A Morphological Study of the Development of the Human Liver [1]

II. ESTABLISHMENT OF LIVER PARENCHYMA, EXTRAHEPATIC DUCTS AND ASSOCIATED VENOUS CHANNELS

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ABSTRACT The establishment of liver parenchyma, extrahepatic ducts and associated venous channels were examined in serial sections of 100 human embryos representative of Horizons XI through XVII.

The liver parenchyma first begins to develop from the cephalic end of the hepatic diverticulum in embryos between the 20- and 25-somite stage. The parenchyma develops as cords from the walls of the diverticulum which anastomose around isolated endothelium-lined spaces (blood islands) in the septum transversum. As growth and anastomoses of the parenchymal cords continue, the isolated endothelium-lined spaces form an interconnecting capillary bed which interdigitates with the developing parenchymal cords. The larger omphalomesenteric veins develop simultaneously with the parenchyma and are continuous with the smaller venous channels which interdigitate with the parenchymal cords. These larger developing veins become surrounded by the developing parenchymal cords. As the parenchymal cords branch from the cephalic end of the diverticulum, that portion of the diverticulum becomes reduced to a small tubular structure, the common hepatic duct, which is always continuous with the parenchyma. As the cephalic portion of the original diverticulum is reduced in size, there is a localized outgrowth from the ventral wall of the caudal end of the original diverticulum. This localized outgrowth becomes the cystic duct and gallbladder. The remainder of the caudal segment of the diverticulum elongates to become the common bile duct. The ventral pancreas develops as a localized outgrowth from the dorsal wall of the common bile duct.

Whereas the early works on liver development (summarized by Lewis, '12) were general in their description, more recent investigations have yielded precise but conflicting points of view. It is generally agreed that the liver parenchyma proliferates as endodermal cords of cells from the cephalic end of a diverticulum and that these grow out into the mesenchyme of the septum transversum and anastomose (Arey, '65; Davies, '63; Hamilton et al., '62; Patten, '68; DuBois, '63). Elias ('55) is in partial disagreement with this interpretation. He states that the parenchymal cells never form cords and that the parenchyma is not solely of endodermal origin.

Most investigators conclude that the vascular pattern of the liver is established through invasion of cords of parenchymal cells into large veins, dividing the large veins into a plexus of smaller vascular channels. This plexus is secondarily tapped by the umbilical vein. The plexus of veins develops into the liver sinusoids, and portal and hepatic veins. Contrary to this interpretation originated by Minot ('00) and Lewis ('04), Lipp ('52) and Elias ('55) described the sinusoids as arising *in situ* as preformed vessels which become surrounded by parenchymal cells.

The lack of a sequential developmental series of human specimens and the use of other non-human species has prevented definitive answers to these problems. The use of non-human species is not reliable

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for extrapolating liver development in man as has been pointed out by Elias ('55) in his extensive comparative work. In his study he found at least 12 different modes of liver development in the various species he studied. Availability of an extensive sequential series of human embryos permitted this more exact study on the morphological development of the liver parenchyma and vasculature.

MATERIALS AND METHODS

This study was based on light microscopic examination of serial sections of 100 human embryos in which the morphological changes in the liver were traced through their complex developmental stages. These embryos were from the Patten Embryology Collection of the Department of Anatomy, The University of Michigan, Ann Arbor, Michigan, and from the collection of the Department of Embryology, Carnegie Institution of Washington, Baltimore, Maryland.

Streeter's ('51) criteria for categorizing embryos into developmental age groups or "horizons" were used, where possible, to determine the developmental stages of the embryos in this study. Embryos within Horizon XII were classified more specifically according to somite stages. When more than one embryo was available at a developmental stage they were cross-checked for morphological similarities and/or differences within that stage and also compared with the preceding and following stages.

Structural changes are reported for the liver in embryos of Horizon XII through XVII.

OBSERVATIONS

Horizon XII

In Horizon XII the hepatic diverticulum was definitively developed and parenchymal growth from the cephalic end of the diverticulum established the right and left lobes of the liver. The primordium of the cystic duct-gall bladder developed as a localized outgrowth from the ventral wall of the diverticulum. The ventral walls of the ductus choledochus and midgut were established. The mass of the septum transversum increased and a hemangioblastic tissue developed within it, thus establishing the parenchymal-endothelial relationship of the liver.

Twenty-two somite embryo. In the 22-somite embryo (fig. 1) the hepatic diverticulum was a well-defined hollow structure. The walls of the diverticulum were of the same thickness as the walls of the caudal region of the foregut, with which it was continuous, but thicker than the walls of the cephalic end of the foregut. The diverticulum was a single unit, but its lumen extended laterally at its cephalic end. This cephalic segment of the diverticulum was in juxtaposition with the mesoderm of the septum transversum on its ventral and lateral surfaces. The caudal end of the diverticulum was smaller with a rounder lumen and was surrounded by the mesodermal cells of the septum transversum. The bulk of this mesoderm was ventral and lateral to the diverticulum. There was little mesoderm between the ventral wall of the foregut and the dorsal wall of the diverticulum; the cephalic end of the diverticulum was separated from the endothelium of the sinus venosus by a small amount of intervening mesoderm. From the ventral and lateral surfaces of the diverticulum, where the endoderm was in contact with the bulk of the mesoderm, short sprouts of endodermal cells extended into the septum transversum. The septum transversum consisted of a mass of loosely arranged mesodermal cells in which appeared small isolated spaces (fig. 2). The mesodermal cells adjacent to the larger spaces were compressed and evenly aligned around the spaces and formed an endothelial boundary. These endothelium-lined spaces resembled capillaries or sinusoids. Although these endothelium-lined spaces were dispersed throughout the septum transversum, the larger ones were located close to the diverticulum. Between these endothelium-lined spaces were endodermal sprouts from the diverticulum. Dorsolateral to the diverticulum (near the omphalomesenteric veins) some of the endothelium-lined spaces were continuous with the larger omphalomesenteric vessels.

At the caudal end of the diverticulum the dorsal wall of the diverticulum was continuous with the ventral wall of the foregut and the lumen of the diverticulum

was continuous with the lumen of the foregut. The ventral wall of the diverticulum was abruptly reduced to a single layer of cells which were part of or continuous with the endoderm of the yolk sac (fig. 3). At this level the lateral and ventral walls of the foregut-diverticulum complex were surrounded by mesoderm. In the mesoderm lateral to the common chambers of the foregut and diverticulum were two vessels, the omphalomesenteric veins, which became progressively smaller at caudal levels and became continuous with the capillary bed of the yolk sac. The mesoderm correspondingly diminished in amount and was confluent with the mesoderm of the yolk sac.

Twenty-three somite embryo. Whereas in the 17-somite embryo (fig. 4) the endoderm representing the primordium of the ventral wall of the hepatic diverticulum lay parallel to the parietal pericardium and was separated from it by a small amount of mesoderm, in the 23-somite embryo this endoderm was nearly perpendicular to the pericardial layer and separated from it by a large amount of mesoderm. It formed the ventral wall of the hepatic diverticulum in the 23-somite embryo (fig. 5). The diverticulum was completely surrounded by loosely arranged mesoderm and as in the 22-somite embryo, the bulk of this mesoderm was ventral and lateral to the diverticulum. There was little or no mesoderm either between the cephalic end of the diverticulum and the caudal surface of the sinus venosus or in the dorsal cleft between the diverticulum and the foregut. The sinus venosus and the omphalo-umbilical trunks were on the cephalic surface of the "T-shaped" diverticulum where a slight transverse groove appeared on the cephalic surface of the diverticulum.

Contrary to the condition observed in the previous embryo, no endodermal sprouts extended from the ventral wall of the diverticulum. However, endodermal cells projected into the septum transversum from the lateral extremes of the "T." Small endothelium-lined spaces were observed in the septum transversum in these areas.

Twenty-five somite embryo. In the 25-somite embryo the hepatic diverticulum had the same general "T-shaped" configuration as in the 23-somite embryo. On the ventral surface of the diverticulum, immediately cephalic to the point at which the thickened endodermal wall was abruptly reduced to a single-cell layered yolk sac, was a prominent bulge in the wall of the diverticulum (fig. 6). This was the primordium of the cystic duct and gallbladder.

