the bulbus. The actively growing free edges of the septum primum have not united with the endocardial cushions, nor have these fused to divide the single atrioventricular channel into right and left channels. The interventricular septum is growing upwards, but will not complete the separation of the ventricles until about the eighth week. The growth of the bulbar ridges is active, but not complete, in the proximal portion of the bulbus, and the positioning of the aortic and pulmonary orifices is therefore not determined. Most of these changes will occur in a few days and, whatever might subsequently happen, the heart found in this foetus could not then be produced. In the fifth and sixth weeks there is an almost solid mass of epithelial cells representing the future lining of the oesophagus. These cells must multiply rapidly at this time as the oesophagus is drawn out by the rapid growth of this region with the development of the heart and lungs. Disturbed or incoordinated
growth may interrupt the continuity of the epithelium and stenosis or atresia may result. The uterine anomaly is unusual. It can perhaps be regarded as a disturbance of the lower end of the Mullerian duct system. It is difficult to explain its formation at any stage of development. In the sixth week the right and left paramesonephric ducts have appeared in the mesenchyme lateral to the cranial extremities of the mesonephric ducts. They are growing downwards and in each a lumen is extending towards the growing tip. Disturbance of growth activity at the lower end of these ducts may create abnormalities which later affect their complex development even after fusion. There are many other active growth changes occurring at this period. The future ureter and pelvis is growing upwards and the primordia of the metanephros is appearing. The kidneys and ureters in this case were not affected but the critical growth period for these and other structures is uncertain. The urorectal septum may not have completed the separation of the rectum and urogenital sinus, but here growth activity at this period is relatively slight.

Case 2. Mrs. X was a primigravida aged 23 years. She had mitral stenosis. Twins were not expected but at thirty-five weeks gestation she was delivered first of a normal live female child and this was followed by a dead-born monster.

The placenta were complete. There were two amniotic cavities enclosed in a single chorion, and the relationship of the membranes was confirmed by histological examination. The umbilical cords arose within 1½ in. of each other. Large communicating channels passed between the arteries of each twin and between the veins.

Child Y is alive and well and shows no congenital defect.

Fœtus Z. Intrapartum stillbirth. There was occipital encephalocoele, complete spina bifida, Arnold-Chiari malformation; gross dysgenesis of the larynx, complete atresia of the trachea and oesophagus, and isolated lung rudiment; cor biloculare with imperfect incorporation of the sinus venosus and bulbous cordis, and diffuse endocardial fibro-elastic thickening. Scoliosis and kyphosis and imperfect development of all limbs was noted. There was gross dysgenesis and extreme hypoplasia of the liver, no recognizable stomach dilatation or pancreatic outgrowth, also absence of the urorectal septum and an imperforate anal membrane. There was a single hydronephrotic kidney with imperforate ureter, and ovaries without a demonstrable duct system.

The lungs were represented by a nodule of tissue 2 mm. in diameter in the neck, and recognizable only by histological examination. No trachea or oesophagus could be found and the larynx was a flat groove in the floor of the pharynx with two cartilage plates lying in front of this. An ovary was identified histologically.

The disturbance of development affected almost every structure, and the primary disturbance may well have been one operating for a period about the fourth week of intra-uterine life. About this period embryonic growth activity, which is slightly more advanced in the head region, is directed to the closure of the neural groove in the region of the spinal cord and to the organization of the overlying mesoderm. The primitive pharynx is forming and the laryngo-tracheal groove on its floor is the site of active growth which will later form the trachea and the paired lung buds. The four divisions of the heart are present and still separate (sinus venosus, atrium, ventricle, and bulbus cordis), but soon the septum primum and the bulbar ridges are to appear and the heart should assume its more adult shape and the auricular and ventricular chambers be divided by their septa. The differentiation of the skeleton of the limb buds is at a critical stage. The anlage of the liver has appeared but the stomach enlargement and the dorsal and ventral outgrowths of the pancreas are scarcely to be recognized. The expanding cloaca has scarcely yet begun to be divided by the growth of the urorectal septum. Development of a part of the genito-urinary system is also active, but even if this were disturbed, renal structures might still be derived at a later date from the caudal end of the Wolffian duct system where developmental activity is somewhat later.

