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ECTOPIA CORDIS IN MAN

BY

R. KANAGASUNTHERAM AND J. A. VERZIN

From the Departments of Anatomy and Obstetrics and Gynaecology, University of Khartoum, Sudan

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Ectopia cordis in man is a relatively rare anomaly and has been known for many years, being first reported in 1671 by Neil Stensen (Willius, 1948). A translation of the relevant excerpt from Stensen's article reads, ". . . the sternum was split and the heart, liver and spleen, most of the intestine and right kidney have passed out through the split being thus uncovered." This description is undoubtedly that of a case of ectopia cordis and antedates the case of Haller (1706, quoted by Byron, 1948) and Martinez (1706), usually regarded as the first to have been reported. Since then over 180 cases have been described.

A survey of the available literature indicates confusion as to the exact meaning of ectopia cordis. Ectopia is derived from the Greek *ektopos*, meaning away from a place, and implies an abnormality in the position of an organ or a part of the body, often congenital in origin. According to this definition ectopia cordis should include conditions such as dextrocardia, in which the heart remains within the thorax. Barlow (1938) is correct in suggesting that if ectopia cordis is to include this type of defect it should be qualified as intrathoracic. It seems, however, that ectopia cordis has been mainly limited to those congenital anomalies in which the heart is not entirely within the chest cavity, and Abbott (1927) qualifies ectopia cordis as a " displacement so that the heart passes out of the thorax and comes to lie either on the outer surface of the body or in the abdominal cavity." Even this definition overlooks malpositions of the heart in relation to the cervical region. Similarly, Kalter and Warkany (1959) disregard the cervical and abdominal types of the defect when they define ectopia cordis or ectocardia as a " congenital exposure of the heart due to insufficient development of the chest." Moreover, it is evident that the term " displacement " is inappropriate when referring to the cervical type of ectopia cordis, since in these cases the heart is merely retained in its embryonic position in the neck. In view of these difficulties we suggest that ectopia cordis be defined as a congenital malposition of the heart, partially or completely outside the thorax.

CLASSIFICATION

Ectopia cordis has been classified by Weese (1818), by Townsend (1833), and by Rauchbussz (1878), but these authors have not taken into consideration all the possible types of the defect and therefore the following classification is suggested.

CERVICAL.—The heart is entirely in the cervical region but the sternum is usually intact.

THORACO-CERVICAL.—The heart is partially in the cervical region but the cranial end of the sternum is defective.

THORACIC.—The sternum is defective and the heart lies outside the thorax, partially or completely.

THORACO-ABDOMINAL.—This subdivision was first suggested by Byron (1948), and, according to Major (1953), the condition should be accompanied by a partially absent or cleft sternum, by a diaphragmatic defect, and by a midline abdominal defect of diastasis recti or omphalocoele type.

ABDOMINAL.—This presupposes a diaphragmatic defect allowing the heart to enter the abdominal cavity.

Although some 180 cases have been reported, the condition is comparatively rare, the nomenclature confusing, and the pathology so obscure that it seems justifiable to report a further case. In this paper an attempt will be made to discuss the pathogenesis of this interesting phenomenon.

NECROPSY REPORT

The body was that of a partially macerated stillborn full-time female. Pregnancy was reported to have been uneventful and labour normal. The infant was well developed, measuring 30 cm. from crown

to rump and weighing 7 lb. An ectopia cordis associated with other developmental anomalies was present (Fig. 1).

EXTRA-CARDIAC ANOMALIES.—These consisted of (a) prolapse of the forebrain vesicles through a defect in the frontonasal region of the skull, (b) median harelip unassociated with cleft palate, and (c) diastasis recti.

FIG. 1.—Full-time foetus showing ectopia cordis with other developmental anomalies.

JUXTA-CARDIAC ANOMALIES.—An elliptical defect extended from the lower border of the first rib to the insertion of the umbilical cord. The manubrium was intact but the rest of the sternum was cleft. At its widest, between the fourth and seventh costal cartilages, the sternal gap measured 4.3 cm. The heart passed through the upper part of the defect while the lower half was occupied by a protrusion of the liver covered by membrane.

CARDIAC ANOMALIES.—The heart was completely exposed and lay entirely outside the thorax. The displacement was such that the heart was at right angles to the chest wall and as a result of foetal flexion it abutted against the chin. The heart was not covered anteriorly by parietal pericardium and so the myocardium and the serous pericardium were exposed. The parietal pericardium was limited to about 1 cm. surrounding the cone of vascular bundle entering the heart. This pericardium fused at its periphery with the marginal tissue of the skin defect.