A cylindrical mass of endoderm projected rostrally from the cephalic end of the diverticulum to the caudal surface of the sinus venosus (fig. 7) and was surrounded by mesodermal cells of the septum transversum.

The mesoderm of the septum transversum surrounded the hepatic diverticulum. The mass of the septum was predominant ventral and lateral to the hepatic diverticulum with only a small amount between the foregut and the diverticulum. Where the septum was most massive, endothelium-lined spaces were present; the larger of these being closest to the diverticulum. Sprouts of endodermal cells extended from the ventral and lateral walls of the diverticulum. No sprouts projected from the dorsal wall. The longest and most prominent of these sprouts were from the lateral walls of the diverticulum and extended to the omphalomesenteric vessels, which were lateral and dorsal to the diverticulum (fig. 8). The sprouts were cylindrical and some of them contained small lumina which were continuous with the larger lumen of the diverticulum (fig. 9). (These endodermal sprouts will be referred to as parenchymal cords or tubules.) The cords of endodermal cells branching from the diverticulum surrounded or partially surrounded the endothelium-lined spaces in the septum transversum and joined one another in an anastomotic network.

Twenty-eight somite embryo. The structure of the hepatic diverticulum was the same in the 28-somite embryo as in the 25-somite embryo. There was a general increase in the amount and size of the cords and endothelium-lined spaces, but also encompassed and isolated small masses of mesodermal cells which were probably hemangioblasts (figs. 10, 11). The thickness of the wall of the diverticulum appeared thinner in areas where endodermal cords projected from the diverticulum than in the dorsal and cephalic walls from which no endodermal cords projected.

From this dorsal and cephalic wall a rod-like column of endodermal cells extended cephalically to the caudal surface of the sinus venosus. Dorsal to the diverticulum, in the region where the rod-like column projected from the diverticulum, a small vascular channel connected the bilateral omphalomesenteric veins. This interconnecting channel was the presumptive transverse portal sinus. All the endodermal cords branching from the diverticulum were ventral to the omphalomesenteric veins and the presumptive transverse portal sinus.

Twenty-nine somite embryo. The developing liver was caudal and dorsal to the developing ventricles of the heart in the 29-somite embryo (fig. 12). The mass of the septum transversum filled a pyramidal space bounded by the pericardium, yolk sac, lateral body walls, and the ventral wall of the diverticulum, including the primordium of the cystic duct and gallbladder. The ventral wall of the ductus choledochus and midgut was formed by a thicker segment of endoderm which extended from the base of the cystic duct-gallbladder primordium to the umbilical stalk.

Most of the parenchymal growth from the "T-shaped" diverticulum was toward the right and left, with only a moderate amount ventrally. A ventral and a dorsal midline column of endodermal cells extended rostrally from the cephalic end of the diverticulum toward the sinus venosus. A midline longitudinal vascular channel, the developing ductus venosus extended from the sinus venosus to the transverse portal sinus. This primordium of the ductus venosus was located immediately dorsal to the dorsal and midline column of cells.

Horizons XIII through XVII

Liver development in embryos of Horizons XIII through XVII consisted of an increased amount of parenchymal cords with an apparent reduction in the size of the segment of the hepatic diverticulum cephalic/distal to the primordium of the cystic duct and gallbladder from which the parenchymal cords projected. This reduced segment of the hepatic diverticulum became the common hepatic duct. The segment of the hepatic diverticulum caudal/proximal to the primordium of the cystic duct and gallbladder increased in length and its cytological configuration changed to a duct epithelium, thus forming the ductus choledochus. The primordium of the ventral pancreas developed from the dorsal wall of the ductus choledochus near the attachment of the ductus to the gut.

The mesoderm of the septum transversum became less dense with the increased number and lengths of the parenchymal cords and appeared to give rise to the intrahepatic vascular network. The reduced density of the septum transversum formed the capsule of the liver.

Horizon XIII. The hepatic diverticulum in embryos of Horizon XIII was of the same general configuration as in embryos at the end of Horizon XII. The area of the septum transversum had increased as had the amount and extent of the parenchymal cords (fig. 13).

The anastomosing networks of parenchymal cords was present throughout most of the septum transversum. These anastomosing cords surrounded endothelium-lined vessels (sinusoidal and presinusoidal channels). The sinusoidal channels were largest deep within the parenchymal mass, adjacent to the diverticulum. At the peripheral borders of the parenchyma, the cords surrounded smaller vessels and/or isolated masses of mesoderm. The mesoderm in these areas was more compactly arranged and small endothelium-lined spaces containing three to six blood cells were found scattered throughout (fig. 14).

All parenchymal cords appeared to be connected to the distal end of the diverticulum cephalic to the primordium of the cystic duct and gallbladder (fig. 15). The parenchymal cords were positioned cephalic, lateral and ventral to the diverticulum; the lateral cords being most prominent in length and number (figs. 13, 16). This configuration of the parenchyma resulted in the liver having the gross shape of a pair of "wings" which lay ventral and lateral to the foregut. In the tips of these "wings" were the omphalomesenteric veins which were partially surrounded by parenchymal cords. The omphalomesenteric veins were continuous with the sinusoidal channels completely surrounded by parenchymal cords.

A conspicuous midline column of endodermal cells extended rostrally from the dorsocephalic end of the diverticulum (figs. 15, 16). It was surrounded by parenchymal cords, but remained isolated from them by a single layer of mesodermal cells (fig. 14). This column did not reach the caudal surface of the sinus venosus as it did in embryos of earlier stages. Parenchymal cells appeared to branch from its most rostral end, separating it from the sinus venosus. No parenchymal cords branched from the dorsal wall of the hepatic diverticulum.

Horizon XIV. The general mass of anastomosing parenchymal cords in embryos of Horizon XIV was nearly double that in embryos of the previous horizons. The mesenchyme of the septum transversum was reduced to a capsule which surrounded the entire liver (figs. 17, 18, 19). Small blood-filled endothelium-lined spaces still existed between the outer layer of the capsule and parenchymal cords. Some of these spaces were partially surrounded by, or adjacent to, the cords. The omphalomesenteric veins were completely surrounded by parenchymal cords and there was general enlargement of the transverse portal sinus and ductus venosus. The ductus venosus was surrounded on three sides by parenchymal cords. The right and left umbilical veins were continuous with the transverse portal sinus at the anterior and lateral border of the liver. The left umbilical vein was twice the size of the right umbilical vein.

Corresponding to the increased parenchymal cords, the segment of the hepatic diverticulum cephalic to the cystic duct-gallbladder primordium was reduced in size. The cystic duct-gallbladder primordium was longer than in previous embryonic stages. It appeared as a finger-like projection from the ventral wall of the diverticulum (fig. 17) being separated from the branching parenchymal cords by a segment of the ventral wall of the diverticulum and by adjacent mesoderm. The ductus choledochus had increased in length over previous stages and was distinguished from the gut tract, with which it was continuous, by its ventral position relative to the gut tract and its continuity with the cystic duct and common hepatic duct.

A dorsal column of endodermal cells extended rostrally from the cephalic end of the hepatic diverticulum (fig. 17). It was positioned at the junction of the ductus venosus and the transverse portal sinus. The column had a distinct lumen and its cellular morphology was similar to that of the diverticulum.

The cellular morphology of the diverticulum was essentially the same as that of the foregut, the walls of the diverticulum being thicker. The cells of the diverticulum were stratified columnar, forming three to four layers and being compactly arranged. In areas of parenchymal branching the cells of the diverticulum were reduced progressively within a short distance from stratified columnar, to simple cuboidal. The cytological difference between the peripheral cells of the diverticulum and parenchymal cells was the position of the nucleus. The nucleus of the diverticulum in these areas was positioned adjacent to the basement membranes while nuclei of the parenchymal cells was centrally located.

