quatrième SEMAINE et deuxième MOIS du développement

4ème semaine :
neurulation (la fin : *fermeture du tube neural*) ;
plicatures (courbures) ;
somitogenèse (formation et différenciation des somites) ;
acquisition d'une asymétrie corporelle bilatérale

2ème mois :
acquisition de la forme humaine (morphogenèse) ;
formation des organes (organogenèse) ;
croissance

(1ère sem. : *zygote* >> *morula* >> 2è sem. : *blastula* >> 3è sem. : *gastrula* >> 4è sem. : *neurula*)

QUATRIEME SEMAINE :
PLICATURES ET SOMITOGENESE

la 4ème semaine est une période d'une activité génératrice intense et riche,

avec le début de la différenciation des ébauches de tous les systèmes,

à partir des trois feuillets embryonnaires qui viennent de se former

grâce a la gastrulation pendant la 3ème semaine

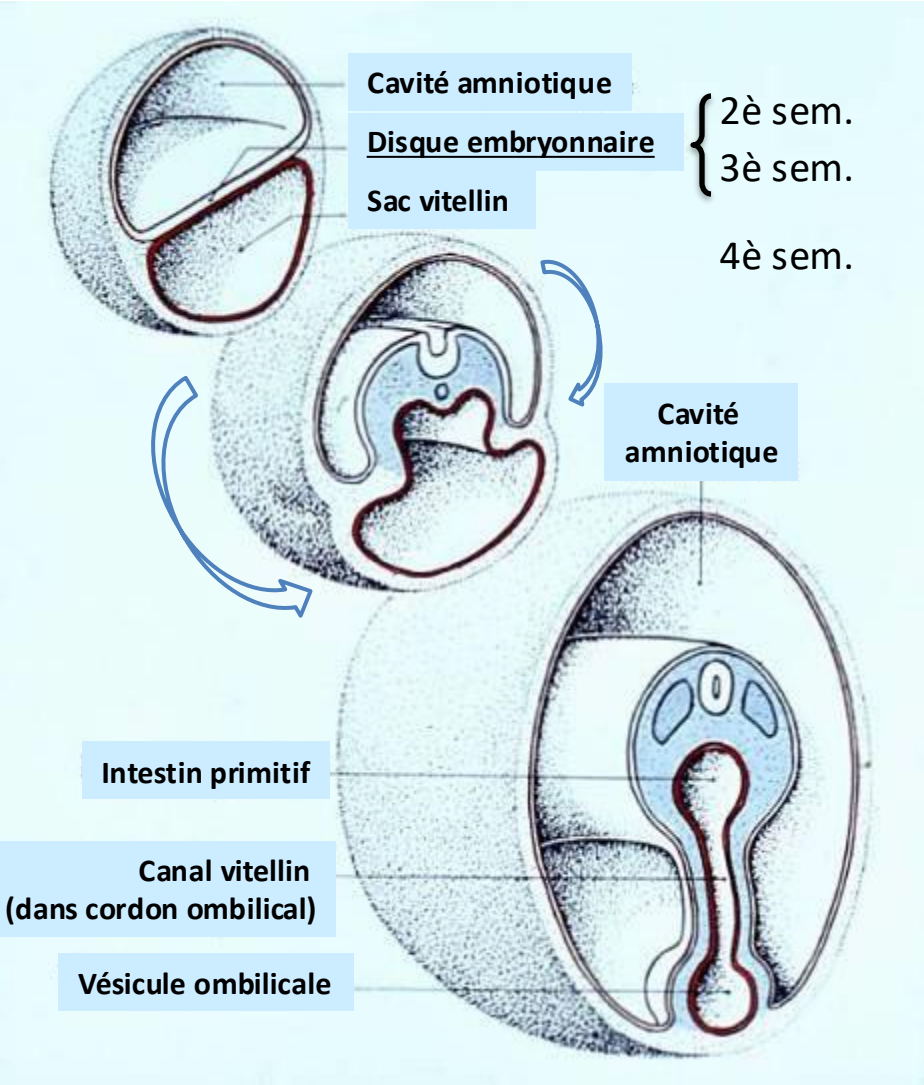
…et pendant le 2ème mois du développement, toutes ces ébauches d'organes vont se développer et différencier (« l'organogenèse »)…