The heart was four-chambered. A curled process 2 cm. long and resembling a pig's tail arose from the surface of the heart near its apex. The interventricular septum was crescent-shaped and represented only the caudal part of the normal septum. The interatrial septum was also deficient. The aorta and the pulmonary trunk arose from the conical cranial end of the right ventricle. Thus the aorta had no direct communication with the left ventricle.

The right lung was composed of four definite lobes, the fourth being the azygos lobe lying in an extension of the pleural cavity between the inferior vena cava and the oesophagus. The left lung was normal and the diaphragm was complete.

REVIEW OF THE LITERATURE (1938–1961)

Up to 1939 the literature on ectopia cordis had been reviewed by Breschet (1826), by Greig (1926), by Roth (1939), and to some extent by Herxheimer (1910). More recently, Byron (1948) stated that 142 cases (including his own) had been reported. We have added a further six cases missed by Byron (Molinengo, 1939; Stephan, 1942; Prendergast, 1943; Ammal, 1946; Burton (2 cases), 1947). Another 33 cases have been recorded since 1948 (Table I). Lee (1957) claimed that he had collected the records of over 200 cases, but we were unable to verify this claim. Millhouse and Joos (1959) reviewed the literature concerning thoracic ectopia cordis and found 50 cases of this type. Blatt and Zeldes (1942) gave a detailed description of all reported cases up to 1938, since when no similar review has been attempted. We have therefore examined the literature from 1938 onwards and collected a further 48 cases which are listed in Table II. Apart from certain instances where the literature was unobtainable, we have included all the available details. Table III shows the relative frequency of the various types of ectopia cordis and indicates that 62.5% are of the thoracic type.

EMBRYOLOGY OF THE HEART, DIAPHRAGM, BODY WALL, AND STERNUM

Towards the beginning of the third week the bilaminar germ disc becomes trilaminar as

TABLE I

REVIEWS OF THE LITERATURE ON ECTOPIA CORDIS

Author	Period Reviewed	No. of Cases
Stensen (1671)	First case report	1
Roth (1939)	1706–1938	108 (with case report)
Blatt and Zeldes (1942)	1706–1938	added 19 (with case report)
Byron (1948)	1706–1948	added 15 (with case report)
This paper	1938–1948	added 7 (6 missed by Byron and 1 case of Taussig reported by Millhouse and Joos (1959)
This paper	1948–1961	34 (with case report)
	Total	184