Horizon XV. There was a marked morphological change of the hepatic diverticulum in embryos of Horizon XV (fig. 20). Its size had increased due to elongation of the ductus choledochus. However, that portion of the diverticulum cephalic to the origin of the cystic duct-gallbladder primordium, which represented the original diverticulum, had decreased in size being no longer a distinct single unit with a large lumen. It consisted of a smaller mass of cells with several small lumina, from which cords of parenchymal cells projected ventrally and laterally. Whereas, in smaller embryos the cystic duct primordium was separated from the caudalmost branches of the ventral wall of the diverticulum, in these embryos the parenchymal cords came off the ventral wall at the junction of the diverticulum and cystic duct. In at least one embryo branches came off the cystic duct. The cystic duct-ballbladder primordium extended almost to the ventral border of the liver. A column of endodermal cells at the cephalic end of the diverticulum ventral to the transverse portal sinus and ductus venosus was identified in these embryos. Where this column of cells projected from the diverticulum there appeared to be an attenuation of the column (fig. 20).

The cells of the parenchymal cords were uniform throughout the mass of the liver. No cellular differences existed between the parenchymal cells adjacent to major blood vessels (transverse portal sinus) and those surrounding the sinusoids. The abrupt transition of the parenchymal cells from cuboidal to columnar was at the hilus of the liver, ventral and caudal to the transverse portal sinus (figs. 21, 22). In this region the diverticulum consisted of a compact mass of cells surrounded by a layer of low columnar cells. The diverticulum was entirely surrounded by mesenchymal cells. The branching cords from the diverticulum consisted of low columnar cells surrounding a small lumen. These short branches were continuous with the parenchymal cords whose cells were cuboidal. At the point where the low columnar cells were continuous with the cuboidal cells the amount of adjacent mesenchyme was reduced to a thin layer.

The remainder of the diverticulum (cystic duct-gallbladder primordium and ductus choledochus) consisted of stratified columnar epithelium typical of that of the gut with which it was continuous. Near the junction of the diverticulum and the gut the primordium of the ventral pancreas projected from the dorsal wall of the ductus choledochus (fig. 20).

Horizons XVI and XVII. The segment of the hepatic diverticulum cephalic to the cystic duct-gallbladder primordium consisted of a single duct in these embryos which was continuous with the parenchyma immediately ventral to the caudal side of the transverse portal sinus (figs. 23, 24, 25). This duct joined the cystic duct and the two ducts were continuous caudally with the ductus choledochus nearer the continuation of the ductus choledochus with the gut tract.

The walls of the aforementioned ducts consisted of columnar cells which were stratified near the gut and simple low columnar near the liver parenchyma. In contrast, the parenchymal cells which were continuous with the ducts were cuboidal cells with centrally located nuclei. The lumina of the gut and extrahepatic ducts were nearly occluded in these embryos due to the stratification of the columnar epithelium.

The short transitional zone between the ducts and liver parenchyma occurred at the caudoventral surface of the transverse portal sinus. The caudal surface of the transverse portal sinus (dorsal to the transitional zone) had no parenchyma bordering it, but was bounded on this surface by mesoderm. The portion of the hepatic diverticulum which consisted of ductal epithelium (extrahepatic ducts) was completely surrounded by mesenchyme in contrast to the parenchyma where blood channels were lined by only a thin layer of endothelium (figs. 23, 24, 25, 26, 27).

In embryos of Horizon XVI the intrahepatic vasculature other than the transverse portal sinus was not divisible into hepatic and portal systems. In embryos of Horizon XVII, however, the right, middle and left hepatic veins were distinguishable from other blood vessels by several criteria, chief of these being their position in the liver. Also endothelial cells of the transverse portal sinus and ductus venosus were closer together and more evenly arranged than those of the hepatic veins. Furthermore, near the hilus the parenchymal cords were more compactly arranged against the linings of the vessels and, in some cases the cells of the cords adjacent to the endothelial lining were flattened and smaller than cells not in contact with the endothelial lining. The terminal portions of both hepatic and portal systems were the sinusoidal plexuses which were continuous with, but indistinguishable from one another. The transverse portal sinus branched into right and left anterior and posterior segmental branches in embryos of both horizons.

The parenchymal cords adjacent to the transverse portal sinus in the region of the hilus had more pronounced lumina than cords from the same area in younger embryos and more than those cords not adjacent to the transverse portal sinus (figs. 26, 27).

An isolated cyst-like structure (fig. 24) composed of columnar cells was present in all embryos of these horizons. It was in a constant position, ventral and cephalic to the transverse portal sinus, in the area of confluence of the transverse portal sinus and ductus venosus.

DISCUSSION

For the most part, the observed morphological development of the liver parenchyma in this study followed closely the classical descriptions of Bremer ('06), Ingalls ('08), Lewis ('12), and Bloom ('26) to the extent that the liver parenchyma proliferates from the walls of the cephalic end of the diverticulum in small irregular masses of anastomosing cords or tubules. This was not the view of Elias ('55), who stated that at no time do the liver cells in human embryos form cords. From sections taken in three different planes (frontal, horizontal and sagittal) of embryos of the same stages of development it was evident that the entire parenchymal network consisted of anastomosing cords or tubules which contained either lumina or potential lumina.

The crescent-shaped mass of anastomosing cords which formed wings and extended dorsally on either side of the intestinal tube, as described by Ingalls, was verified by observations of the advancing growth of parenchyma from the most lateral walls of the cephalic portions of the "T-shaped" diverticulum. Although the parenchyma arose from the ventral walls of the diverticulum as well, the more pronounced growth from the lateral walls resulted in an early impression of the definitive right and left lobes of the liver.

My interpretation of the relationship between the developing parenchyma and the blood vessels differs from the classical descriptions of Minot ('00) and Lewis ('04). Minot coined the term "intercresence" for the process involved in establishing this relationship. "Intercresence" implied a reciprocal interaction between pre-established blood vessels and the liver parenchyma in such a manner that large vessels were broken down by the invasion of the growing parenchymal cords. My interpretation is that within the loosely arranged mesenchyme of the septum transversum small endothelium-lined spaces or blood islands developed, the majority of which were near the walls of the diverticulum. The parenchymal masses or cords from the walls of the diverticulum projected into the mesenchyme of the septum transversum and anastomosed around these pre-existing endothelium-lined spaces. The parenchymal sprouts nearest the diverticulum surrounded the largest of these vesicles while those cords farther away from the diverticulum surrounded either smaller endothelium-lined spaces and/or small masses of mesenchyme. The older the embryo and the greater the amount of parenchymal proliferation, the more well-defined were the endothelium-lined spaces. The endothelium-lined spaces nearest the diverticulum surrounded by anastomosing cords appeared to coalesce. The parenchymal cords surrounding mesenchyme in young embryos appeared to surround endothelium-lined spaces or anastomosing vessels in older embryos. This might indicate that, once the mesenchyme was isolated by the anastomosing cords, cellular rearrangement occurred with subsequent formation of small vessels. In still older embryos the network of parenchymal cords and vascular channels was extensive and the amount of mesenchyme in the septum transversum seemed to have diminished appreciably, leaving only a thin peripheral layer at the boundaries of the cords. What appeared to have developed from the mass of the septum transversum of younger embryos was an anastomosing vascular network which interdigitated with an anastomosing parenchymal network. In contrast to the classical interpretation, the vessels developed *in situ*, concurrently with the developing parenchyma, and did not form as a result of the interruption of large preformed channels. This corroborates the interpretations of Lipp ('52) and Elias ('55) that the liver parenchyma cells invade the mesenchyme of the septum transversum and surround pre-existing sinusoids.

Elias ('64) hypothesized a "recruitment" of mesoderm into the formation of the liver parenchyma. Throughout this study, however, no evidence was obtained to substantiate his interpretation. All the parenchymal cords seemed to be of endodermal origin, and mesoderm contributed only to the formation of vascular channels, blood and stroma. The developing septum transversum which formed at early stages was continuous with mesoderm surrounding the yolk sac and appeared to have the same proclivity for angiogenesis and for hematopoiesis as the yolk sac mesoderm, although

this tendency became manifest at a later stage of development.

The major venous channels (the omphalomesenterics and umbilical veins and the ductus venosus) were relatively small and appeared to develop from the mesenchyme in the region of the septum transversum. They were continuous with the smaller vessels which interdigitated with the parenchymal cords. These major vessels developed simultaneously with growth and development of the parenchymal cords and the sinusoidal network; they maintained a rather constant morphological position within the parenchymal framework of the older embryonic and adult livers.

