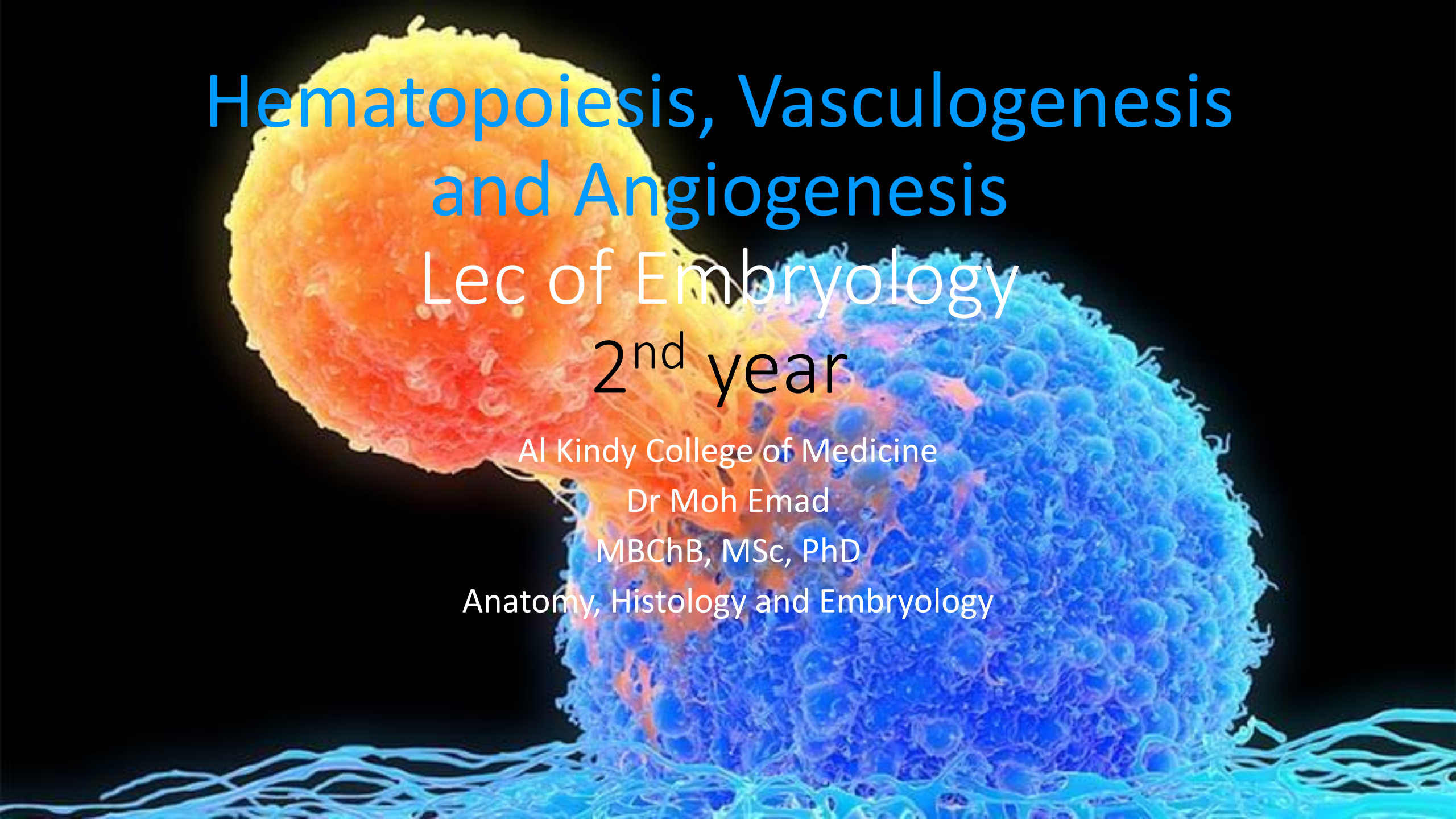


Hematopoiesis, Vasculogenesis and Angiogenesis

Lec of Embryology

2nd year

Al Kindy College of Medicine

Dr Moh Emad

MBChB, MSc, PhD

Anatomy, Histology and Embryology

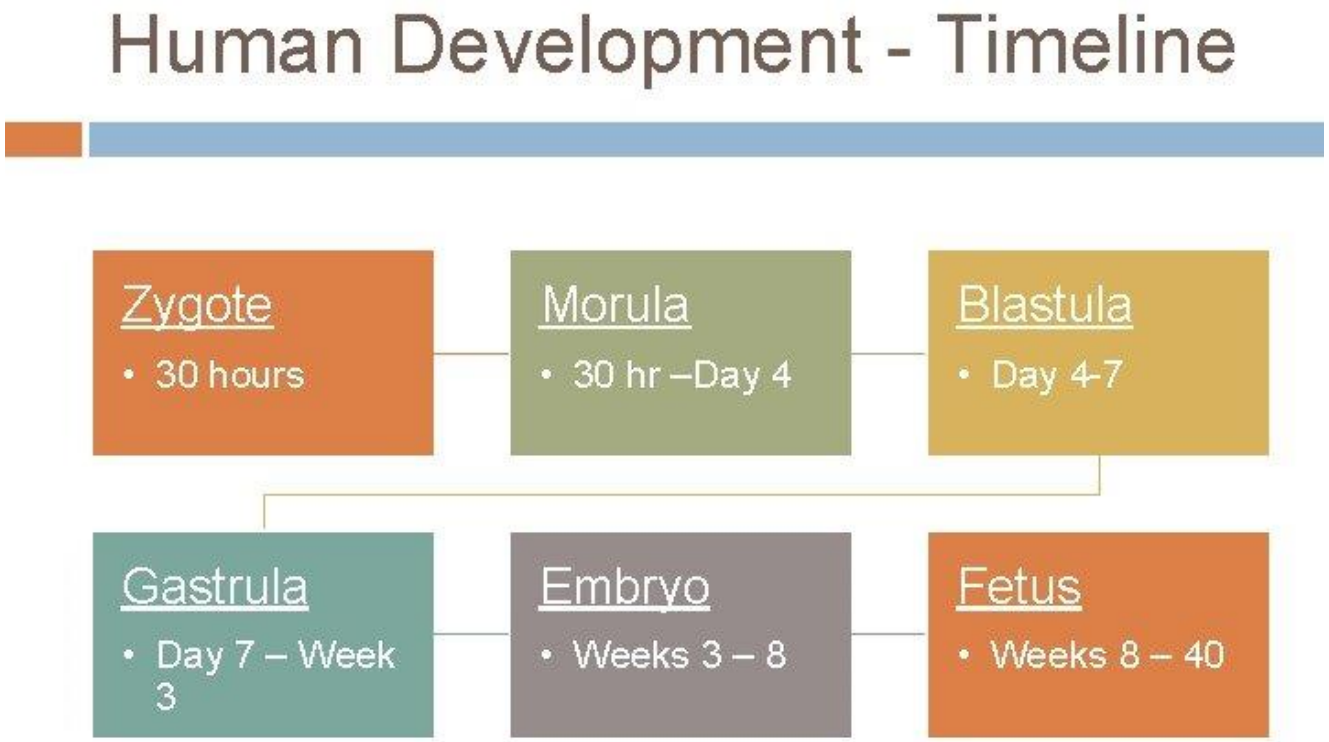
Objectives:-

- To memorize the definition of Hematopoiesis: Definition, sites with dates and cell lines
- To memorize the definition of vasculogenesis, Angiogenesis, types and sites.
- To link some clinical cases with embryonic explanations