TABLE II

CASES OF ECTOPIA CORDIS REPORTED BETWEEN 1938 AND 1961

No.	Author	Sex	Length of Gestation (Weeks)	Type§	Extra-cardiac Anomalies	Age at Operation	Survival
1	Puddu and Cammarella (1938)	M	‡Premature	Thoracic	Small meningocoele; hare-lip; omphalocoele; reduced index finger (left); bilateral equinovarus	—	5 days
2	Hofmann (1938)	F	Term	Abdominal	Supernumerary ribs (right)	20 days	Died soon after operation
3	Molinengo (1939)						
4	Sosyal (1940)	U‖	U	Thoracic	U	U	U
5	Kühnel (1940)	M	Term	Thoraco-abdominal	Cleft sternum	—	26 hours
*6	Finocchietto (U)	U	U	Thoracic	U	U	U
7	Stephan (1942)	M	U	Probably abdominal since only the ensiform was absent	—	—	33 hours
8	Prendergast (1943)	F	Term	Thoracic	Transposition of aorta and pulmonary artery; absent ductus arteriosus	—	65 ,,
9	George (1945)	U	Term	,,	—	—	6 ,,
*10	Taussig (1946, approx.)	U	U	,,	"Grossly malformed"	—	U
11	Ammal (1946)	U	U	,,	—	—	3 ,,
12	Burton (1947)	M	U	Thoraco-cervical	Cleft sternum	U	Alive
13	,,	F	U	Thoracic	,, ,,	12 years	,,
14	Byron (1948)	F	Term	,,	Cleft sternum; incomplete descent of caecum; abdominal ascites	22 hours	Died soon after operation
15	Klassen (1949)	M (twin)	Premature	,,	Cleft sternum	Soon after birth and at 8 months	Died soon after second operation
16	Friedlieb and McDonald (1950)	M	Term	,,	Cleft sternum; coarctation of aorta; bilateral talipes equinovarus; omphalocoele	12 hours	Died soon after operation
17	Feeney (1950)	U	U	,,	U	U	U
18	Santy and Duroux (1951)	M	U	Abdominal	Diaphragmatic defect	77 years	Successful
*19	Sweet and Parks (1952)	U	U	Thoracic	U	U	U
20	Becker (1952)	F	34	,,	Cleft sternum	Soon after birth	Died soon after operation
21	Wilson (1952)	F	37	,,	Bilateral hare-lip; cleft palate; cleft sternum	—	9 hours
22	Nguyen-Huu and Cazes (1952)	F	Term	,,	Hare-lip; cleft palate; left superior vena cava; retro-oesophageal subclavian arteries	At birth	Died 11½ hours after operation
23	Major (1953)	F	,,	Thoraco-abdominal	Cleft sternum; protrusion of liver through abdominal defect	,, ,,	Alive 12 mths after operation
*24	University of Wisconsin Hospital (1953)	M	,,	Thoracic	Pulmonary veins absent; stenosis of pulmonary artery	U	U
25	Saxén and Kinnunen (1954)	F	,,	,,	Cleft sternum	—	6¼ hours
26	Maciejewski (1954)	F	U	Abdominal	—	—	33 years
*27	John Gaston Hospital Memphis, Tenn. (1954)	F	U	Thoracic	U	U	U
28	Scott (1955)	M	Term	Thoraco-abdominal	Cleft sternum	3 years	Alive at 7 years
29	Ruckes (1955)	F	,,	Abdominal	Umbilical hernia	At birth	Died 6½ hours after operation
30	Dominiczak (1956)	F	,,	Thoracic	—	—	15 hours
*31	Steiner-Pritzker (1956)	F	,,	,,	—	—	—
32	Lee (1957)	M	,,	Thoraco-abdominal	—	19 hours	Died 55 min. after operation
33	,,	M	Premature	,,	Diaphragmatic defect; lobulated kidney; abdominal testes	—	1½ hours
34	Crelin (1957)	F	28	Thoracic	Eventration of abdominal viscera; cleft sternum; oblique facial cleft; frontal, parietal and interparietal portions of occiput missing; single cerebral hemisphere with single tubular ventricle; corpus callosum absent	—	12 ,,
35	Sabiston (1958)	M	Term	Thoraco-cervical	Cleft sternum	28 months	Alive 2 years after operation
36	Gavrilov and Kolomatskii (1958)	F	U	Thoraco-abdominal	Diaphragmatic defect	—	U
37	,, ,,	F	U	Cervical	Hernia of brain; cleft palate; common truncus arteriosus	—	U
†38	Douglas (1958)	U	U	Thoracic	Persistent left superior vena cava; cleft sternum	Soon after birth	Died soon after operation
39	Ferreira and Pimentel (1958)						
40	Hurwitt and Lebendiger (1959)	M	28	,,	Cleft palate; diastasis recti	At birth	Died soon after operation

[Continued overleaf

TABLE II—*continued*

No.	Author	Sex	Length of Gestation (Weeks)	Type	Extra-cardiac Anomalies	Age at Operation	Survival
41	Meitner (1959)	M	Term	Thoracic	Cleft sternum; harelip; cleft palate; hydrocephaly; bilateral anophthalmia	—	3 days
42	Millhouse and Joos (1959)	M	38	,,	—	—	8 ,,
43	,, ,,	M	Term	,,	—	At birth	Died 52 hours after operation
44	Lederman (1959)	M	Premature	,,	Transposition of great vessels; hypoplasia of pulmonary artery	—	5 days
45	Brown (1960)	F	U	,,	Cleft sternum	At birth	Alive 1 year after operation
46	Lumsden (1960)	F	37	Thoracic or thoraco-abdominal	Eventration of liver, spleen, and intestine	—	12 hours
47	Lambert (1960)						
48	This paper	F	Term	Thoracic	Prolapse of forebrain vesicles; median harelip; diastasis recti	—	Stillborn

* Cases quoted directly from Millhouse and Joos (1959), who obtained them from personal communications.
† Douglas calls his case "ectopia cordis cervicalis." The photograph and anatomical description ("through a deficiency in the centre part of the chest") suggest, however, that the ectopia was rather of the thoracic type.
‡ When the length of gestation was not given by the author we relied on the weight of the infant. If this was 5½ lb. (2,500 g.) or below, we regarded the infant as premature.
§ When the type of ectopia cordis was not specifically stated in the relevant articles, we based our diagnosis on the anatomical description or on the photograph.
‖ U=unknown.

mesoderm differentiates from the primitive streak while Hensen's node contributes to the formation of the notochordal process. The mesoderm spreads peripherally and by about the 18th day the intraembryonic coelom makes its first appearance in the region of the future pericardial cavity. Coelom formation is generally described as a splitting of the lateral sheet of the intra-embryonic mesoderm into somatic and splanchnic layers. It is perhaps more accurate to regard the coelomic cavity as resulting from the rapid coalescence of discrete coelomic spaces (Wyburn, 1938; Patten, 1946; and Hamilton, Boyd, and Mossman, 1952). Moreover, the coelom has a significant role to play in the nutrition of the early embryo (Streeter, 1942).