Throughout the period of parenchymal proliferation from the cephalic end of the diverticulum, that portion of the diverticulum cephalic to the primordium of the cystic duct-gallbladder was reduced in size to a small, single duct-like structure which was always continuous with the network of parenchymal cords immediately ventral and caudal to the developing transverse portal sinus. As the diverticulum became reduced in size to the single common hepatic duct, that portion of the diverticulum between the cystic duct and gut increased in length and a localized dilation or outgrowth developed from its dorsal wall. This was the ventral pancreas.

As the original diverticulum became smaller, one of the original projections from its dorsal and cephalic surfaces appeared more conspicuous. It extended cephalically from the cephalic end of the diverticulum and was located adjacent to the ventral surface of the transverse portal sinus. At first it was a cylindrical mass of parenchymal cells, then became cord-like and finally attenuated, separating from the diverticulum and taking on the characteristic morphology of a duct or cyst. This isolated duct-like structure was constant in appearance and position in the embryos of Horizons XVI, XVII and XVIII. It was always found immediately ventral to the transverse portal sinus near the junction of the transverse portal sinus with the ductus venosus. Its significance was not determined. It may represent the remnants of the original diverticulum and perhaps represents the cyst-like structures of the liver parenchyma which have been described (Moschowitz, '06).

It is not difficult to visualize the etiology of anomalies such as multiple hepatic ducts. Branching of the parenchymal cords from the diverticulum and the latter's subsequent reduction in size has a close spatial relationship with development of the cystic duct and gallbladder. As the parenchymal cords branch from the ventral wall of the diverticulum near the junction of the cystic duct and gallbladder it is conceivable that they might emanate from the proximal walls of the cystic duct and gallbladder.

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PLATE 1

EXPLANATION OF FIGURES

Photomicrographs of transverse sections of a 22-somite human embryo. Photomicrographs are by courtesy of the Carnegie Institution of Washington.

1 Photomicrograph of a section through the cephalic portion of the hepatic diverticulum (D). The omphalo-umbilical vessels (OU) are dorsolateral to the diverticulum. The diverticulum is surrounded laterally and ventrally by mesoderm of the septum transversum (ST). × 75.

2 Photomicrograph of the same section as shown in figure 1, illustrating the hepatic diverticulum in detail. Short parenchymal sprouts (arrows) of the ventral and lateral walls of the diverticulum project into the septum transversum and partially surround some isolated endothelium-lined spaces (s). × 150.

3 Photomicrograph of a section at the level where the ventral wall of the hepatic diverticulum is continuous with the yolk sac endoderm. Note the thin wall of endoderm which is the presumptive ventral wall of the ductus choledochus (arrow). Omphalomesenteric veins (O) are lateral to the diverticulum. The umbilical veins (U) are in the lateral body wall. (see fig. 5 for a sagittal view of a comparable embryo). × 75.

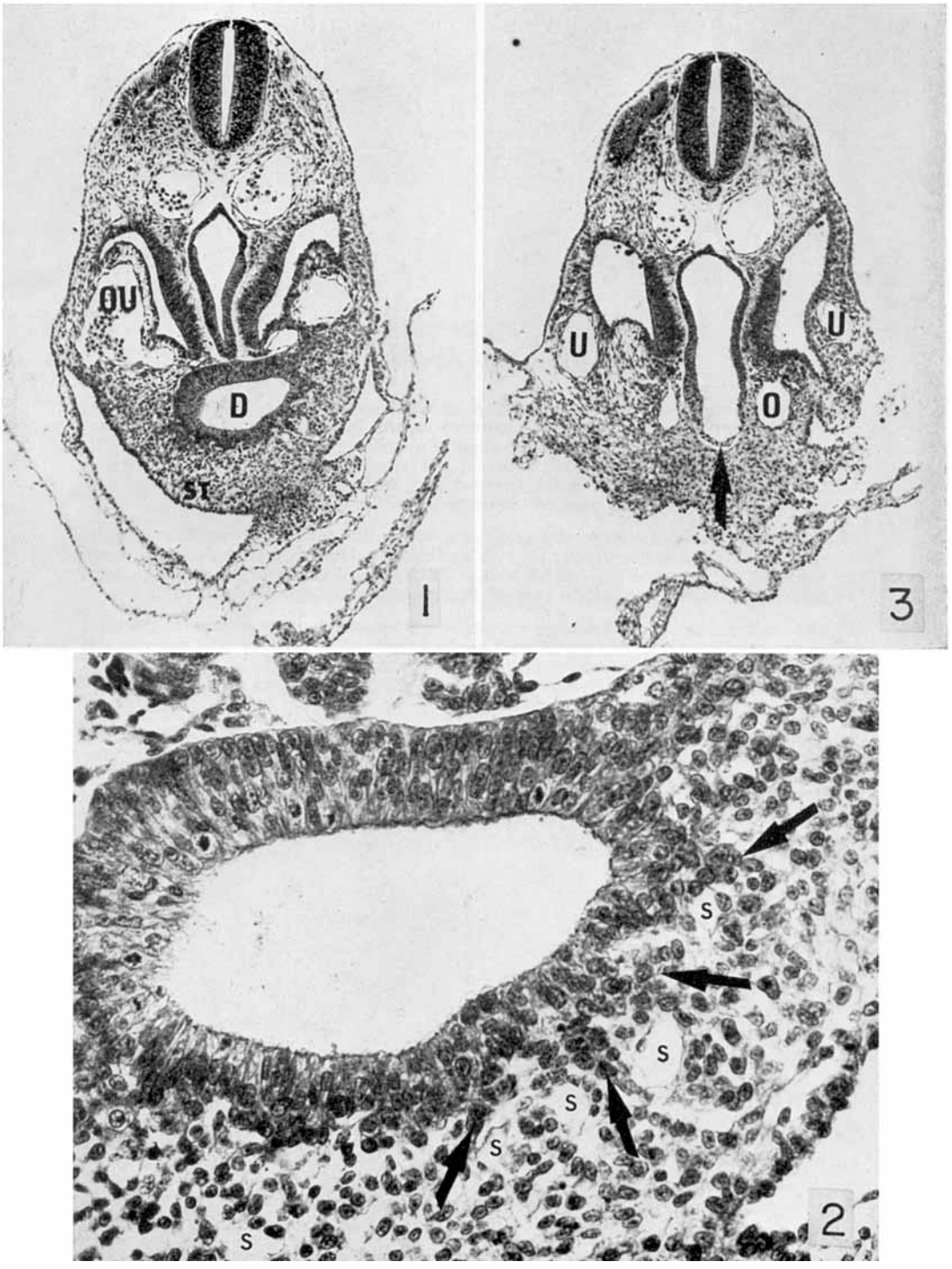
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PLATE 2

EXPLANATION OF FIGURES

4 Photomicrograph of a sagittal section of a 17-somite embryo. The segment of thickened endoderm (between the arrows) ventral to the anterior intestinal portal is the presumptive hepatic diverticulum. An area of contact exists between the endoderm and the endothelial lining of the sinus venosus (SV). The thickened endoderm is separated from the parietal pericardium ventral to the area of contact by mesoderm of the septum transversum. × 75.

5 Photomicrograph of a sagittal section of a 23-somite human embryo. The cephalic segment of the hepatic diverticulum is established. The mass of the septum transversum (ST) between the ventral wall of the hepatic diverticulum and the parietal pericardium has increased to that of the 17-somite embryo (fig. 4). × 75.

6 Photomicrograph of a transverse section of a 25-somite human embryo at the level of the caudal end of the ventral wall of the hepatic diverticulum. The primordium of the cystic duct gallbladder (arrow) is present as a localized thickening and dilation of the hepatic diverticulum. (see fig. 12 for a sagittal view of a comparable embryo). × 75.

7 Photomicrograph of a frontal section through the hepatic diverticulum of a 25-somite embryo. A midline column of endodermal cells (arrow) extends from the cephalic end of the diverticulum to the endothelial lining of the sinus venosus. × 75.