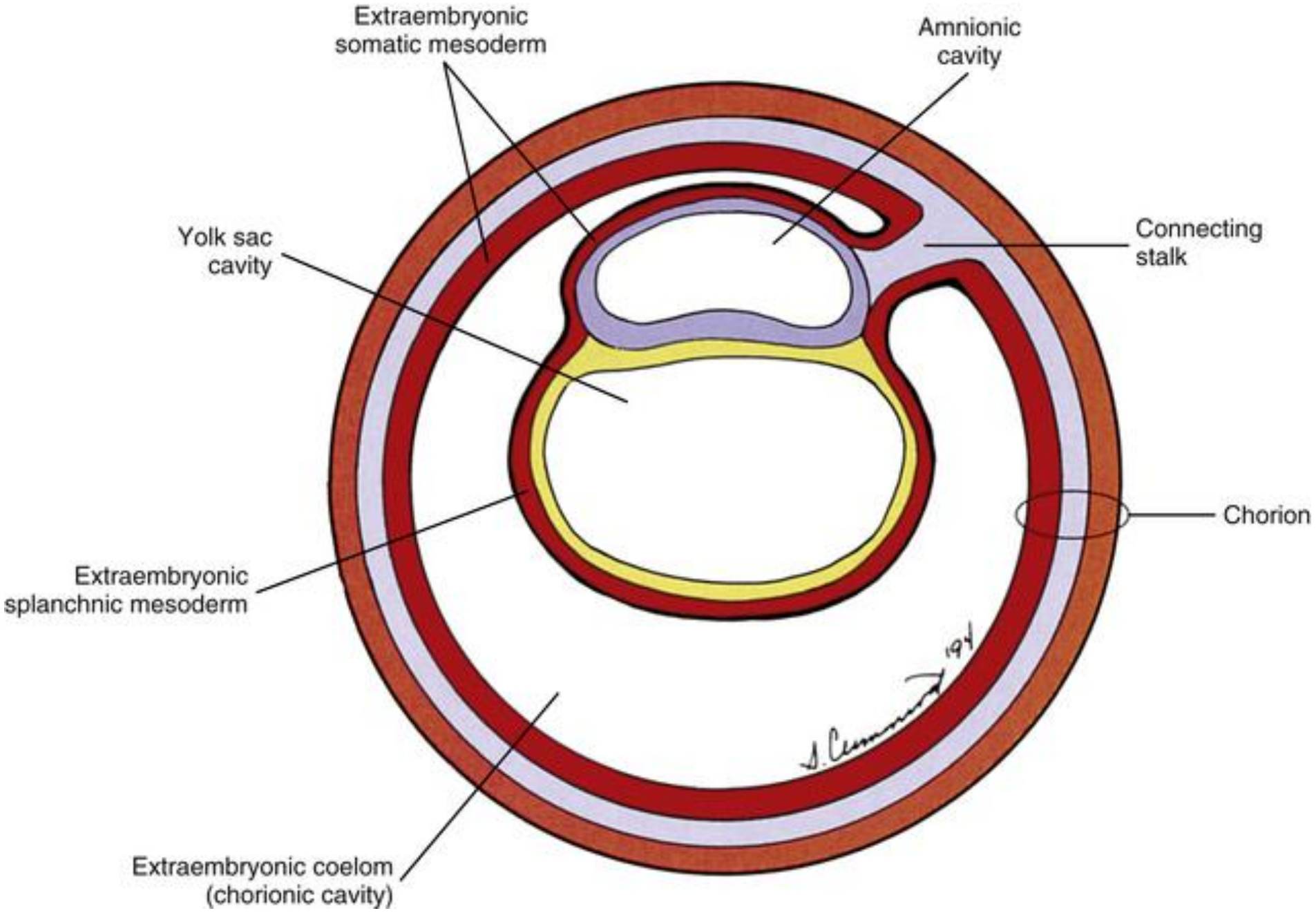
Remember that :-

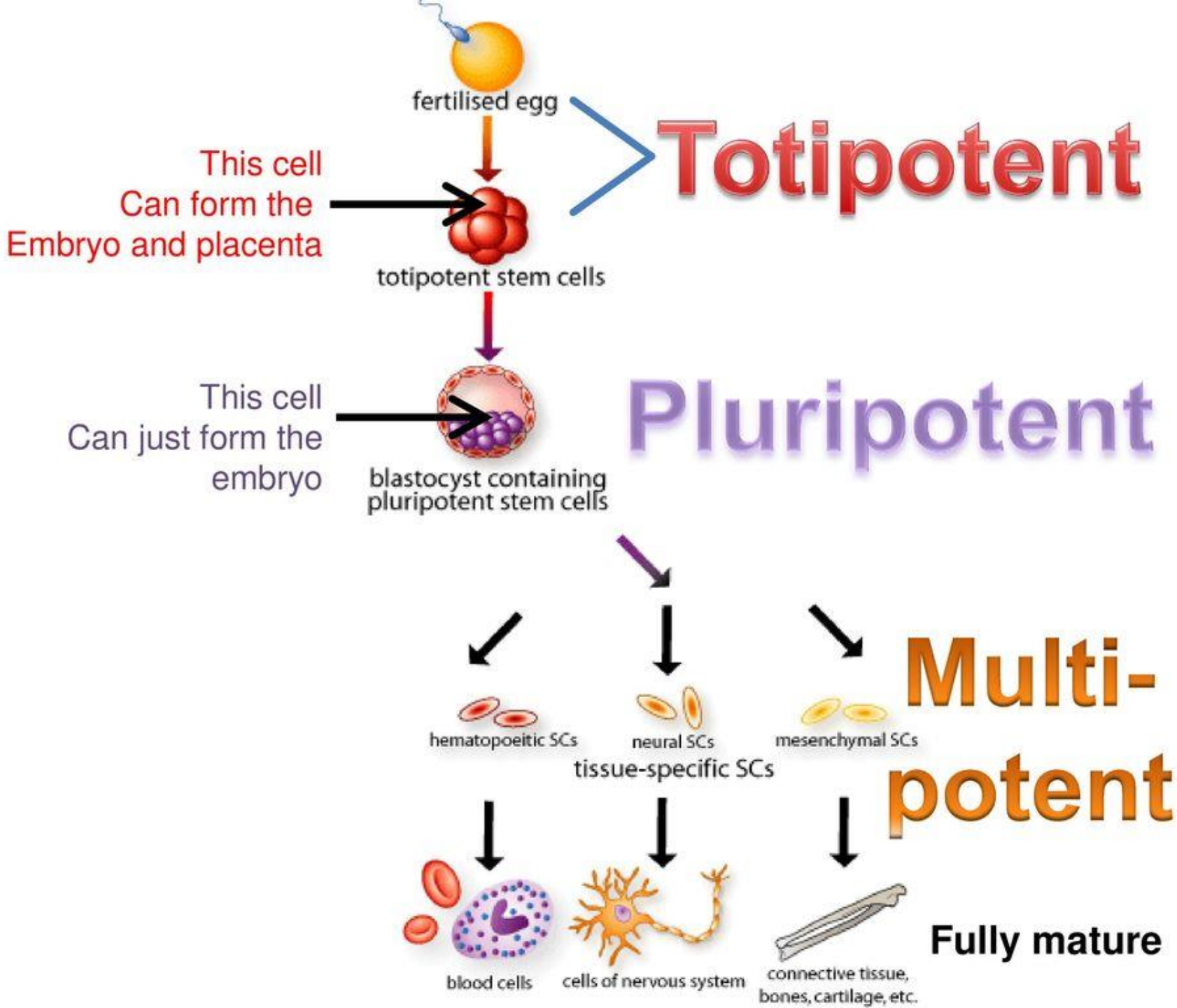
- The first two weeks after conception are known as the germinal stage, the third through the eighth week is known as the embryonic period, and the time from the ninth week until birth is known as the fetal period.