4ème SEMAINE : 11 évènements

1. L'embryon prend une forme cylindrique
2. Le cordon ombilical est défini
3. Oblitération du cœlome extraembryonnaire
4. Fermeture du tube neural
5. Fermeture de l'épithélium de revêtement
6. Formation et différenciation des somites
7. *Différenciation du mésoderme intermédiaire (cordons néphrogènes), avec différenciation du système urinaire : pro- et mésonéphros*
8. *Fusion des tubes cardiaques*
9. *Différenciation du tube digestif ; bourgeons pulmonaires*
10. *Bourgeonnement des membres*
11. Formation des placodes optiques et otiques

QUATRIEME SEMAINE

1. L'embryon prend une forme cylindrique (à conséquence des plicatures)

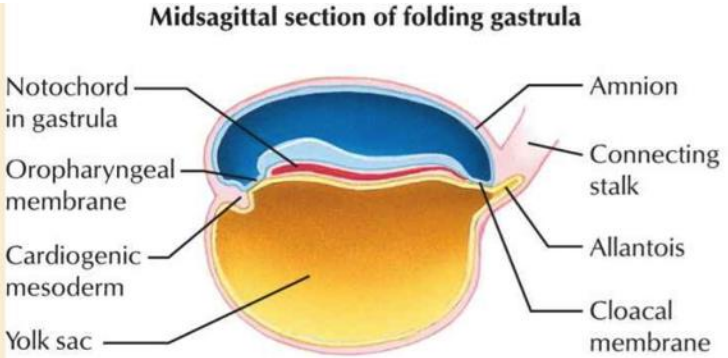


1ère sem.: l'embryon devient **blastocyste**; (*segmentation*)

2ème sem.: l'embryon est le **disque bilaminaire**; (*implantation*)

3ème sem.: l'embryon est le **disque trilaminaire**; (*gastrulation et neurulation*)

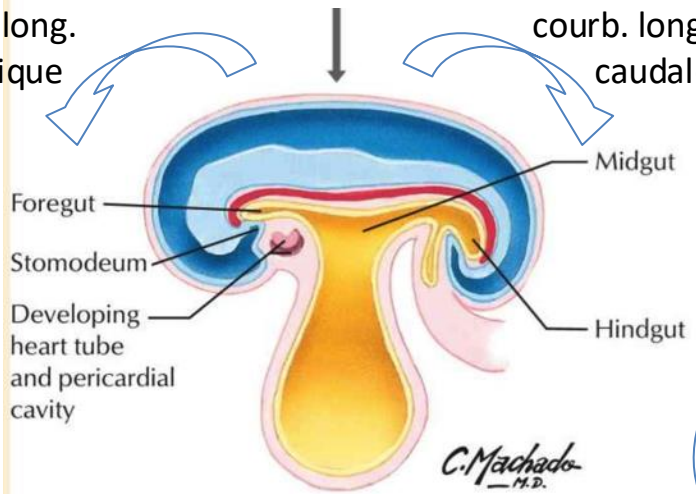
4ème sem.: l'embryon devient un **cylindre** (*plicatures et somitogenèse : acquisition de l'asymétrie bilatérale*)

