Part II. Physiology

THE DEVELOPMENT OF HEPATIC VASCULAR STRUCTURES*

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In this short paper there is neither the time nor the need to attempt to analyze all aspects of liver development in the human embryo. I shall instead, discuss a few aspects of early liver morphogenesis which may be of interest in view of the related papers which have been or will be presented at this conference.

By the start of the third week of human development, the liver can be identified as a blunt hollow diverticulum which projects ventrally from the presumptive duodenal region of the endoderm of the fore-gut. From this diverticulum cords of hepatic parenchymal cells are seen growing out from its cephalic part into the mesenchyme of the septum transversum. At this stage the gut is drained by a symmetrical pair of omphalomesenteric veins which end cephalically in the lateral horns of the sinus venosus of the heart. Lacunar sprouts from these vessels grow out into the mesenchyme surrounding the rapidly proliferating hepatic cords, and soon meet in the mid-line. This union is enlarged to form a transverse anatomosis ventral to the gut and cephalic to the hepatic diverticulum. This is the first and most cephalic of the well recognized three transverse anatomoses between the omphalomesenteric veins, and will become the portal sinus of the embryonic liver. During the fourth week the vascular spaces within the liver have developed so rapidly, that the hepatic cords appear to be surrounded by large endothelially lined blood spaces.

The liver parenchymal cells spread laterally and cephalically in their growth, and as the liver increases in size, there develops in the mid-line, at the zone of attachment of the gastro-hepatic omentum, a progressively elongating extension of the portal sinus. This mid-line channel is the ductus venosus. During this period of about a week, the paired umbilical veins have been carrying placental blood back to the heart as they course through the lateral body wall. However, as the developing lateral body folds have gradually circumscribed the umbilical ring, the umbilical veins have been brought into close proximity, and have fused. The right member of the pair soon drops out, and the left remains as the single umbilical vein. While this has been going on, the liver has been increasing in size, fusing with the lateral body wall. This makes posible an anastomosis between the umbilical vein and the portal sinus within the liver. Thus by the fifth week the umbilical venous blood has essentially abandoned its original round-about course to the heart, and instead pours into the left

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side of the portal sinus, and thence passes to the heart, most of it taking the path of least resistance, the ductus venosus, although some percolates more slowly among the sheets of parenchymatous hepatic cells.

Another related phenomenon has been taking place during this week. The sinus venosus of the heart has shifted to the right from its original mid-line position. Associated with this shift is a gradual dropping out of the left omphalomesenteric vein between the liver and the sinus venosus. The right omphalo-mesenteric connection between liver and heart enlarges, and will persist into the adult as the diaphragmatic part of the inferior vena cava.

As the gastroduodenal portion of the digestive tube shifts its orientation in such a manner that the duodenum comes to course transversely caudal to the liver, the connection of the left omphalomesenteric vein with the liver is lost. The entire venous drainage of the gut passes through the old right omphalomesenteric vein into the right side of the portal sinus.

Healey and Emery have already emphasized that the liver is divisible into right and left halves. My studies entirely confirm this fact. The one thing that should be emphasized is that this pattern is established extremely early in development. I have made a series of eleven wax-plate reconstructions of the venous channels within the livers of a series of human embryos during the second month of gestation. These show that the portal sinus, the major portal and hepatic veins, and the ductus venosus are sketched out in an embryo of 5 mm. length, and are clearly identifiable in an embryo of 9 mm. (5½ weeks).

There is no need to belabor the accepted fact that in the human fetus, as in the fetuses of other mammalian forms, the ductus venosus acts as a path of low flow resistance to the inflow of umbilical blood. However, there is one point which I would like to emphasize. Barron (1942), and Barclay, Franklin, and Pritchard (1945) reported the existence of a smooth muscle sphincter at the origin of the ductus venosus from the portal sinus in the fetuses of several mammalian forms. Chacko and Reynolds (1953) have described the existence of such a sphincter in the human embryo and fetus. There have been several hypotheses proposed concerning the role of this sphincter in controlling the relative amounts of blood which would pass through the ductus venosus as compared with the hepatic sinusoids. Such a control would be expected to vary the overall resistance to flow through the liver, and hence be reflected in alterations of the blood pressure in the umbilical vein. It is tempting to extrapolate these ingenious hypotheses to the human embryo, and to incorporate the concept of a ductus venosus sphincter into our understanding of its circulatory dynamics. I have studied a series of sections of the origin of the ductus venosus from embryos of three weeks of age to term. These were stained with hematoxylin and eosin, Masson's trichrome stain, Weigert's orcein stain for elastic fibers, and Periodic acid-Schiff counterstained with colloidal iron. This latter stain differentiates clearly the smooth muscle of the hepatic artery, and so is regarded as a practical means of determining the presence or absence of smooth muscle in the sections. In the entire series of approximately 60 specimens studied, I found a variable amount of intimal "lipping" and a fairly constant thickening of the endothelium at the origin of the ductus venosus. However, in no section could I identify a smooth muscle sphincter at this location. For this reason I feel we must be careful in our thinking not to assign to an assumed sphincter at this region properties which are based on the functional characteristics of smooth muscle as we know them in the adult.