- extra-embryonic hematopoiesis (formation of blood cells outside of the embryo) precedes intra-embryonic blood cell development.



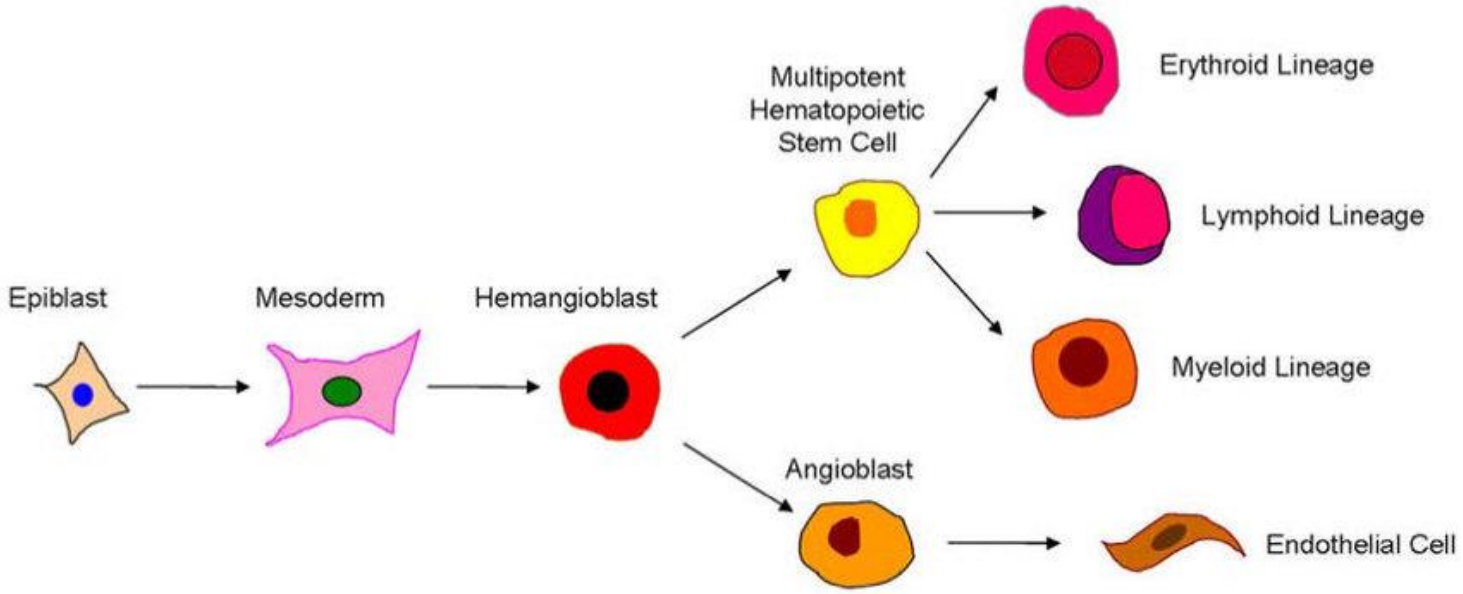
- Recall these sites !!



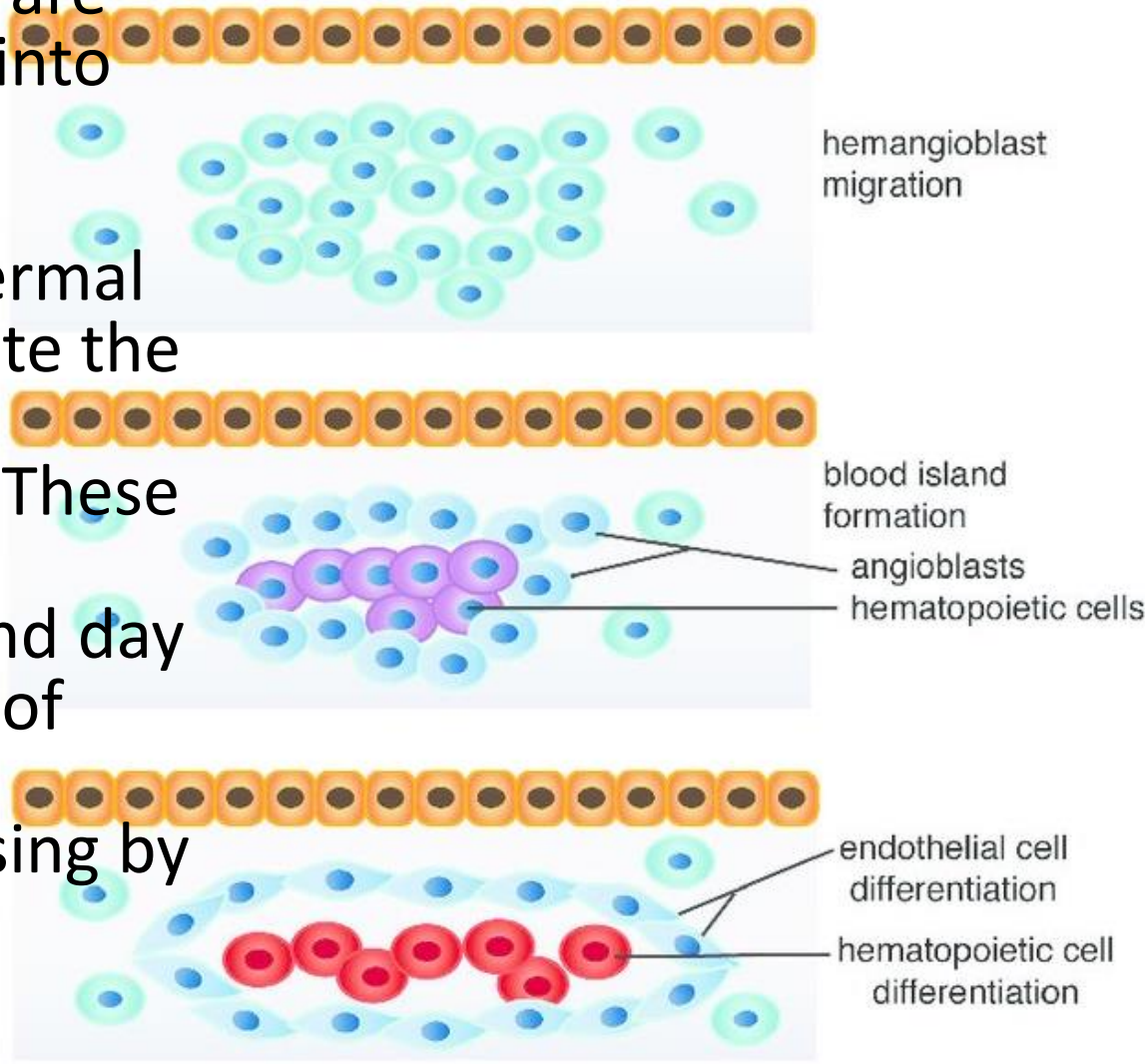

fertilised egg
This cell
Can form the
Embryo and placenta
totipotent stem cells
Totipotent
This cell
Can just form the
embryo
blastocyst containing
pluripotent stem cells
Pluripotent
hematopoeitic SCs
neural SCs
mesenchymal SCs
tissue-specific SCs
Multi-
potent
blood cells
cells of nervous system
connective tissue,
bones, cartilage, etc.
Fully mature