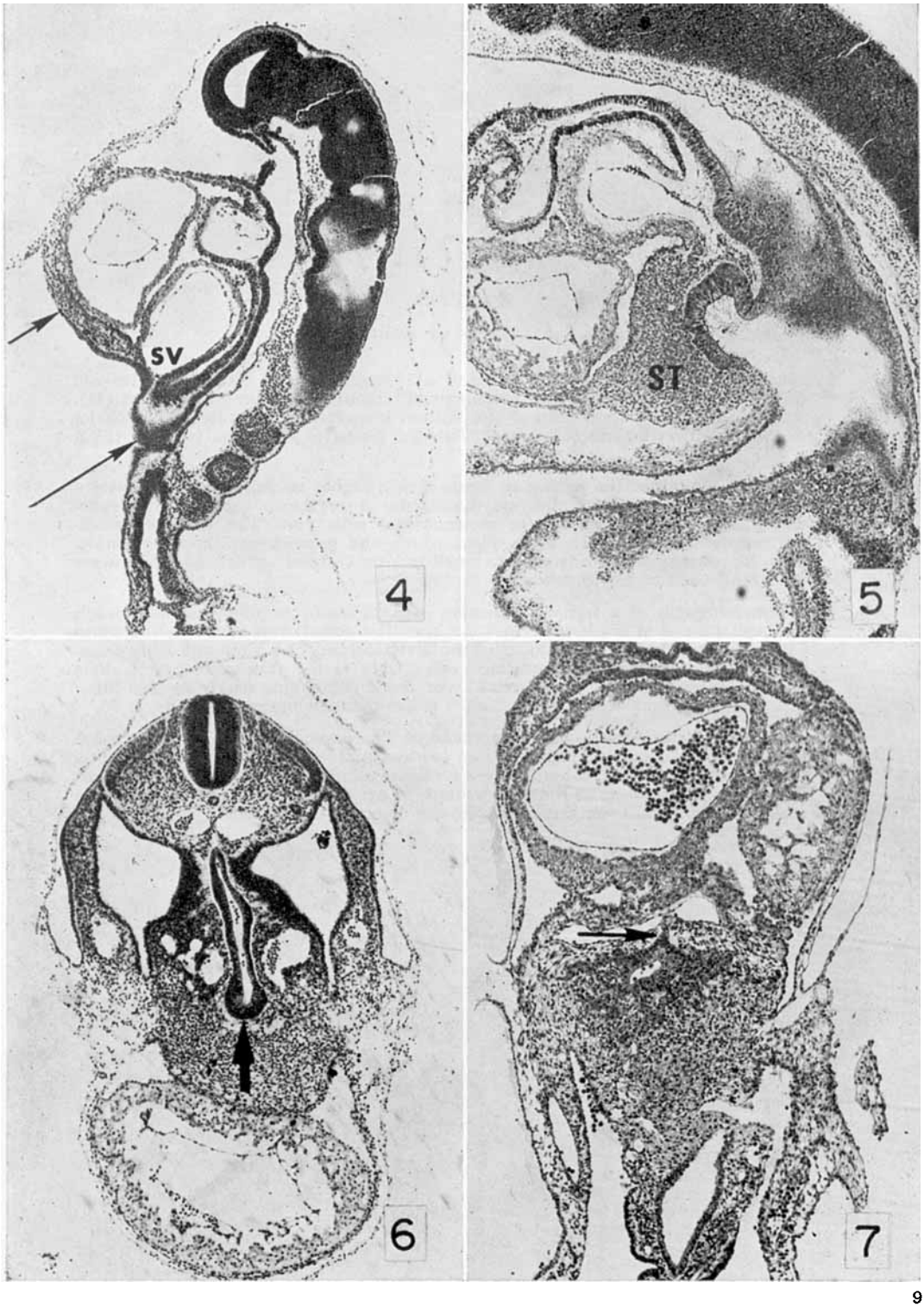
SV
4
ST
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PLATE 3

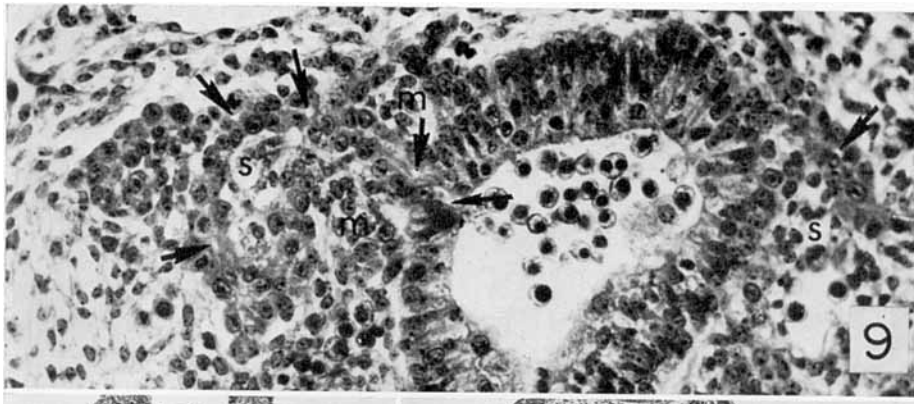
EXPLANATION OF FIGURES

8 Photomicrograph of a frontal section of a 25-somite embryo through the hepatic diverticulum. The parenchymal cords extend laterally from the diverticulum (D). A small amount of mesoderm of the septum transversum separates the cephalic end of the diverticulum from the endothelial lining of the sinus venosus (SV). × 75.

9 Photomicrograph of the section in figure 8 at a higher magnification. The parenchymal cords extend laterally into the septum transversum and surround endothelium-lined spaces (s) and/or mesenchymal cells (m). The wall of the diverticulum is thin in the areas from which the parenchymal cords emanate. Also the parenchymal cords contain small lumina (arrows) which are continuous with the lumen of the diverticulum. × 150.

10 Photomicrograph of a transverse section of a 28-somite human embryo through the cephalic end of the hepatic diverticulum. The dorsal wall of the diverticulum (D) is thicker than the remainder of the diverticulum. The communicating channel between the omphalomesenteric veins (OM) is the transverse portal sinus (arrow). Parenchymal cords extend from the diverticulum nearly to the edges of the septum transversum and adjacent to the omphalomesenteric veins. × 75.

11 An area of figure 10 at higher magnification. The parenchymal cords anastomose and surround endothelium-lined spaces (s) and masses of loosely arranged mesodermal cells (arrows). The larger endothelium-lined spaces are near the diverticulum. The lumen of the diverticulum is irregular with projections in areas where parenchymal cords emanate from the diverticulum. × 150.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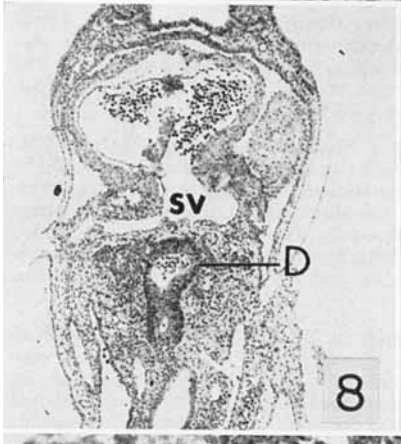
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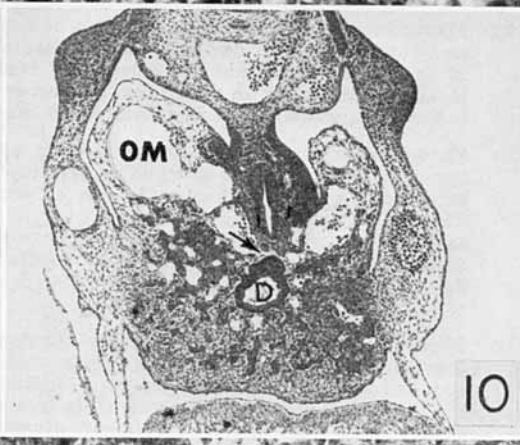
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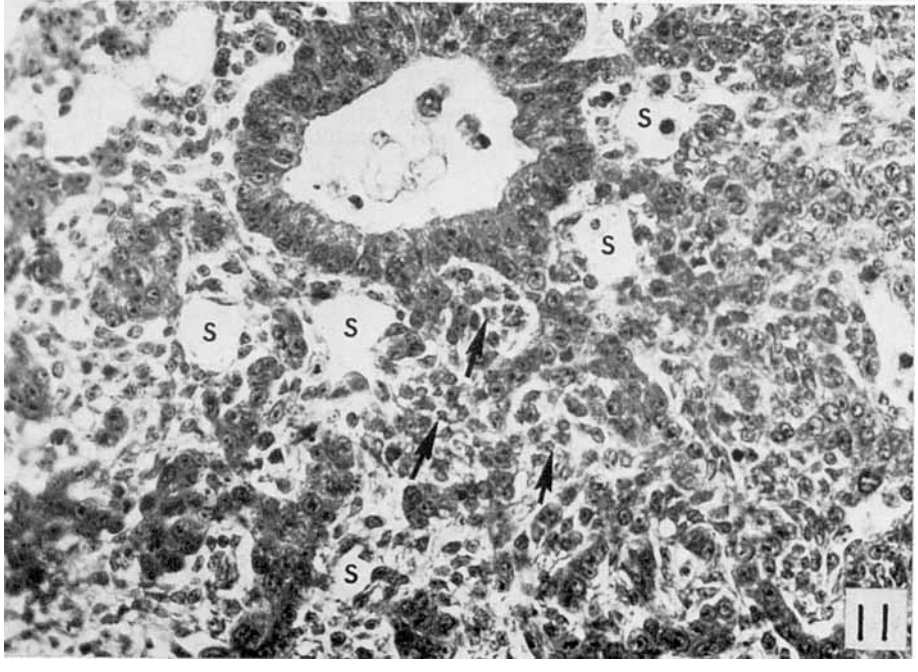
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PLATE 4