The heart develops as paired primordia in the visceral mesoderm overlying the anterior end of the yolk sac (Fig. 2) while the parietal pericardium and septum transversum are formed simultaneously from the somatic mesoderm adjoining the developing heart. With the folding of the embryo the paired cardiac tubes come to lie on the ventral and cranial part of the foregut and fuse to form the single heart tube. Similarly a single pericardial cavity is soon established and the septum transversum now comes to lie caudal to the heart.

The septum transversum forms the major part of the diaphragm. Wells (1954) describes the diaphragm as a single structure with six subdivisions, transverse septal, membranous (pleuroperitoneal membranes), costal, retroglandular, aortic, and mesogastric. The transverse septal

TABLE III

ECTOPIA CORDIS ACCORDING TO TYPE (1938–1961)

Type	No. of Cases
Cervical	1
Thoraco-cervical	2
Thoracic	30
Thoraco-abdominal	6
Abdominal	4
Uncertain	2
Unknown	3
Total	48

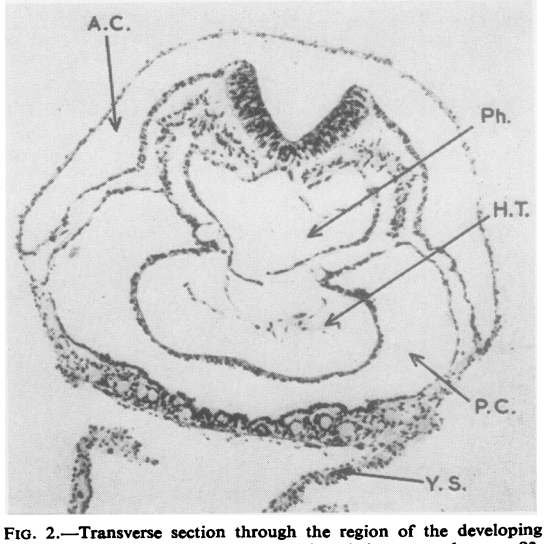

FIG. 2.—Transverse section through the region of the developing heart in a 1.8 mm. crown-rump length human embryo, ×83. A.C.=amniotic cavity; Ph.=pharynx; H.T.=heart tube; P.C.=pericardial coelom; Y.S.=yolk sac.

portion forms not only the central tendon but also the sternal as well as parts of the costal and lumbar portions of the diaphragm. The muscular elements of the diaphragm are said to be derived from the cervical myotomes, but Wells (1954) believes that at least a part of the diaphragmatic musculature is formed *in situ*.

The somatic mesoderm contributes to the connective tissue of the anterior body wall while the muscular elements are derived from the mesoderm of the somites. The epidermis of the body wall is formed from the embryonic ectoderm. In the thoracic wall and the supra-umbilical portion of the abdomen there is a stage when the embryonic ectoderm appears to be further away from the midline with the result that confluent somatic and visceral mesoderms form the lining of the ventral surface of the heart and the supra-umbilical body wall (Fig. 2).

The sternum begins to develop about the fifth week of intra-uterine life as paired lateral condensations of mesenchymal cells in the thoracic region. They are converted into precartilage and advance towards the midline where they fuse into the single sternal anlage. The process of fusion proceeds craniocaudally and is complete by the ninth week. Simultaneously, the rib cartilages grow ventrally from the vertebrae and become attached to the sternum. In an experimental study on the morphogenesis of the mouse sternum, Chen (1953) found that fusion of the bilateral sternal bands could be prevented by delaying the movement of the sternal halves towards one another.

Discussion

It is probable that ectopia cordis originates during the very early stages of development, perhaps as early as the third week of embryonic life. The end-results of the anomaly are well known, but almost nothing is known of the critical developmental stages. Although several facts regarding the stages leading to such malformation can be ascertained from the descriptions of the different grades of the defect, much remains a speculation. Ectopia cordis in other mammalian embryos, whether experimentally induced or resulting from genetic incompetence, may afford certain clues, but due care should be taken in transferring such findings to the study of man.