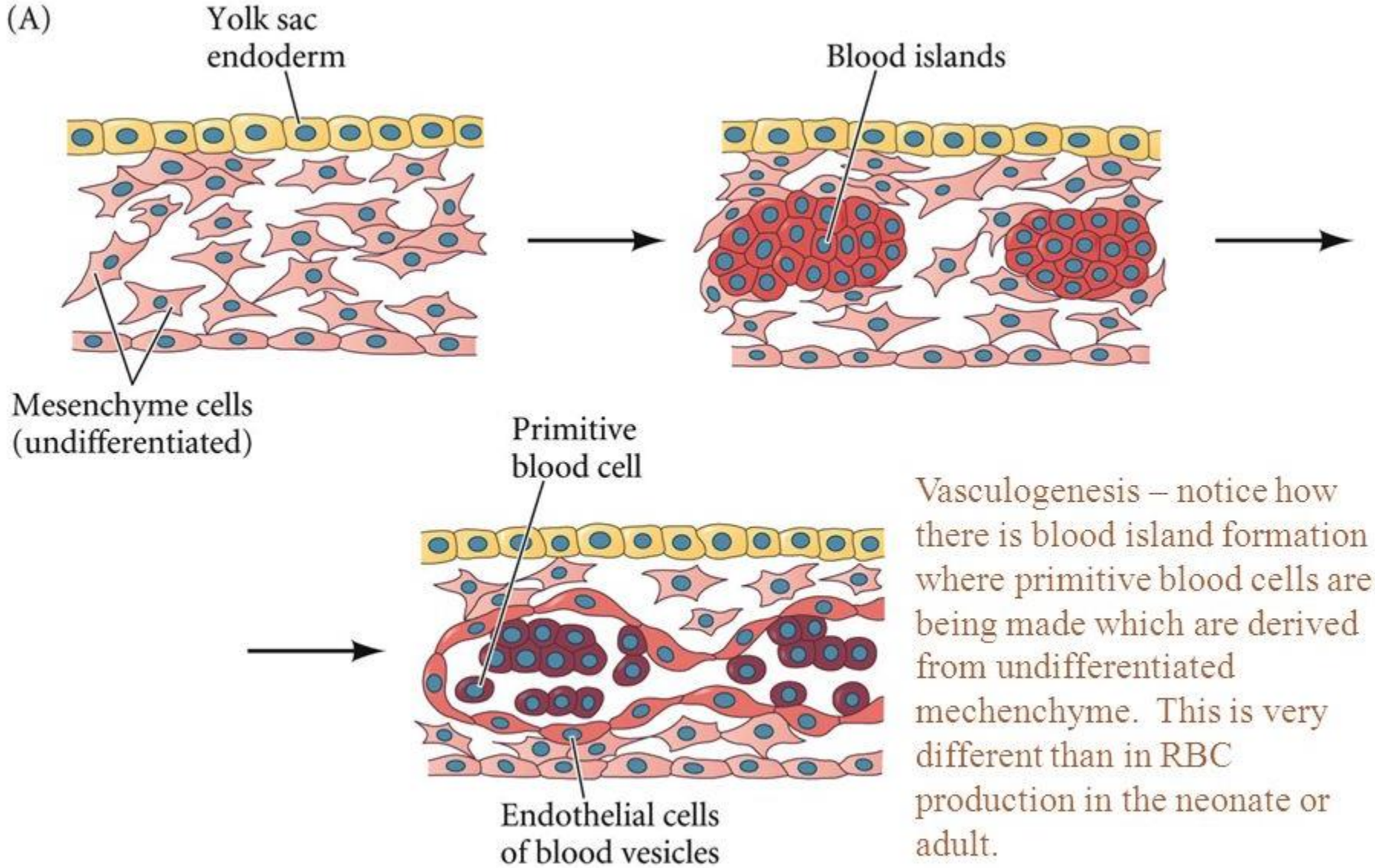
Yolk sac Hematopoiesis

- Around week two of gestation, mesodermal cells congregate within the yolk sack of the developing embryo to form well defined cell clusters. These clusters of blood cells possess both vasculogenic and haematopoietic potential and are therefore classified as hemangioblasts.



- The peripheral cells differentiate into endothelium, and by extension will form blood vessels. However, the remaining are pluripotent cells that will differentiate into granulocyte, erythrocyte, lymphocyte, thrombocyte, and monocyte cells lines subsequently. These primitive mesodermal cells move more peripherally to facilitate the creation of the vessel lumen, and are attached to the vascular endothelium. These clusters of cells, are referred to as blood islands, begin to appear around day 16 of development and form the basis of extra-embryonic haematopoiesis. Subsequently they are completely missing by the 8th gestational week.





Vasculogenesis – notice how there is blood island formation where primitive blood cells are being made which are derived from undifferentiated mechenchyme. This is very different than in RBC production in the neonate or adult.

The yolk sac is the first supplier of blood cells to the embryonic circulation. The cells supplied are predominantly **nucleated** erythrocytes containing embryonic hemoglobin (**primitive** erythrocytes).

- Most of the blood cells formed in the yolk sac are primitive erythrocytes, occasionally primitive megakaryocytes and macrophages are also present in very small quantities. Morphologically, the primitive erythrocytes are megaloblasts produce embryonic hemoglobin

(i.e. Hb Portland-1 [ζ2γ2], Hb Portland-2 [ζ2β2], Hb Gower-1 [ζ2ε2] and Hb Gower 2 [α2ε2]).

It should be noted that embryonic hemoglobin has a short life span and is no longer detectable by around the 12th week of gestation. The synthesis of fetal hemoglobin (Hb F; α2γ2) begins simultaneously with embryonic hemoglobin. Hb F is more durable outlives embryonic hemoglobin and persists into extra-uterine life.

- By day sixty60, the yolk sac no longer serves as an erythropoietic organ. Rather, the task of supplying erythrocytes and other lineages of mature blood cells to the circulation is transferred to intraembryonic organs, including the liver, spleen, thymus, and bone marrow. With the onset of the functional circulatory system, these organs are seeded with hematopoietic progenitors and definitive hematopoietic stem cells (HSCs) generated in the extraembryonic and/ or intraembryonic mesoderm.