I would now like to turn to another aspect of liver development, namely the formation of the hepatic part of the inferior vena cava. We may schematize the fetal liver from the beginning of the third month of development on, as consisting of two halves, each made up of three segments. With respect to these segments, the hepatic veins lie intersegmentally. In the adult there are only three named hepatic veins, the left, middle, and right. The left lies between the left posterior and the left anterior segments; the middle between the middle and right anterior segments; and the right between the right anterior and the right posterior segments. However, if there is a complete symmetry of this venous pattern, one would expect five hepatic veins. One of these predicted hepatic veins would lie between the left anterior and the middle segments of the liver. There is such a vessel, which I have called the anteromedial hepatic vein, in the fetal liver (FIGURE 1). It can be identified by its position in the adult human also, although it is not a vein of noteworthy size.

The second vein which one would expect to find to complete the pattern, would lie between the right posterior and the caudate segments of the liver. In embryos of the fourth week one can identify such a venous channel. I suggest that this be called the right posterocaudate hepatic vein. As the liver increases in mass during the subsequent week, its dextro-dorsal surface comes into contact with the dorsal wall of the peritoneal cavity. Over a wide zone the liver is in direct contact with this wall at a region where the right suprarenal gland is forming. During this period there develops the mid-line anastomosis between the right and left subcardinal veins which permits the venous drainage from both sides of the body caudal to the adrenals to flow into the right subcardinal vein. Rather rapidly this large amount of blood takes advantage of the presence of the right posterocaudate vein, as a low-resistance route to the heart. This hepatic vein thus receives much more blood than the others, and consequently enlarges. From this time on it is called the hepatic part of the inferior vena vaca. Thus in the human embryo, the "mesenteric" portion of the inferior vena cava (developing in the caval plica) does not exist as it does in other mammalian forms such as the pig. For a few weeks this channel shows morphological evidence of its origin as a hepatic vein, since its wall is essentially identical with that of the other hepatic veins, and it receives blood both from the hepatic sinusoids (ventrally) and from multiple channels from the stroma of the right suprarenal gland (dorsally). I believe that this embryological origin of the inferior vena cava explains the well recognized variability of the level at which the right hepatic vein enters the inferior vena cava in the adult. From this point of view this level of confluence is simply the point at which two hepatic veins join, and would be expected to be as variable as is the comparable point of confluence of left and middle hepatic veins. It also explains the fact that in the adult much of the caudate lobe drains directly into the inferior vena cava by discrete venous channels. This is under-

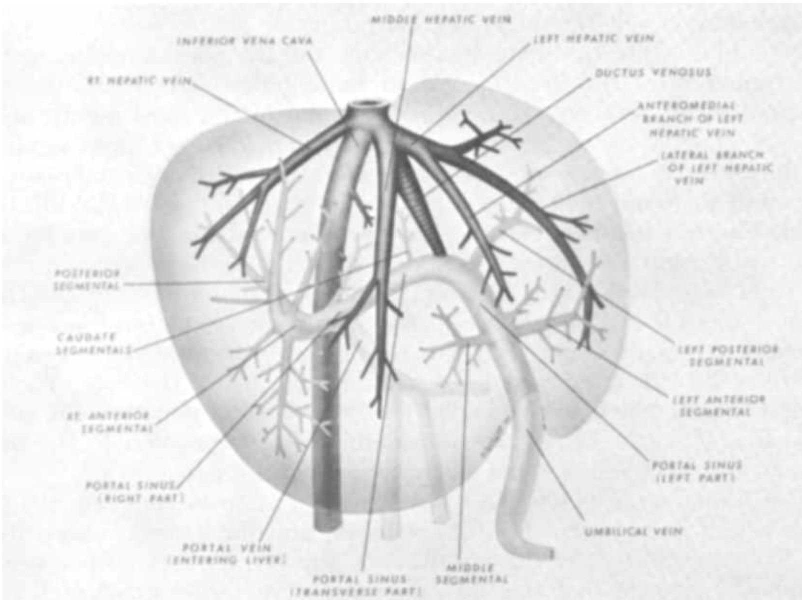

FIGURE 1. Diagram of liver veins. (Right anterior oblique projection.)

standable if one recognizes that the inferior vena cava at that level is merely retaining its original relationships as the right posterocaudate hepatic vein of the young embryo.

References

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Discussion of the Paper

J. E. HEALEY, JR. (*M. D. Anderson Hospital, Houston, Texas*): In the adult liver we consider the middle hepatic vein as the mid-line structure lying in the main lobar fissure. In the fetus and newborn we have seen the ductus venosus draining into either the left hepatic vein or the left side of the middle hepatic vein.

I would like to comment regarding the segmental anatomy of the liver. We presented a terminology based on the ductal arrangement. Elias, has in the past, presented a terminology based on the portal vein distribution and now Barry, a terminology based on hepatic venous drainage. This observation confirms the point that there is a great need to confer with all those who have studied the segmental anatomy so that a common terminology may be developed.

H. ELIAS (*Chicago Medical School, Chicago, Ill.*): It is remarkable how much Barry's, Healey's, and my observations agree. In fact, there is a complete identity of the structure of the vascular pattern in all these studies, though they were carried out independently. What we are still lacking is a common nomenclature, as Healey says. The presence or absence of the intimal swellings at the base of the ductus venosus which Barry has shown us must determine the physiological caliber of this channel. Thus it is on the development of these "cushions" that the eventual geography of the liver must depend.