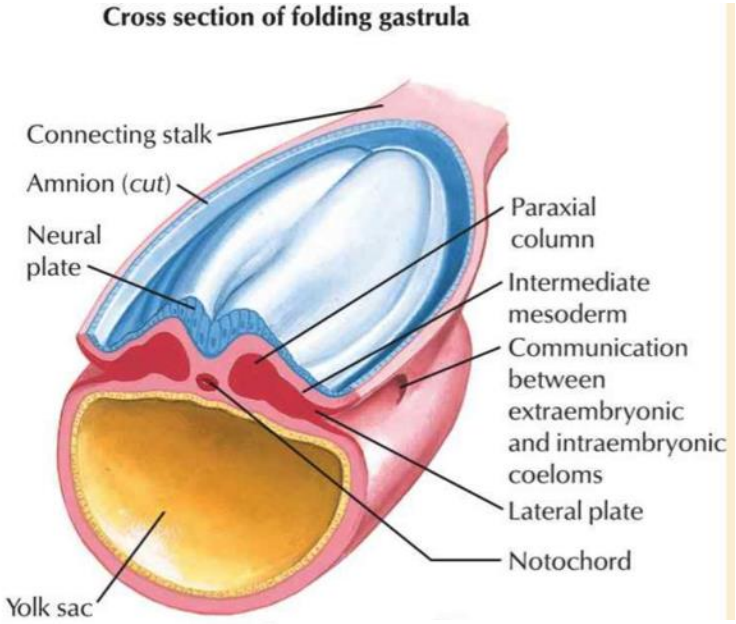


courbures longitudinales

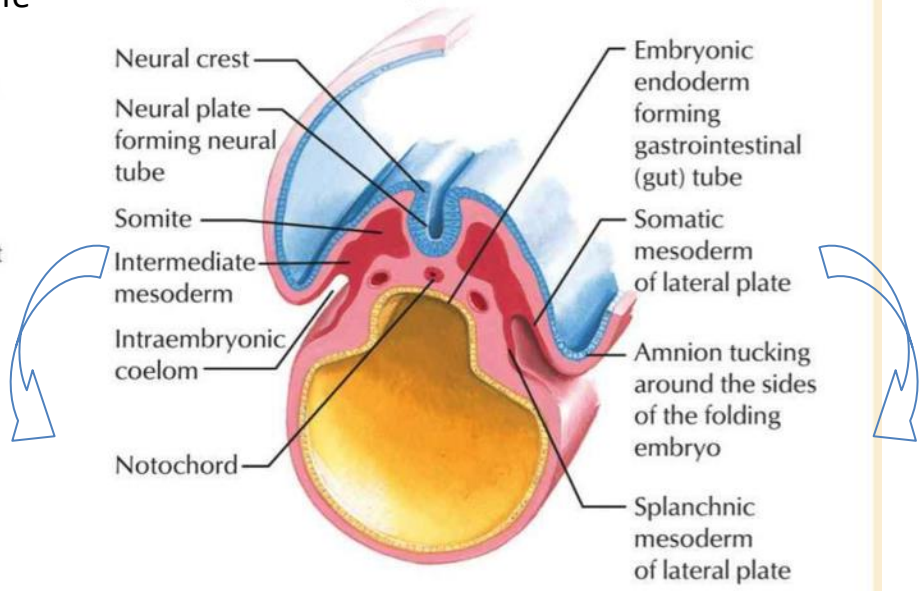
courb. long. céphalique

courb. long. caudale





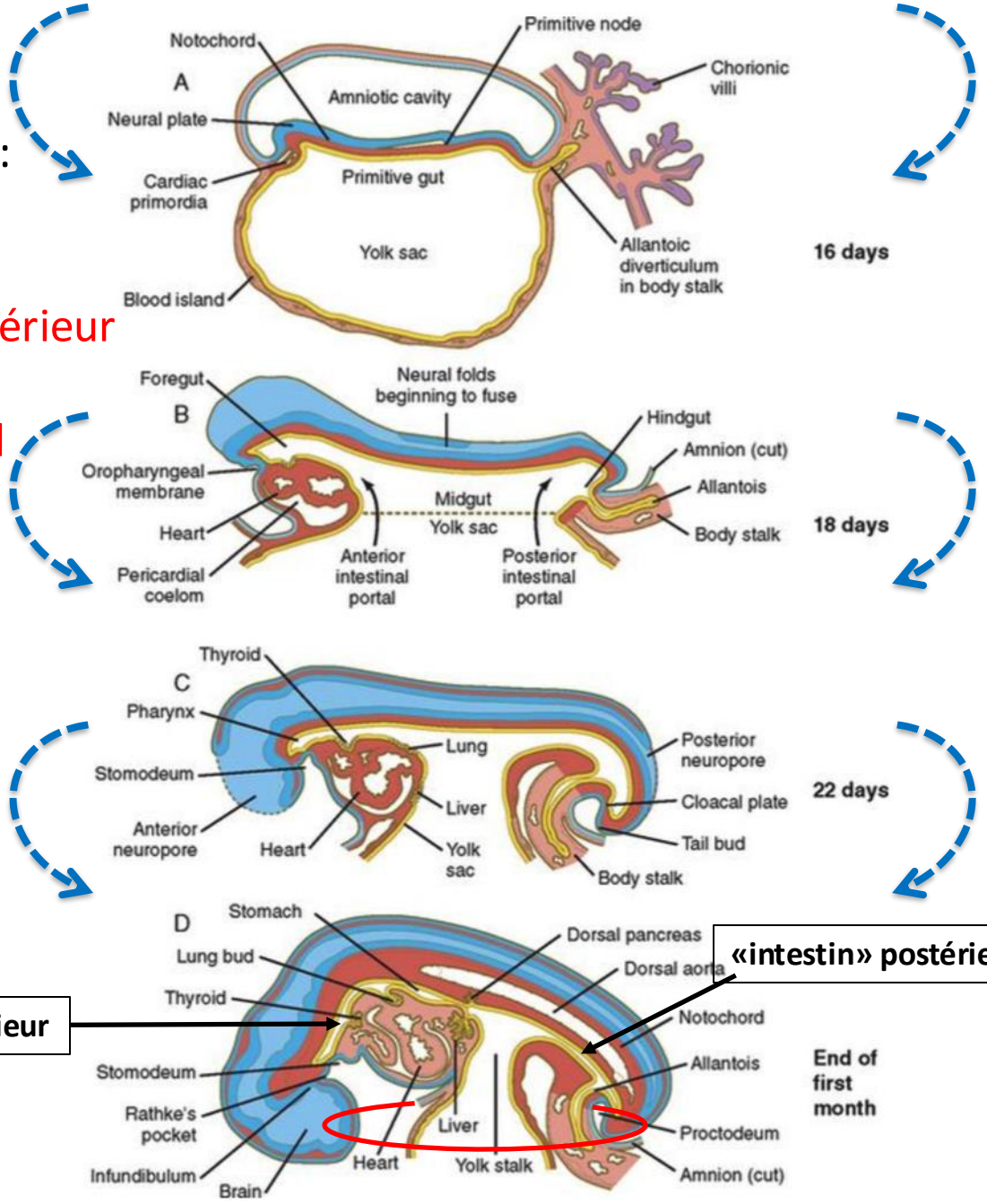
courbures transversales (=latérales)