ζ= pronounced as zeta
ε= pronounced as e
γ= pronounced as g
Adult Hb = α2 β2

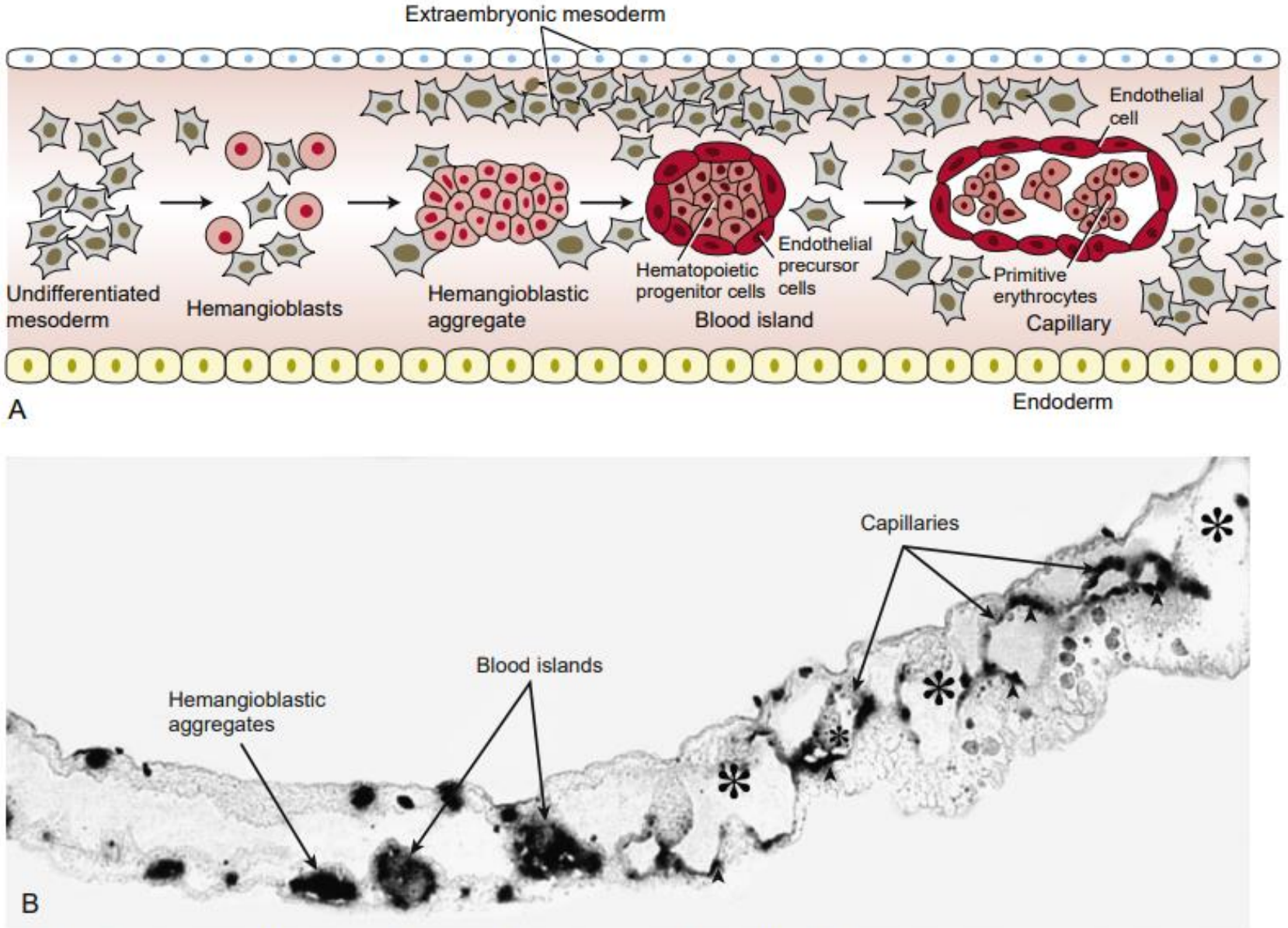


Figure 13-1. Hematopoiesis and blood vessel formation begin within the yolk sac wall with the formation of clusters of hemangioblasts. *A,* Drawing illustrating the formation of clusters of hemangioblasts and their differentiation into hematopoietic progenitor and endothelial precursor cells. Blood cells are surrounded by differentiating endothelial precursor cells forming blood islands. *B,* Expression of Vegfr2 mRNA, an early marker for the hemangioblasts within the yolk sac wall of a fifteen-somite avian embryo. As the blood islands develop, endothelial cells retain Vegfr2 expression, whereas hematopoietic progenitor cells progressively lose it. Asterisks indicate developing blood vessels.

Embryonic liver Hematopoiesis

- Foetal circulation coincides with the onset of the heart beating. This allows for yolk sac derived blood cells to enter embryonic tissue. Conveniently, haematopoietic stem cells are able to begin colonizing future sites of haematopoiesis. The liver – which is derived from both endoderm (the foregut diverticulum) and mesoderm (septum transversum) – is the first intra-embryonic site of haematopoiesis.
- As blood cells move from the yolk sac to the liver, the morphology also changes from megaloblastic primitive erythrocytes to definitive macrocytic erythrocytes (nucleus removed). Consequently, there is also a switch from embryonic haemoglobin to foetal haemoglobin.
- This organ remains the main hematopoietic organ of the embryo and fetus until initiation of bone marrow hematopoiesis near parturition (birth).
- The shift from generating primitive nucleated erythroblasts to enucleated erythrocytes synthesizing fetal hemoglobin (definitive erythrocytes) occurs by five weeks of gestation. This shift occurs at the time when the liver is colonized with Hematopoietic stem cells (HSCs): cells that have the potential to generate all the hematopoietic cell lineages of the adult including erythroid, myeloid, and lymphoid cells.
- HSCs colonize the bone marrow and contribute blood cells as early as ten and one-half weeks, but the bulk of the hematopoietic burden is still carried by the liver until birth.
- Eventually, midway through the 8th week of gestation, all haematopoietic activity ceases in the yolk sac.

Thymus

- During the third month, lymphocytes and dendritic cells infiltrate the thymus, and by twelve weeks, each thymic lobule is 0.5 to 2 mm in diameter and has a well-defined cortex and medulla
- Hassall's corpuscles in the medulla are thought to arise from the ectodermal cells of the third pharyngeal cleft. Hassall's corpuscles produce signals necessary for the development of regulatory T cells. The loosely organized epithelial reticulum is thought to be of endodermal origin.
- The thymus is highly active during the perinatal period and continues to grow throughout childhood, reaching its maximum size at puberty. After puberty, the gland involutes rapidly and is represented only by insignificant fibrofatty vestiges in the adult

Bone marrow

- Coincidentally, the final haematopoietic site to develop in utero, takes over haematopoietic activity into extra-uterine life. The bone marrow is colonized by HSCs in the 11th week of gestation; long after blood cells production has ceased in the yolk sac, and is well happening in the thymus and liver.
- The osteoblasts (which are also mesodermal in origin) are thought to aid in haematopoiesis by sustaining the bone marrow stroma that supports the haematopoietic stem cells. A mixture of dense fibrils and loose mesenchyme surrounding a central artery is the point at which marrow haematopoiesis begins. These areas are known as the **primary logettes** and are curiously located as far from the ossifying trabecular bone as possible.

Summary : To summarize the chronological sequence of the embryological appearance of haematopoietic stem cells:

1. Within the third week of gestation (day 17) the yolk sac begins to show haematopoietic activity.
2. Early in week 4 (day 23) the first wave of haematopoietic cells colonize the liver. This coincides with a tapering off of yolk sac blood cell activity.
3. The abdominal arterial clusters show haematopoietic activity towards the end of week 4 (day 27).
4. The second weave of haematopoietic cells colonize the liver early in week 5 (day 30).
5. The bone marrow is colonized in week 11 of gestation.