EXPLANATION OF FIGURES

12 Photomicrograph of a sagittal section of a 29-somite human embryo. The dorsal and ventral columns (arrows) of endodermal cells extend from the cephalic end of the diverticulum and are dorsal and ventral to the sinus venosus (SV). The localized thickening in the caudal portion of the ventral wall of the diverticulum is the presumptive cystic duct and gallbladder (CG). × 75.

13 Photomicrograph of a transverse section of a human embryo of Horizon XIII through the level of the developing liver cephalic to the diverticulum. The lateral extent of the parenchymal cords give a "wing-shaped" configuration to the liver. The omphalomesenteric veins (OM) are in the dorsolateral tips of these wings and are partially surrounded by parenchymal cords. The parenchymal cords also anastomose and surround sinusoidal vessels which contain blood cells. The mesoderm of the septum transversum (ST) lies ventral to the anastomosing cords. × 75.

14 Photomicrograph of the same section illustrated in figure 13 at higher magnification. An isolated mass of endodermal cells (large arrow) is present and surrounded by a single cell layer of mesodermal cells and parenchymal cords. In the septum transversum ventral to the parenchymal cords are endothelium-lined spaces filled with blood cells (small arrows). Some of these blood-filled spaces are partially surrounded by parenchymal cords. × 150.

15 Photomicrograph of a sagittal section of a human embryo of Horizon XIII. The primordium of the cystic duct-gallbladder (CG) projects from the ventral wall at the caudal end of the diverticulum. A distinct column of cells extends dorsocephalically from the diverticulum (arrow). The transverse portal sinus (TPS) and the ductus venosus (DV) can be seen as small vessels dorsal to the column of endodermal cells. × 75.