Courbures longitudinales :

-formation du tube digestif
(«intestin») antérieur et postérieur

-formation du cordon ombilical

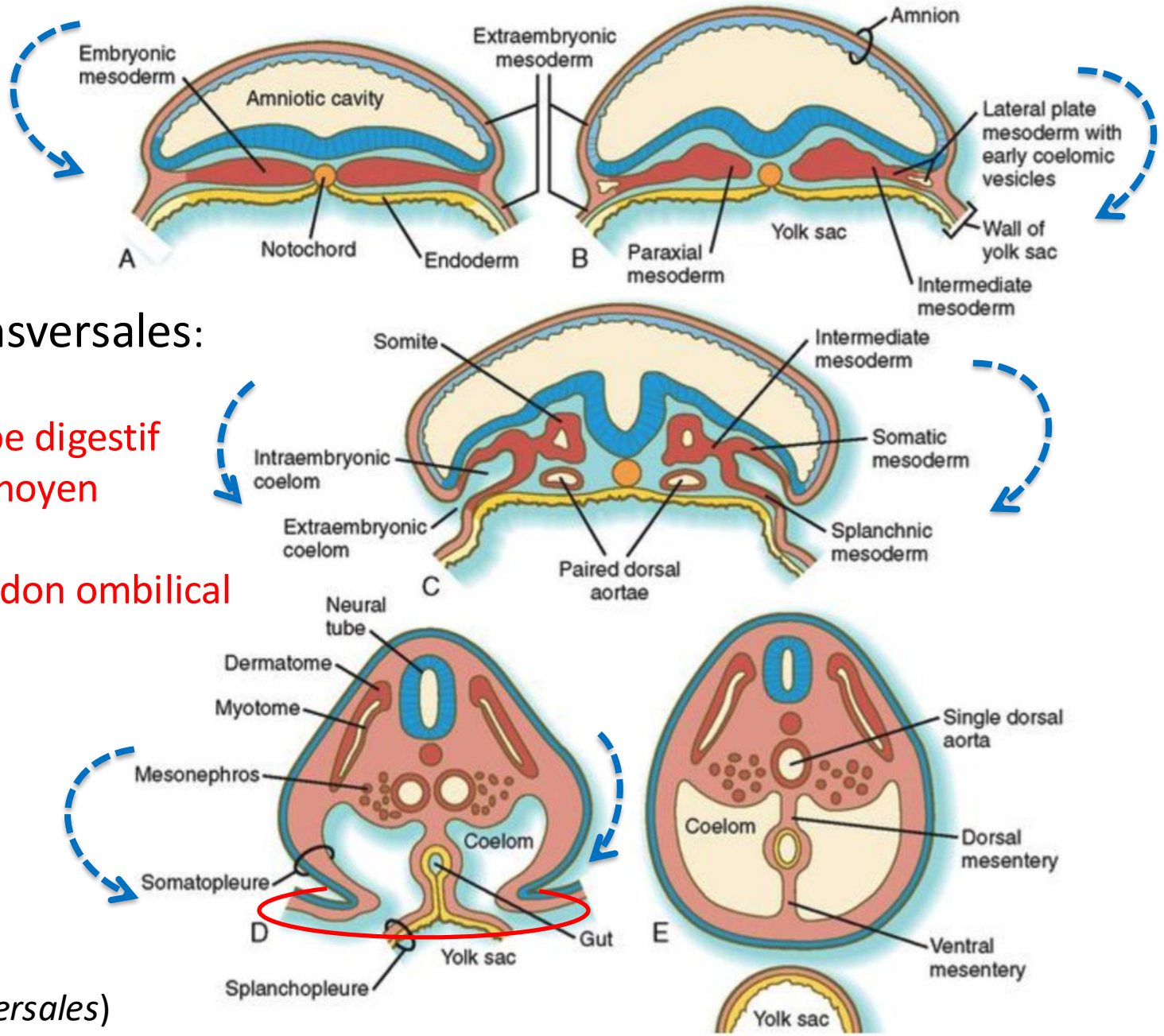


(*coupes sagittales*)