Suggested Mechanism for Production of Abnormalities

In both cases multiple sections of the partition between the foetuses showed no extension of chorion into the partition between the two foetuses. Both, and especially case 2, showed anastomoses of large blood vessels of the two circulations. In neither case was one foetus parasitic on the other. Competition between the circulations of two foetuses for the utero-placental site is likely to be keenest in the early growth period when villi are growing out from the entire surface of the chorion. Later, when the site of villous attachment normally comes to cover only a part of the larger chorion, there is a more ample area for each circulation to develop in some independence from the other and from localized defects in the maternal decidua.

It is perhaps reasonable to suggest that one twin in both of these pregnancies experienced inadequate nutrition early in gestation, but, unlike most blighted ova, survived to experience an ample nutrition which permitted continued growth as gestation continued. Any extraneous influence, such as maternal toxæmia or infection, should have affected genetically equal twins equally. This deficiency of nutrition is not likely to have been a complete deprivation of one or more specific substances, though those substances whose transfer at that period of gestation was most difficult would be most seriously reduced. It is most useful to regard the disturbance as a somewhat non-specific influence causing an ‘arrest of development.’ Ingalls (1947) and Ingalls and Gordon (1947) have elaborated the earlier work of Stockard on
ARCHIVES OF DISEASE IN CHILDHOOD

non-mammalian embryos and have suggested that development can be arrested in a variety of ways and that the result is not specific to the agent, but depends on the time of development at which the agent acts. The disturbance operates not on some specific organ or stage of differentiation, but on whatever organ or organs happen to be undergoing the most active growth changes at that time.

A profound knowledge of normal development might enable the time of a developmental arrest to be established and perhaps related sometimes to the operation of a known agent such as German measles. Developmental changes are crowded together, especially in the second month, but, if the arrest of development has affected several organs whose development has been at a recognizable stage, the coincidental occurrence of abnormalities in different organs might be significant and suggest a non-specific environmental agent operating at a period critical for the development of all of them. A disturbance in growth activity and in the production of those chemical substances which are concerned with organ differentiation will cause retardation and disorganization in those organs which are at that moment developing most actively. Other parts of the body, which are also growing, but at a slower rate, and whose demands are less exacting, may be less disturbed. When conditions improve these may continue their growth with little disturbance and establish their normal connexions. A stage of development once omitted cannot take place at a later period, but its omission may disturb development at a later stage or in another organ. Embryological data are much concerned with when developmental processes start and finish, but neither of these events may be of essential importance and data on the critical periods of growth in different organs are most desirable. There are many difficulties in the detailed study of multiple congenital anomalies, and embryology has contributed little to an understanding of the mechanism of their occurrence. The coincidence in different organ systems of what may be regarded as arrests of development is often surprising in cases, such as those presented, where there are multiple abnormalities. Especially when the genetic contribution is revealed by the existence of a monozygotic and normal twin, this seems to favour an environmental causation as opposed to a genetic basis.

Though these two cases are presented to suggest that environment sometimes determines congenital malformation, it is not intended to suggest that the environment is the only cause of congenital malformation. If this viewpoint should receive further support efforts to improve the supply of the metabolic constituent or constituents limiting embryonic growth at the critical period, perhaps by increasing the level in the maternal blood, are relevant and might result in some reduction in the incidence of congenital malformation. A belief in the exclusive operation of an unalterable genetic inheritance must be avoided.

Summary

Two sets of twins with monochorionic placentae and placental vessel anastomoses are regarded as monozygotic twins. One of each set showed malformations affecting many different organs. Since the genetic inheritance of the malformed twin should be similar to that of its normal partner, it is suggested that the malformations arose from an arrest of normal development when the placenta of one twin was at some environmental disadvantage in obtaining nutrition from the utero-placental site for a short period early in intra-uterine life. The abnormalities found were consistent with some such non-specific influence causing an arrest of development of those structures whose formation might be in a critical stage at about the sixth and fourth week respectively.

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