Any explanation as to the mode of formation of ectopia cordis must give due recognition to the different varieties of the defect and to the normal course of development of the heart and body wall. In a shrewd speculation, Patten (1946) postulates that the anomalous development begins about the third week of embryonic life when the demarcation between intra- and extra-embryonic coelom is being established by the folding of the embryo. He also suggests that when the ventral body walls of the cardiac region are being formed they must catch the heart outside their place of convergence rather than inside, as occurs normally (Fig. 3). While this hypothesis could adequately explain cases of the thoracic type, such as the one reported here, it overlooks those cases of partial ectopia in which the pericardium and skin are found covering the ectopic heart (Fig. 4). It is difficult to believe that there are differences in the mode of formation of partial and complete ectopia

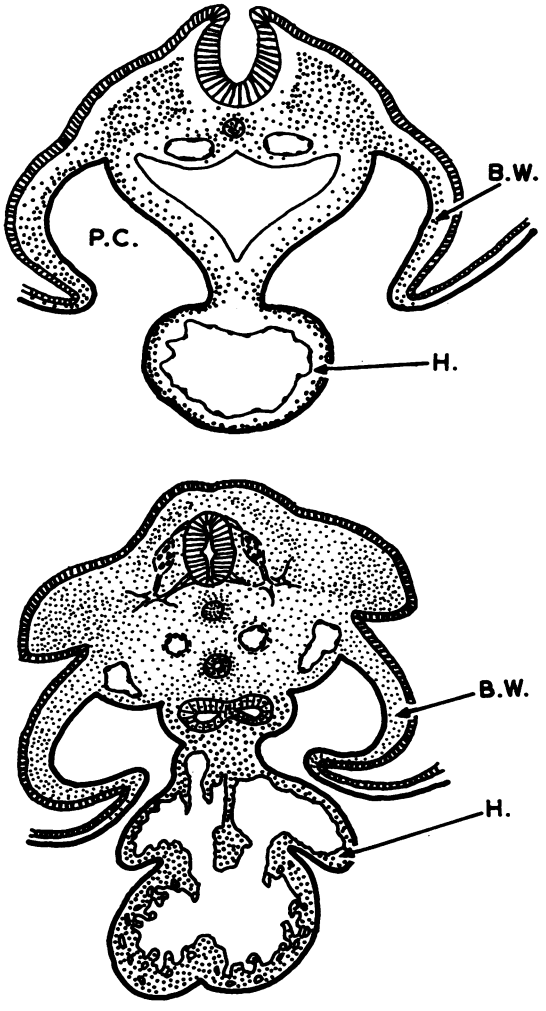

FIG. 3.—Diagrammatic representation of the formation of ectopia cordis (after Patten, 1946). P.C.=pericardial coelom; B.W.=body wall; H.=heart.

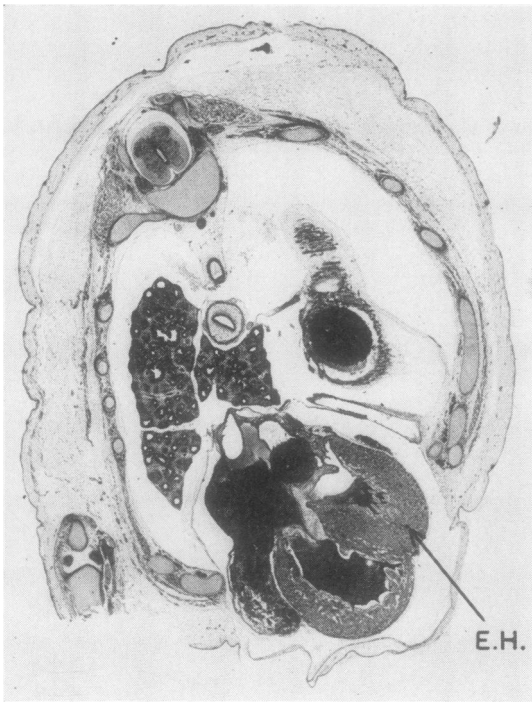

FIG. 4

FIG. 4.—Transverse section through the region of ectopic heart in a 29 mm. crown-rump length dog embryo, ×44. (By kind permission of the Editor, *Journal of Research in Veterinary Science*, April, 1960.). E.H.=ectopic heart.

FIG. 5.—Transverse section through the region of the developing lung and pleural cavity in a 13.5 mm. crown-rump length human embryo, × 127. S.Pl.C.=spaces around pleural cavity; Pl.C.=pleural cavity; L.=lung; Oe.=oesophagus; A.=aorta.