Courbures transversales:

-formation du tube digestif («intestin») moyen

-formation du cordon ombilical



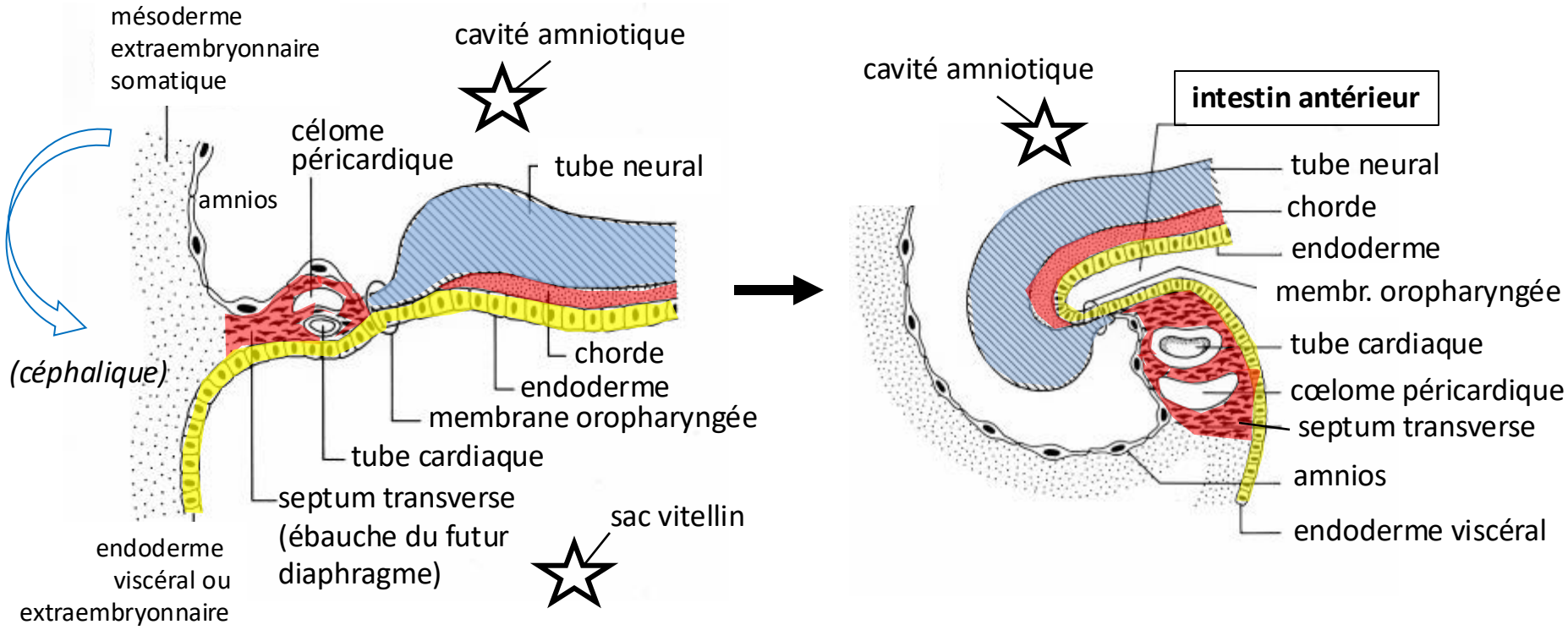
(*coupes transversales*)