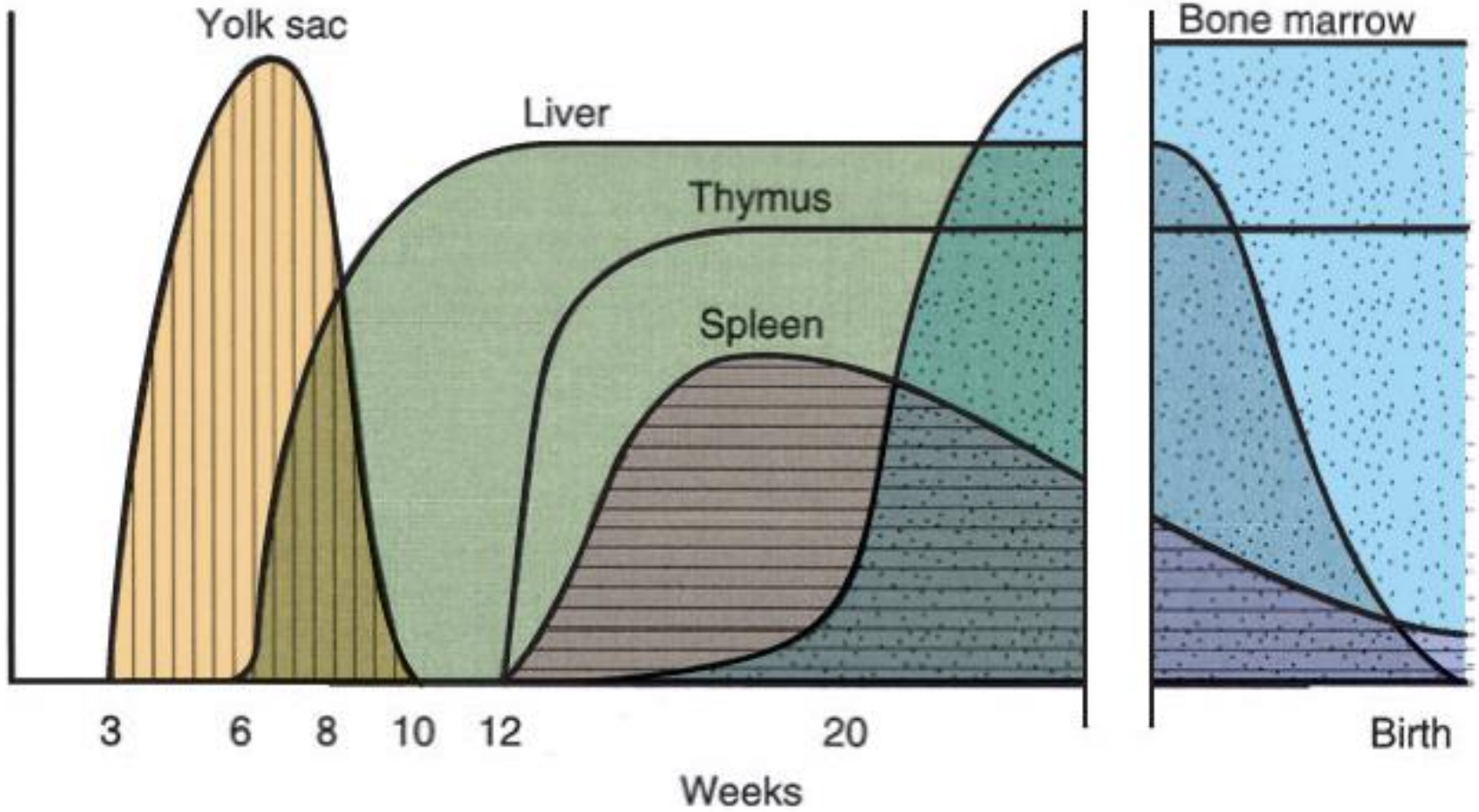


FIGURE 4.3. A schematic diagram showing the contribution of various organs to hematopoiesis during development. During the period of yolk sac hematopoiesis, the earliest **embryonic form** of hemoglobin is synthesized, called **hemoglobin** $\xi_2\varepsilon_2$. During the period of liver hematopoiesis, the **fetal form** of hemoglobin (**HbF**) is synthesized, called **hemoglobin** $\alpha_2\gamma_2$. During the period of bone marrow hematopoiesis (about week 30), the **adult form** of hemoglobin (**HbA**) is synthesized, called **hemoglobin** $\alpha_2\beta_2$, and gradually replaces hemoglobin $\alpha_2\gamma_2$. **Hemoglobin** $\alpha_2\gamma_2$ is the predominant form of hemoglobin during pregnancy because it has a higher affinity for oxygen than the adult form of hemoglobin and thereby "pulls" oxygen from the maternal blood into fetal blood.

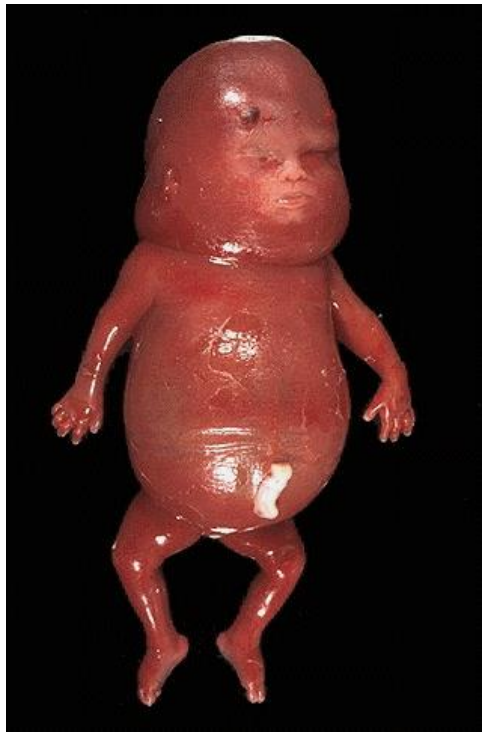
CLINICAL CONSIDERATIONS

- **Thalassemia syndromes** are a heterogeneous group of genetic defects characterized by the lack or decreased synthesis of either the α-globin chain (α-thalassemia) or β-globin chain (β-thalassemia) of hemoglobin α2β2.
- Thalassemias are inherited blood disorders characterized by decreased hemoglobin production. Symptoms depend on the type and can vary from none to severe. Often there is mild to severe anemia (low red blood cells or hemoglobin).[1] Anemia can result in feeling tired and pale skin. There may also be bone problems, an enlarged spleen, yellowish skin, and dark urine. Slow growth may occur in children.

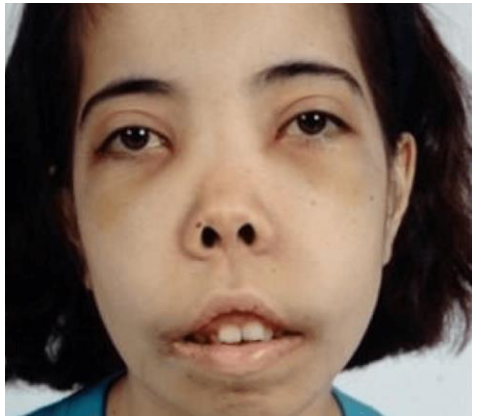
α-Thalassemia is an autosomal recessive genetic disorder most commonly caused by a deletion of the HBA1 gene and/or the HBA2 gene for the α1-globin subunit of hemoglobin and α2-globin subunit of hemoglobin, respectively.

β-Thalassemia is an autosomal recessive genetic disorder caused by missense or frameshift mutations in the HBB gene for the β-globin subunit of hemoglobin.

Hydrops fetalis is the most severe form of α-thalassemia and causes severe pallor, generalized edema, and massive hepatosplenomegaly and invariably leads to intrauterine fetal death.



β-Thalassemia major (Cooley anemia) is the most severe form of β-thalassemia and causes a severe, transfusion-dependent anemia. It is most common in Mediterranean countries and parts of Africa and Southeast Asia.



β-Thalassemia major

VASCULOGENESIS (DE NOVO BLOOD VESSEL FORMATION)

Vasculogenesis is the process of blood vessel formation in the embryo, occurring by a de novo production of endothelial cells and organize their selves into small capillary vessels (primary vascular plexuses).

closely followed by Angiogenesis (new blood vessels formation from pre-existing vessels by budding "sprouting" and vascular intussusception "splitting"of new vessels from existing endothelial cords).

These small capillaries lengthen and interconnect (remodeled), establishing an initial primary vascular network to accommodate growth of the embryo and develop into a system of arteries and veins. By the end of the third week, this network completely vascularizes the yolk sac, connecting stalk, and chorionic villi.