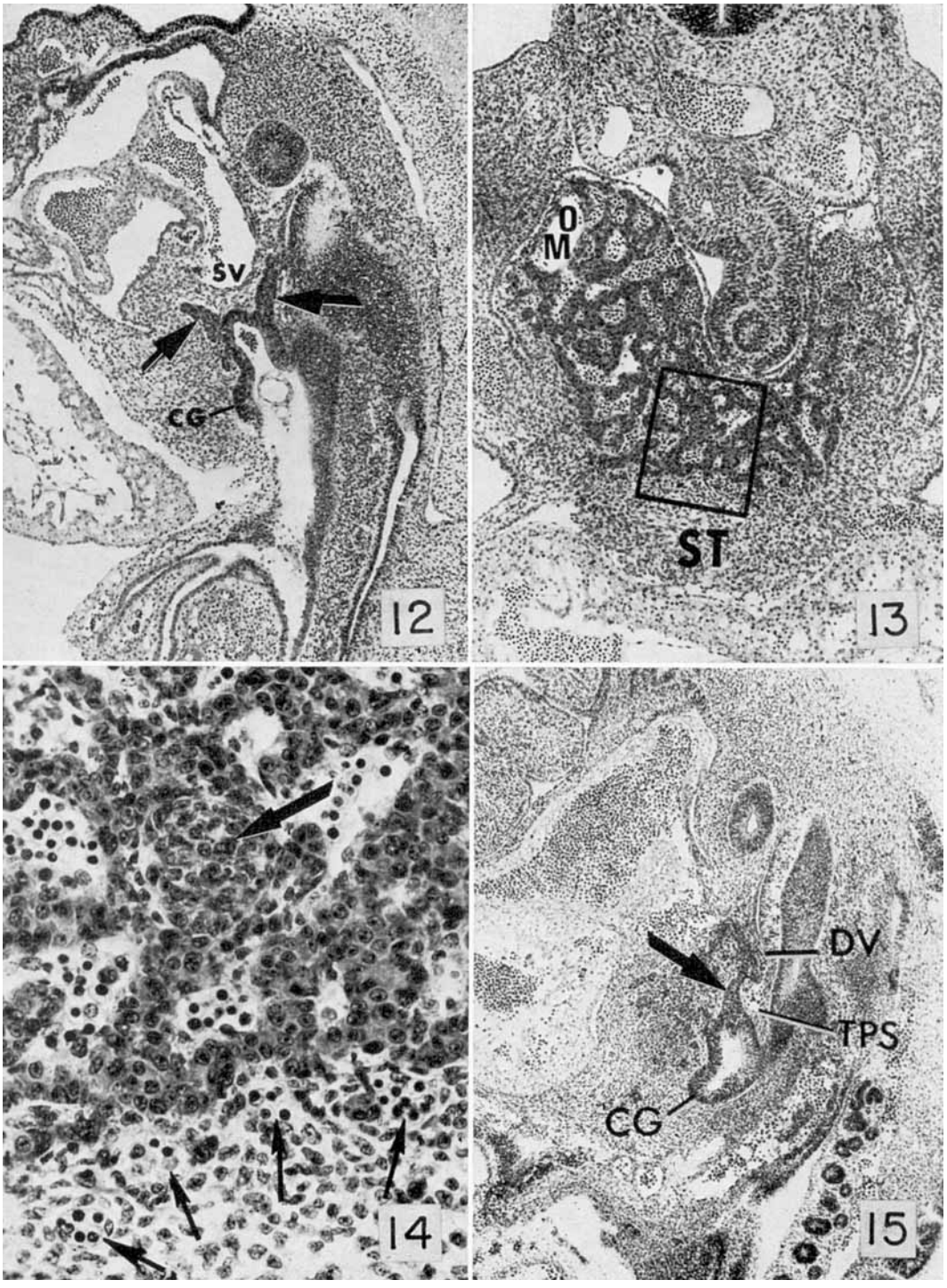

SV
CG
12
O
M
ST
13
14
DV
TPS
CG
15

PLATE 5

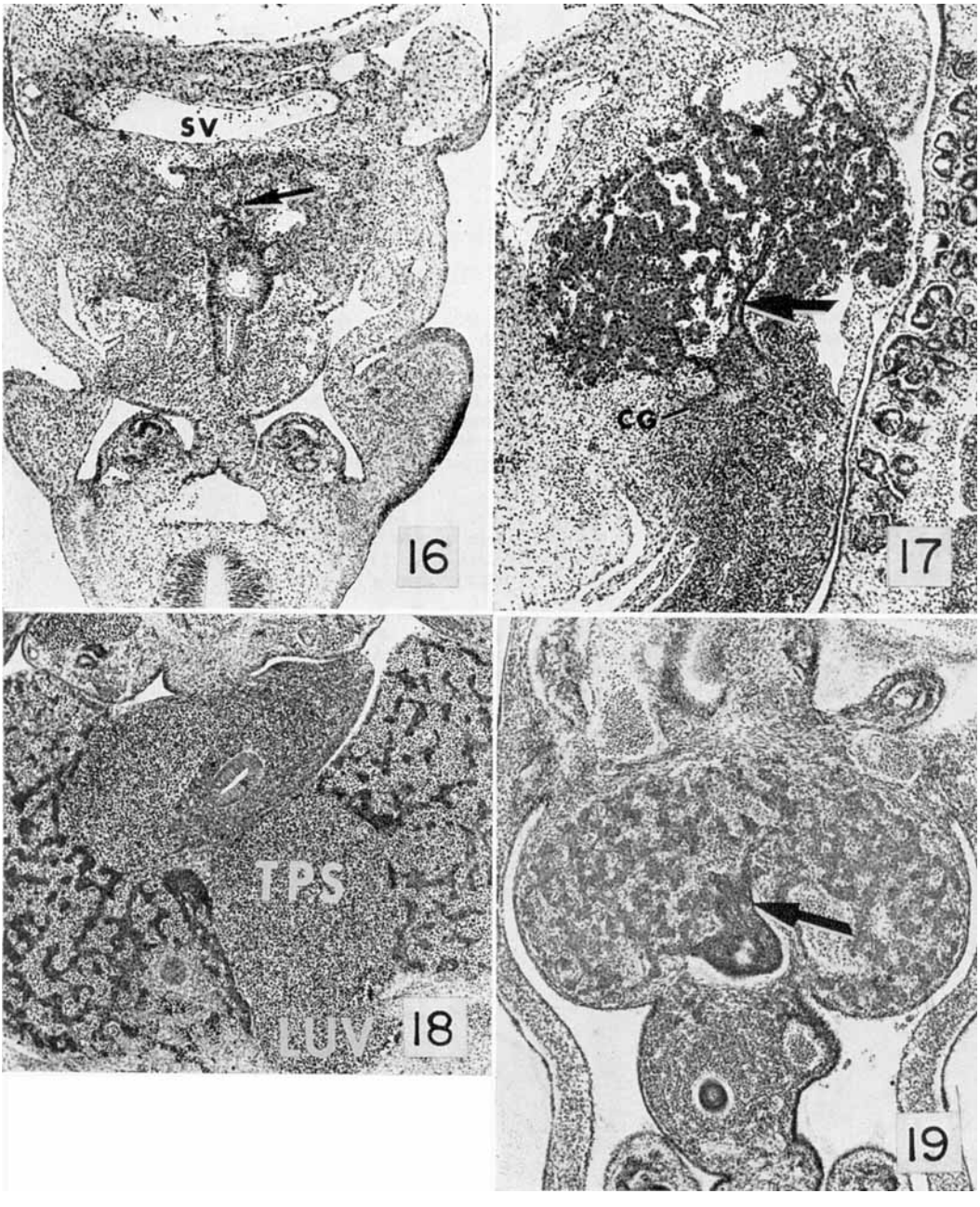
EXPLANATION OF FIGURES

16 Photomicrograph of a frontal section through the heart and hepatic diverticulum of a human embryo of Horizon XIII. The lateral extent of the parenchymal cords approaches the boundaries of the septum transversum. A midline column of endodermal cells (arrow) projects from the cephalic end of the diverticulum and is surrounded by parenchymal cords. × 75.

17 Photomicrograph of a sagittal section of a human embryo of Horizon XIV. A duct-like column of cells with a lumen projects dorsocephalic to the diverticulum (arrow). The total mass of hepatic cords has increased and the size of the diverticulum has decreased from that of the embryos of Horizon XIII (fig. 15). The primordium of the cystic duct-gallbladder (CG) is separated from the caudalmost parenchymal cords by mesenchyme and a segment of the ventral wall of the diverticulum. × 75.

18 Photomicrograph of a transverse section of a human embryo of Horizon XIV through the hilus of the liver. The left umbilical vein (LUV) forms part of the major vascular system of the liver and is continuous with the transverse portal sinus (TPS). The sinusoidal system of the liver is engorged with blood. × 75.

19 Photomicrograph of a frontal section of a human embryo of Horizon XIV through the liver and the hepatic diverticulum (arrow). The parenchymal cords completely fill the septum transversum. The septum transversum is reduced to a thin capsule and a sinusoidal plexus. The cephalic segment of the hepatic diverticulum is reduced in size as compared to that in embryos of Horizon XIII. Compare the amount and extent of the parenchymal cords and the size and configuration of the diverticulum with those in figure 16. × 75.


SV
16
CG
17
TPS
LUV
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19

PLATE 6

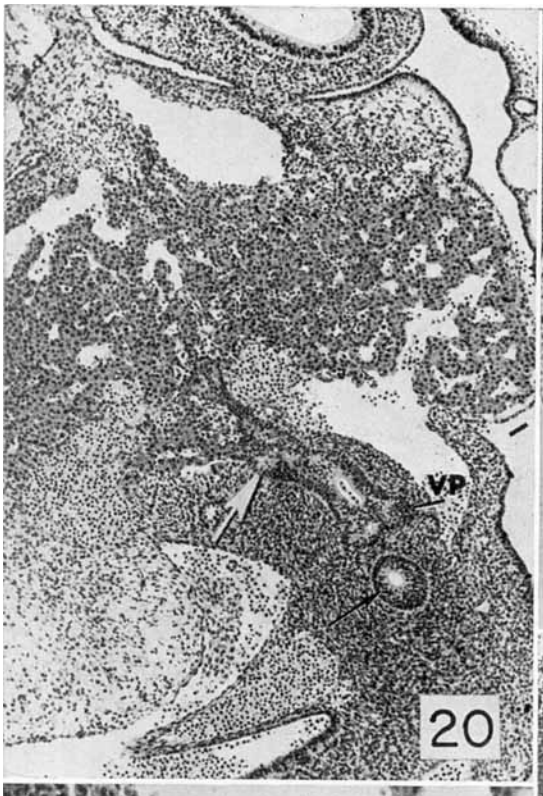
EXPLANATION OF FIGURES

20 Photomicrograph of a sagittal section of a human embryo of Horizon XV. The parenchymal cords emanate from the diverticulum at the junction of the original diverticulum and the primordium of the cystic duct-gallbladder (large arrow). Compare the size and configuration of the diverticulum and the number of parenchymal cords with those of embryos represented in figures 4, 5, 12, 15 and 17. The segment of the hepatic diverticulum between the primordium of the cystic duct-gallbladder and the gut (small arrow) is the ductus choledochus (between arrows). The ventral pancreas (VP) projects from the dorsal wall of the ductus choledochus. × 75.

21 Photomicrograph of a transverse section of a human embryo of Horizon XV at the level of the hilus of the liver. The hepatic diverticulum (arrow) lies immediately ventral to the transverse portal sinus (TPS). The majority of the epithelial cords are lateral to the diverticulum at this level. × 40.

22 Photomicrograph of the area indicated in figure 21 at higher magnification. The diverticulum and its short branches (arrows) are surrounded by mesenchyme. The two branches are continuous with parenchymal cords which have little or no mesenchyme adjacent to them. The nuclei of the cells of the diverticulum and its branches are basal, whereas the nuclei of the parenchymal cord cells are central. × 160.

23 Photomicrograph of a sagittal section of a human embryo of Horizon XVI. The ductus choledochus is a distinct structure and possesses a dorsal diverticulum (arrow) between the gut (G) and cystic duct (CD). The diverticulum is the ventral pancreas. The original diverticulum (D) is represented by a short, duct-like segment (common hepatic duct) and is continuous with the liver cords immediately ventral and caudal to the transverse portal sinus (TPS). × 75.