QUATRIEME SEMAINE

1. L'embryon prend une forme cylindrique

a) courbures longitudinales

- céphalique:



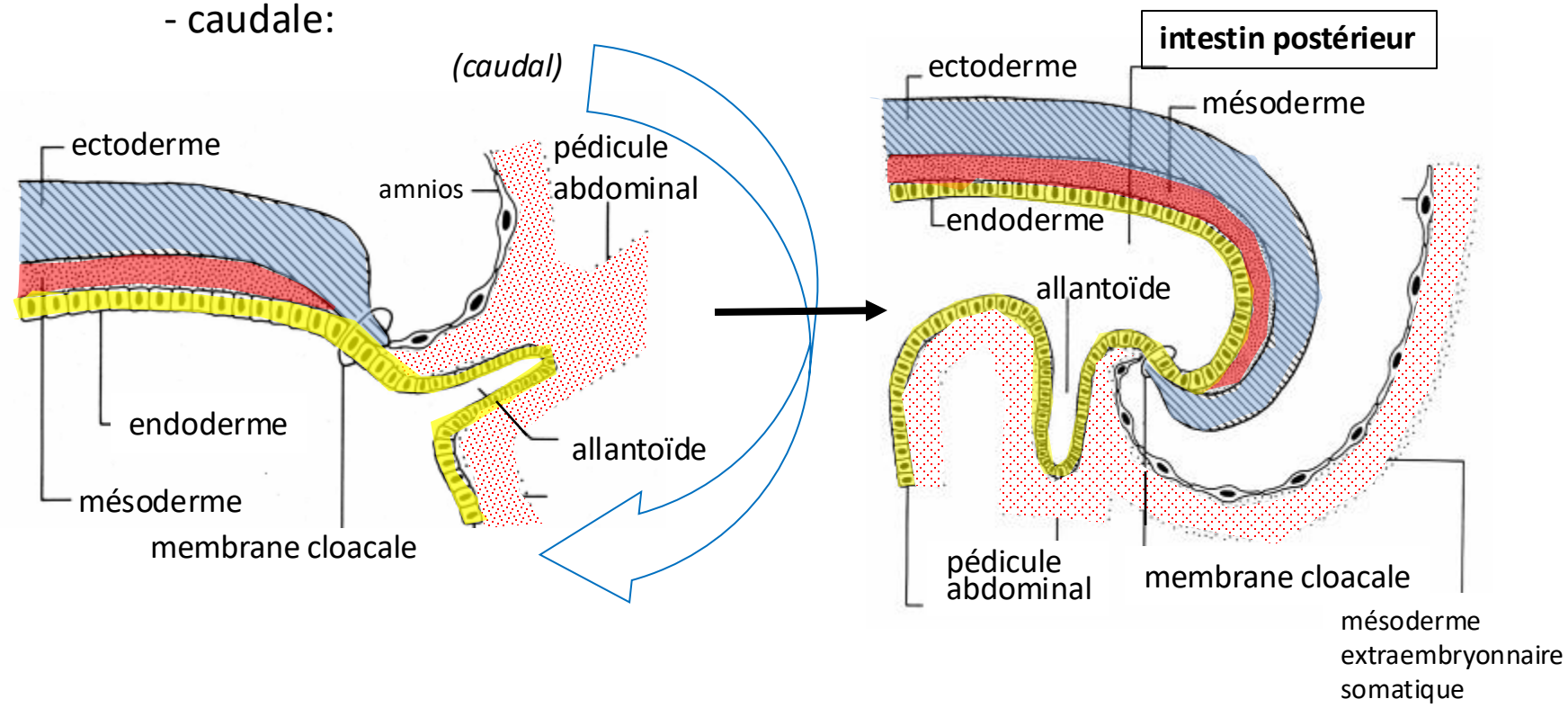
La <u>courbure longitudinale céphalique</u> amène l'aire cardiogène en position ventrale, et en arrière par rapport à la future bouche, et devient dorsale par rapport au célome péricardique. Elle détermine la formation de *l'intestin primitif antérieur*.