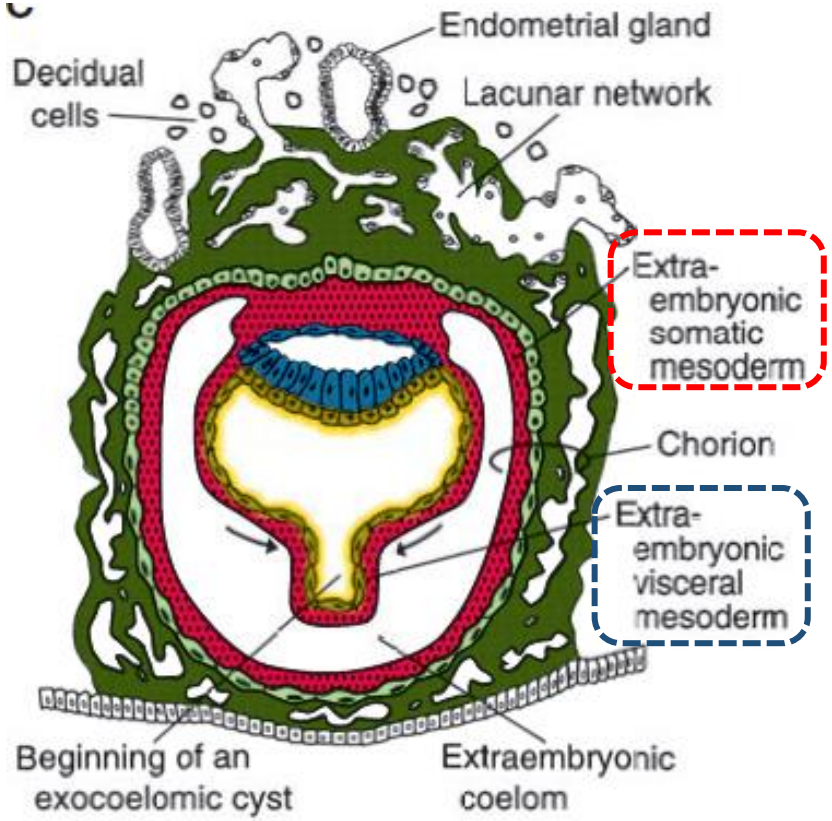
blood vessels form in the yolk sac on about day seventeen, but not in the embryonic disc until day eighteen

Vasculogenesis occurs in two general locations as follows:

A. In extraembryonic mesoderm:

1. Angiogenesis occurs first within extraembryonic visceral mesoderm around the yolk sac on day 17.

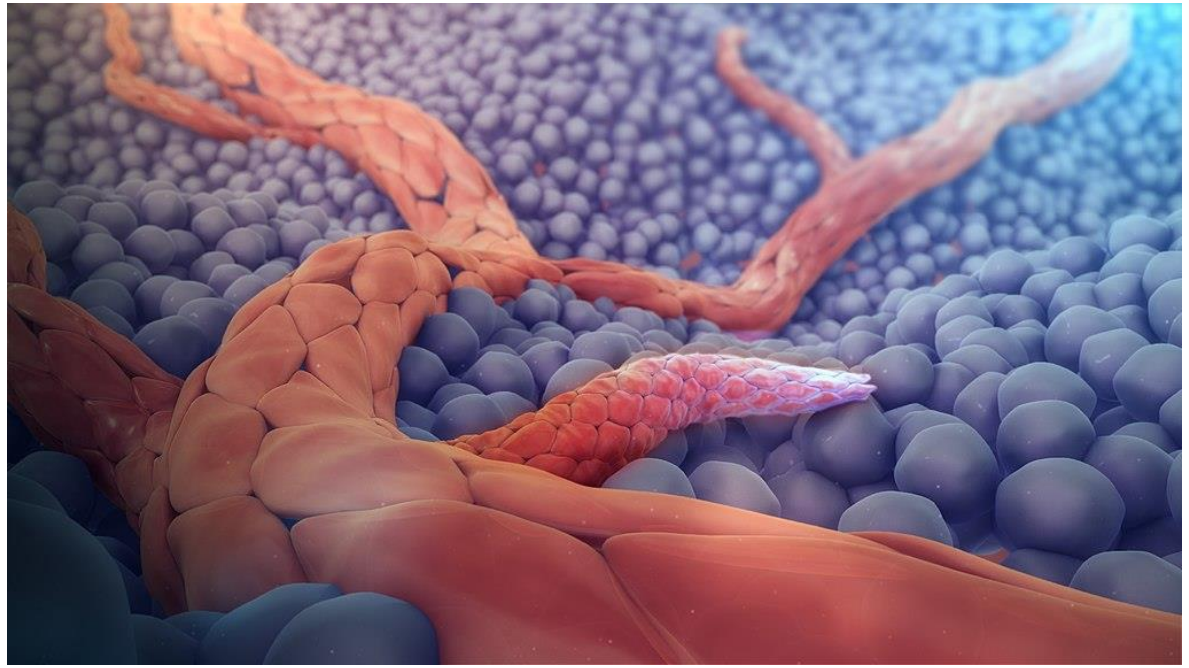
2. By day 21, angiogenesis extends into extraembryonic somatic mesoderm located around the connecting stalk to form the **umbilical vessels** and in secondary villi to form **tertiary chorionic villi.**

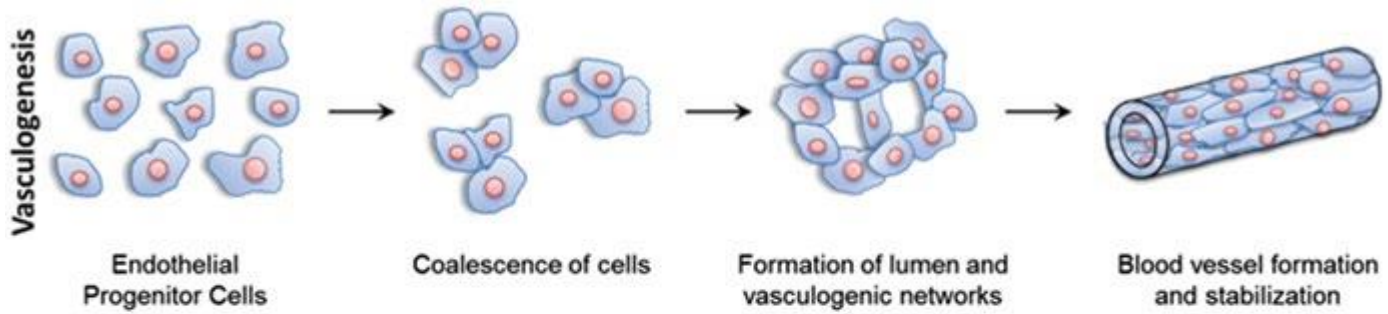


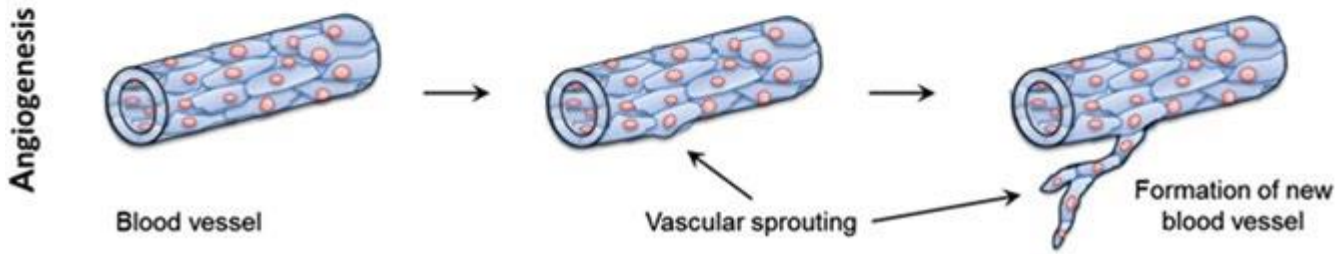
B. In intraembryonic mesoderm:

1. Forming blood vessels form **within** the embryo by the same mechanism as in extraembryonic mesoderm.

2. Eventually, blood vessels formed in the extraembryonic mesoderm become continuous with blood vessels within the embryo, thereby establishing a blood vascular system between the embryo and placenta.