VP
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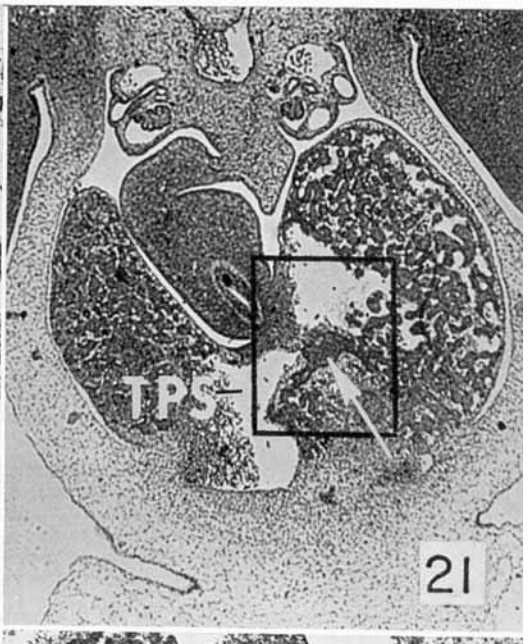
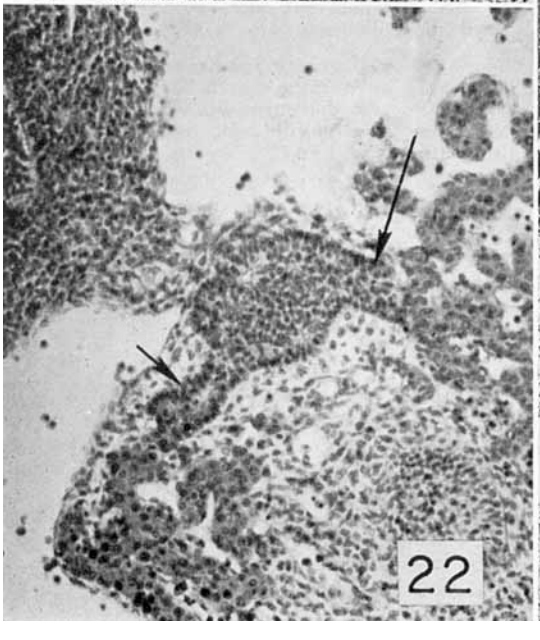

TPS
21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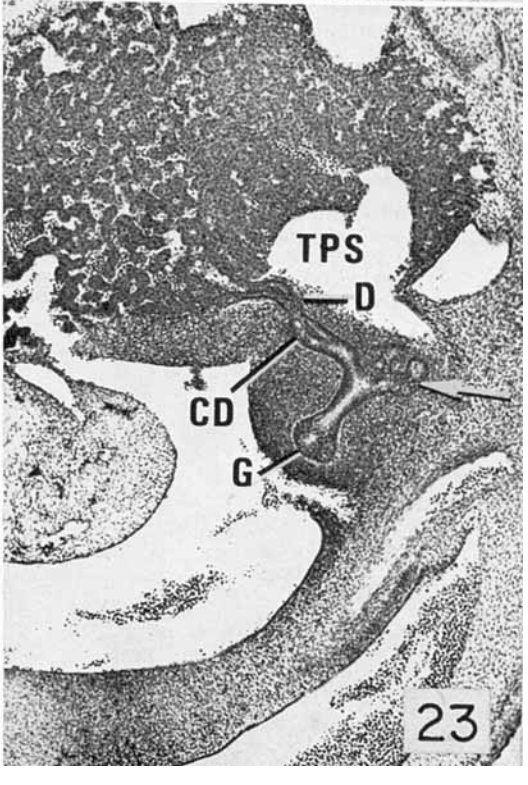

TPS
D
CD
G
23

PLATE 7

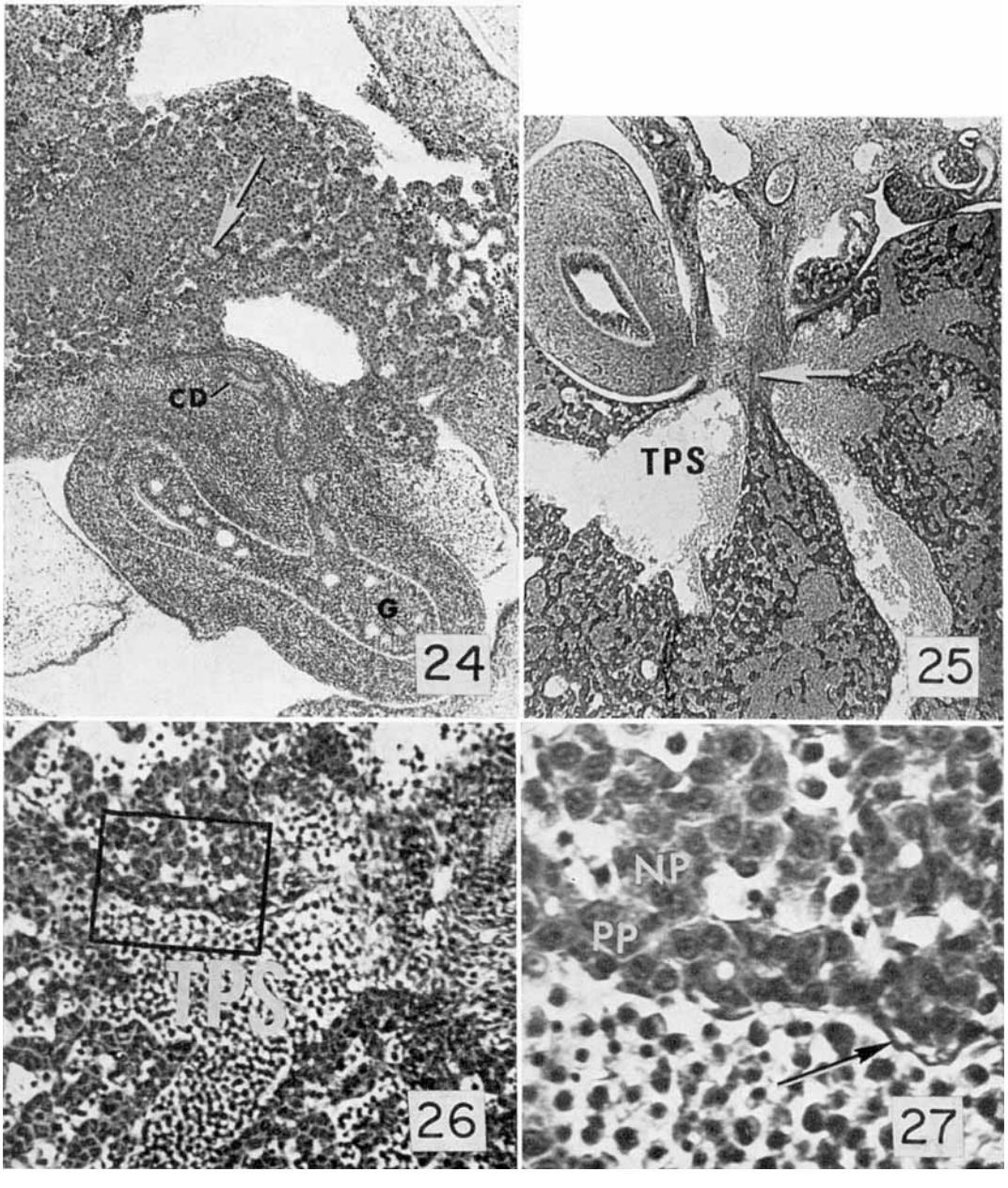
EXPLANATION OF FIGURES

24 Photomicrograph of a sagittal section of a human embryo of Horizon XVII. The lumina of the gut (G) and the extrahepatic ducts are filled with epithelial cells. The diverticulum cephalic to the cystic duct (CD) consists of a small single duct (common hepatic duct) continuous with the parenchymal cords on the caudoventral surface of the transverse portal sinus (TPS). There is a cyst-like structure (arrow) on the ventral surface of the transverse portal sinus. × 75.

25 Photomicrograph of a transverse section of a human embryo of Horizon XVII through the hilus of the liver. The diverticulum (arrow) cephalic to the cystic duct is a small, single duct (common hepatic duct) which is lined by columnar cells and surrounded by mesenchyme. It is continuous with the parenchymal cords which are not surrounded by mesenchyme. This common hepatic duct is located on the caudoventral surface of the transverse portal sinus (TPS). × 40.

26 Photomicrograph of a transverse section of a human embryo of Horizon XVII through the transverse portal sinus (TPS). The parenchymal cords adjacent to the transverse portal sinus are evenly aligned and contain lumina. × 40.

27 Photomicrograph of area indicated in figure 26 at higher magnification. The parenchymal cords are separated from the sinus by a thin endothelial lining (arrow). These periportal parenchymal cords (PP) are continuous with the nonperiportal cords (NP). All the parenchymal cord cells are morphologically similar. The periportal cords nearest the hilus contain lumina. × 160.


CD
G
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TPS
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TPS
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NP
PP
27