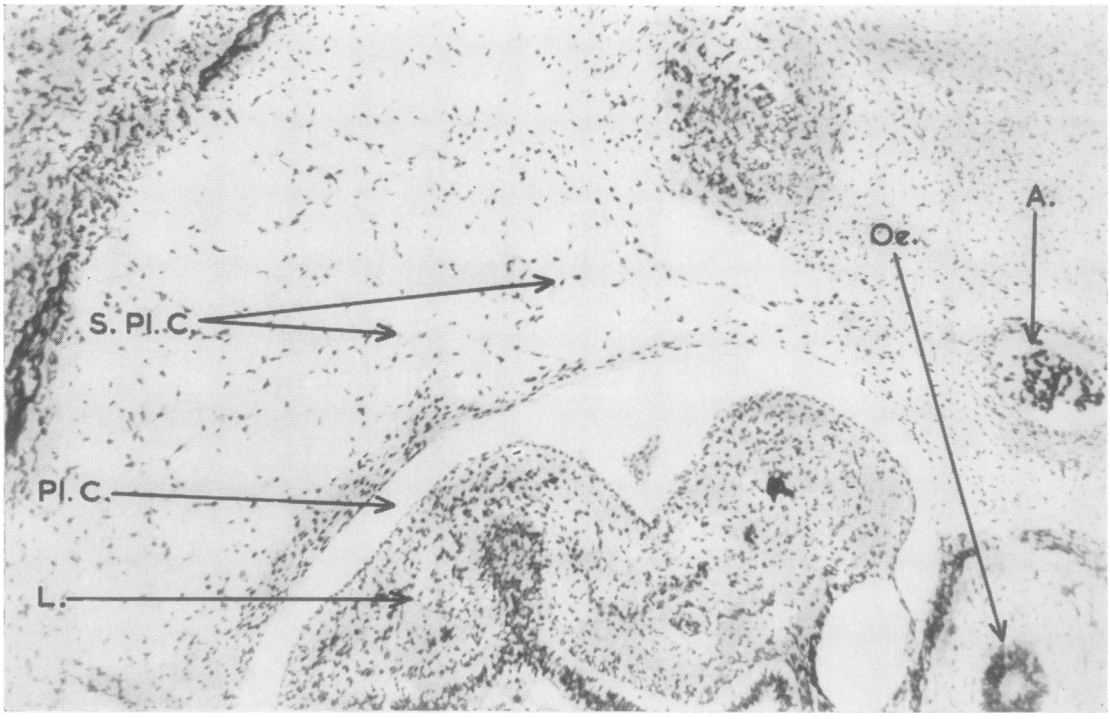

FIG. 5

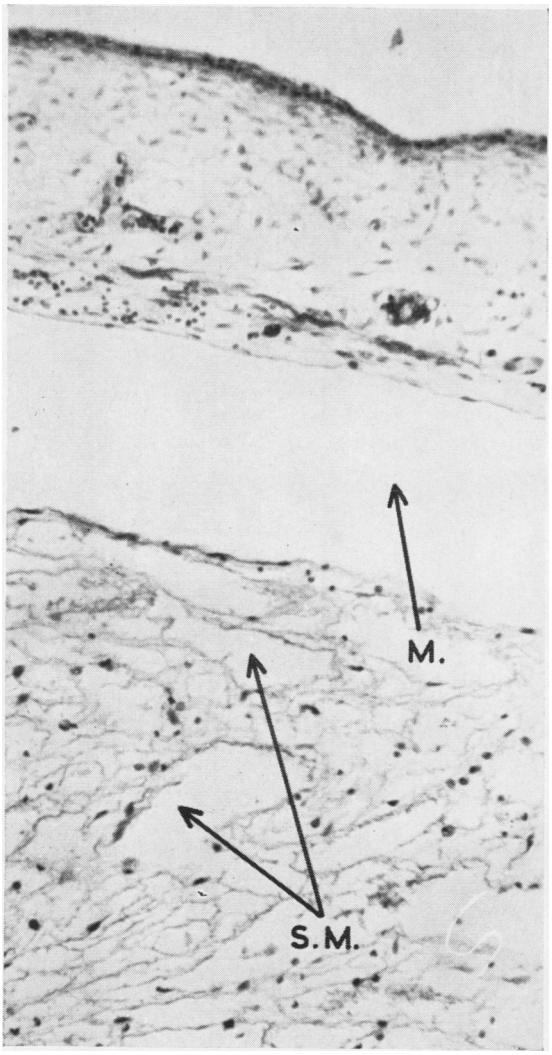

FIG. 6.—Transverse section through the region of a meningocoele in a 29 mm. crown-rump length dog embryo, × 135. (By kind permission of the Editor, *Journal of Research in Veterinary Science*, April, 1960.) S.M. = spaces around meningocoele; M. = meningocoele.

cordis, and we think that herniation of the pericardium and partial or total ectopia cordis are but different grades of the same malformation.

Cantrell, Haller, and Ravitch (1958) discuss a syndrome of congenital defects involving the abdominal wall, sternum, diaphragm, pericardium, and heart. They are of the opinion that the loss of a part of the diaphragm and pericardium results from a defective portion of mesoderm in the septum transversum. Such a mesodermal failure could result from a diminished activity of the primitive streak, as described by Wyburn (1937) in the human embryo. It is, however, known that defects similar to those occurring in man are also found in the lower mammals in which the primitive streak is more active. Furthermore, Cantrell *et al.* (1958) say that there could be a diaphragmatic defect without a corresponding affliction of the pericardium and *vice versa*. According to them, this requires a highly specific loss of the somatic mesoderm of the one without any alteration of that of the other.