Vasculogenesis
Endothelial Progenitor Cells
Coalescence of cells
Formation of lumen and vasculogenic networks
Blood vessel formation and stabilization


Angiogenesis
Blood vessel
Vascular sprouting
Formation of new blood vessel

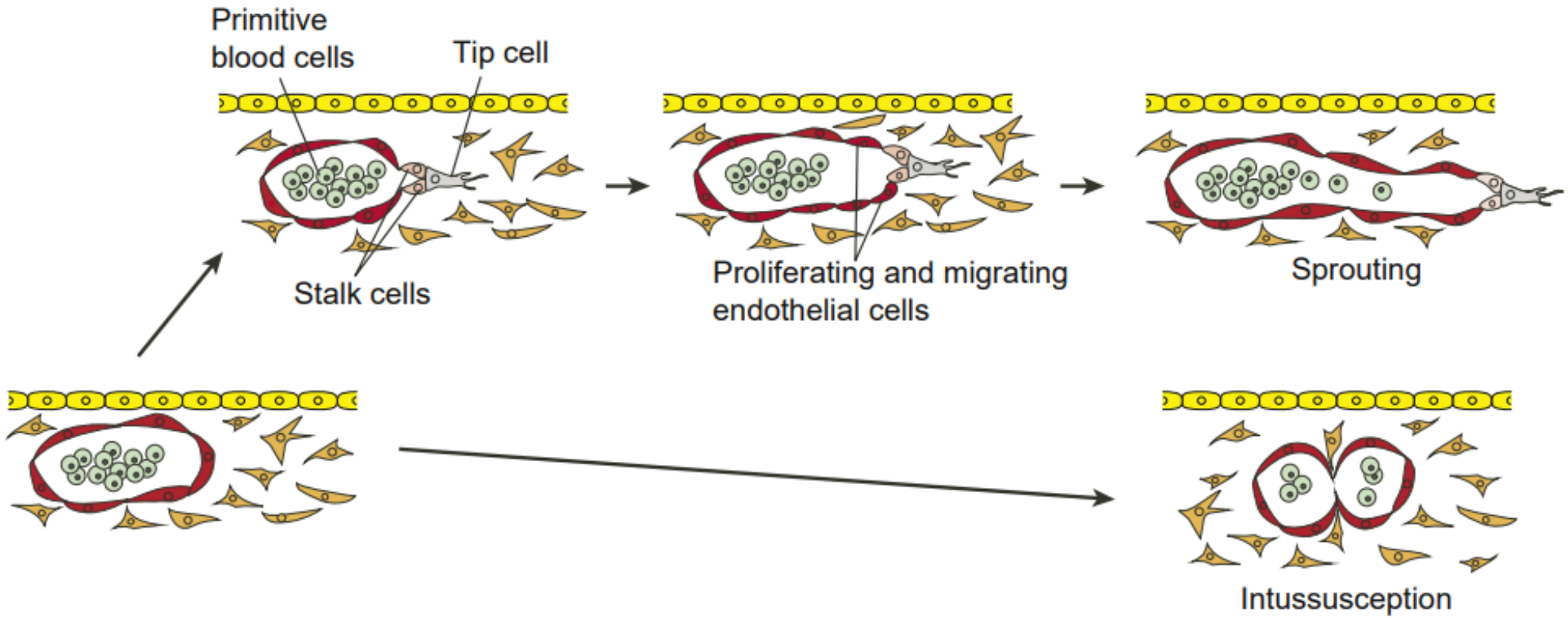


Figure 13-7. The primitive vascular network established through vasculogenesis is expanded and remodeled by angiogenesis. Expansion by angiogenesis occurs by sprouting from existing vessels or by intussusception, a splitting of existing vessels.

CLINICAL CONSIDERATIONS

- Angiomas: Blood and lymphatic vessels are stimulated by angiogenic factors to grow into developing organs. If vessel growth is not inhibited at the appropriate time, or if it is stimulated again later in life, blood or lymphatic vessels may proliferate until they form a tangled mass that may have clinical consequences. Excessive growth of small capillary networks is called a capillary hemangioma or nevus vascularis (from chromosomal anomalies); a proliferation of larger venous sinuses is called a cavernous hemangioma. Hemangioma of infancy is the most common benign tumor of childhood (incidence of about 2.5% in neonates and up to 10% to 12% in 1-year-olds, These tumors grow rapidly and consist mainly of endothelial cells with or without lumen. Most cases of hemangioma of infancy pose no immediate or long-term danger. However, they can be potentially life threatening if they grow in vital organs (e.g., in the skull or vertebral canal, where they can lead to nervous system dysfunction, or in airways, where they can obstruct breathing)

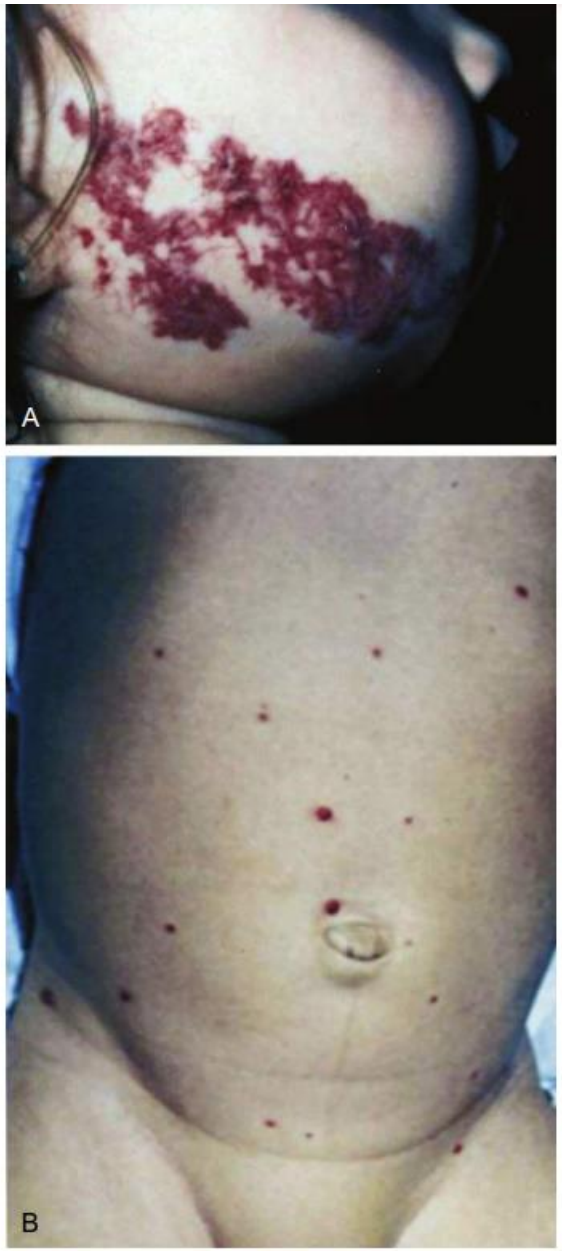


Figure 13-10. Hemangioma of human infancy. *A,* Hemangioma of infancy involving the region of the mandible and having airway involvement. This patient was treated with oral corticosteroids, which regresses these tumors in about a third of patients, thereby avoiding the need for surgical intervention for an otherwise progressing airway obstruction. *B,* Multifocal hemangiomas in an infant.