Kanagasuntheram and Perumal Pillai (1960), in their description of a case of ectopia cordis in a dog embryo (Fig. 4), note that the covering over the ectopic heart was overstretched and thin and so postulate that the mechanical action of the ectopic heart could ultimately break through this

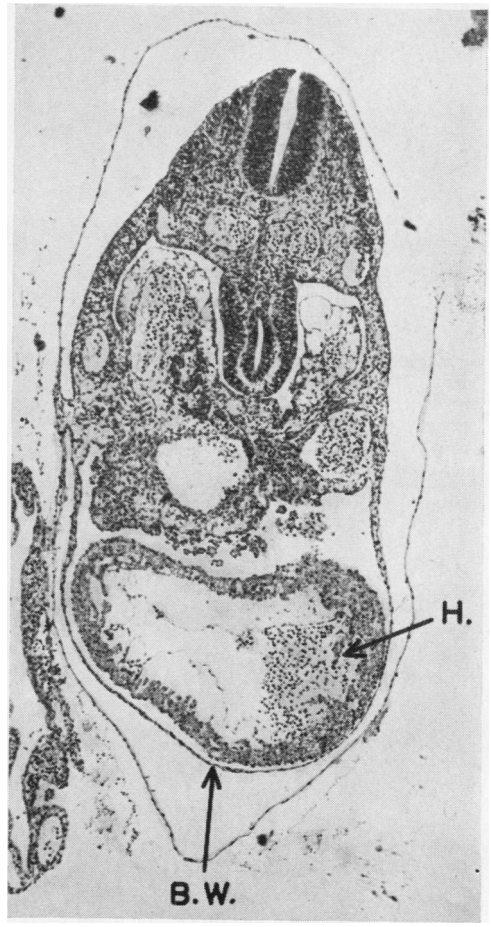

FIG. 7.—Transverse section through the body wall of a 4.0 mm. crown-rump length human embryo, × 135. H. = heart; B.W. = body wall.

thin membrane. Although this may be a plausible explanation for the thoracic type of ectopia cordis, it does not throw any light on the mode of formation of the abdominal type of defect.

A fourth possibility invokes an abnormal mode of formation of the coelomic cavity during the early embryonic stages when the coelom begins to develop by the coalescence of isolated mesenchymal clefts. A defective coalescence of these clefts leading to abnormal adhesions of the stomach and lung to the body wall was observed by Kanagasuntheram (1957). The possibility of excessive formation of coelomic spaces, resulting in a reduction of the mesodermal elements, has not been sufficiently explored. Fig. 5 shows normal cavitation occurring in the body wall adjoining the pleural cavity in a human embryo, and Fig. 6 depicts abnormal cavitation near the site of a meningocoele in a dog embryo. In both instances the spaces referred to would probably be absorbed into the pleural cavity or meningocoele on the disappearance of the thin partitions separating them from the main cavities. Abnormal cavitation could indeed lead to a partial or total loss of a portion of somatic mesoderm resulting in different degrees of loss of the diaphragm, pericardium, or body wall. This becomes intelligible when one examines a young human embryo in which the body wall is still very thin (Fig. 7). Hypothetical stages leading to the formation of various anomalies are shown in Fig. 8. When the deficiency in the primitive mesoderm of the body wall is established, the muscular elements derived from somites could

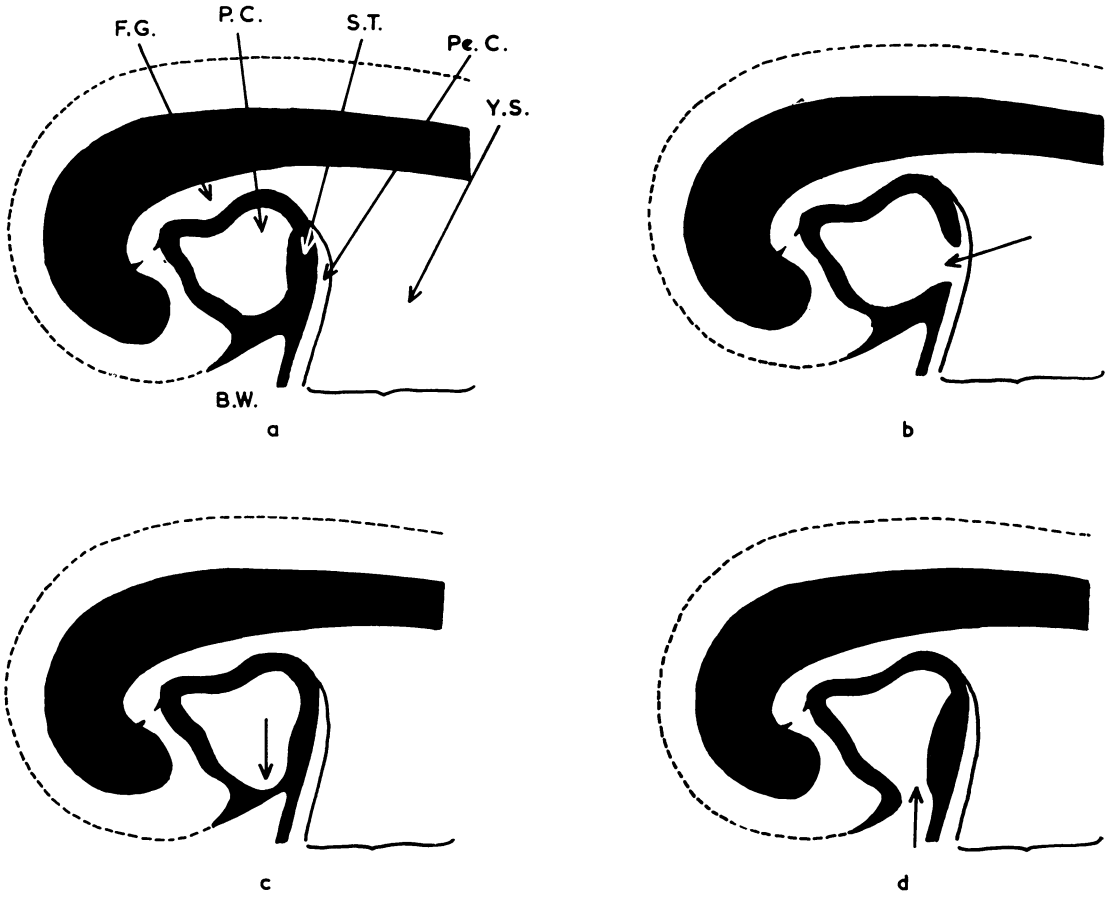

FIG. 8.—Hypothetical stages in the formation of the thoracic and abdominal types of ectopia cordis: (*a*) normal stage; (*b*) ectopia cordis abdominalis; arrow indicates site of destruction of septum transversum due to excessive pericardial coelom formation; (*c*) and (*d*) two stages in the formation of thoracic ectopia cordis; arrows indicate site of destruction of body wall. F.G.=foregut; P.C.=pericardial coelom; S.T.=septum transversum; Pe C.=peritoneal cavity; Y.S.=yolk sac; B.W.=body wall.

only migrate ventrally and medially to the edge of the defect. They would undergo normal differentiation and so most of the muscles of the ventral body wall would appear to be normal except for divarication of the rectus abdominis muscles. Similarly, such a defect in the primitive mesenchyme of the body wall could effectively prevent medial migration and fusion of the sternal bands (Chen, 1953). A similar mechanism could be envisaged to operate in the diaphragm.

The abnormal position of the heart in the cervical type of ectopia cordis is explicable on the basis of its situation near the mandibular arch during early development and its subsequent descent into the thorax. Thus all degrees of cervical ectopia cordis, ranging from those in which the heart projects from the region of the mouth cavity to those in which it is partly inside the thorax, represent various grades of arrested descent. The abdominal type of ectopia cordis would entail further abnormal descent of the heart into the abdomen associated with a deficiency of the septum transversum.

The hypothesis advanced here not only offers an explanation of the mode of formation of the different grades of thoracic and abdominal types of ectopia cordis but also could account for instances where the pericardium is represented by only a few fibrous strands. Further support for this hypothesis is suggested by excessive coelomic cavity formation elsewhere, such as the expansion of the pleural cavity to accommodate an azygos lobe of the lung, a feature of the present case.

SUMMARY

A case of thoracic ectopia cordis with extracardiac anomalies is described. The literature relating to all varieties of ectopia cordis is reviewed from 1938 onwards. A possible explanation of the mode of formation of this defect is offered.

We wish to thank Professor H. Butler for his interest during the preparation of this paper, and Professor J. D. Boyd for the loan of the 1.8 mm. and 4 mm. human embryos. Our thanks are also due to Mr. J. F. Crane, Department of Anatomy, University of Cambridge, for the photomicrographs, Mr. J. Dew for Fig. 1, and Mrs. R. Kanagasuntheram for the line drawings.

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