QUATRIEME SEMAINE

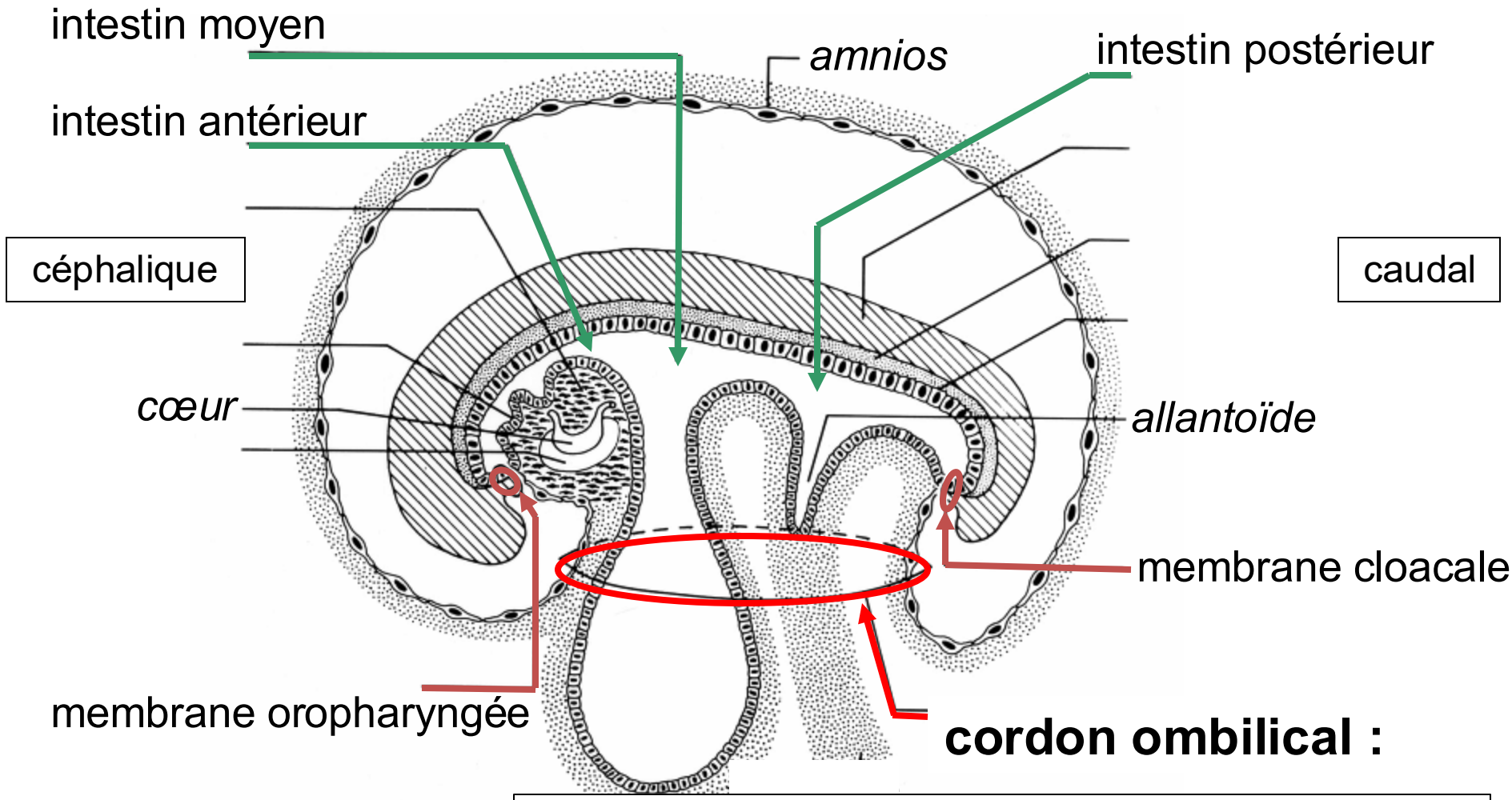
1. L'embryon prend une forme cylindrique

a) courbures longitudinales

- caudale:



La <u>courbure longitudinale caudale</u> amène l'allantoïde en position ventrale, et en avant par rapport au futur anus. Formation de *l'intestin primitif postérieur*.

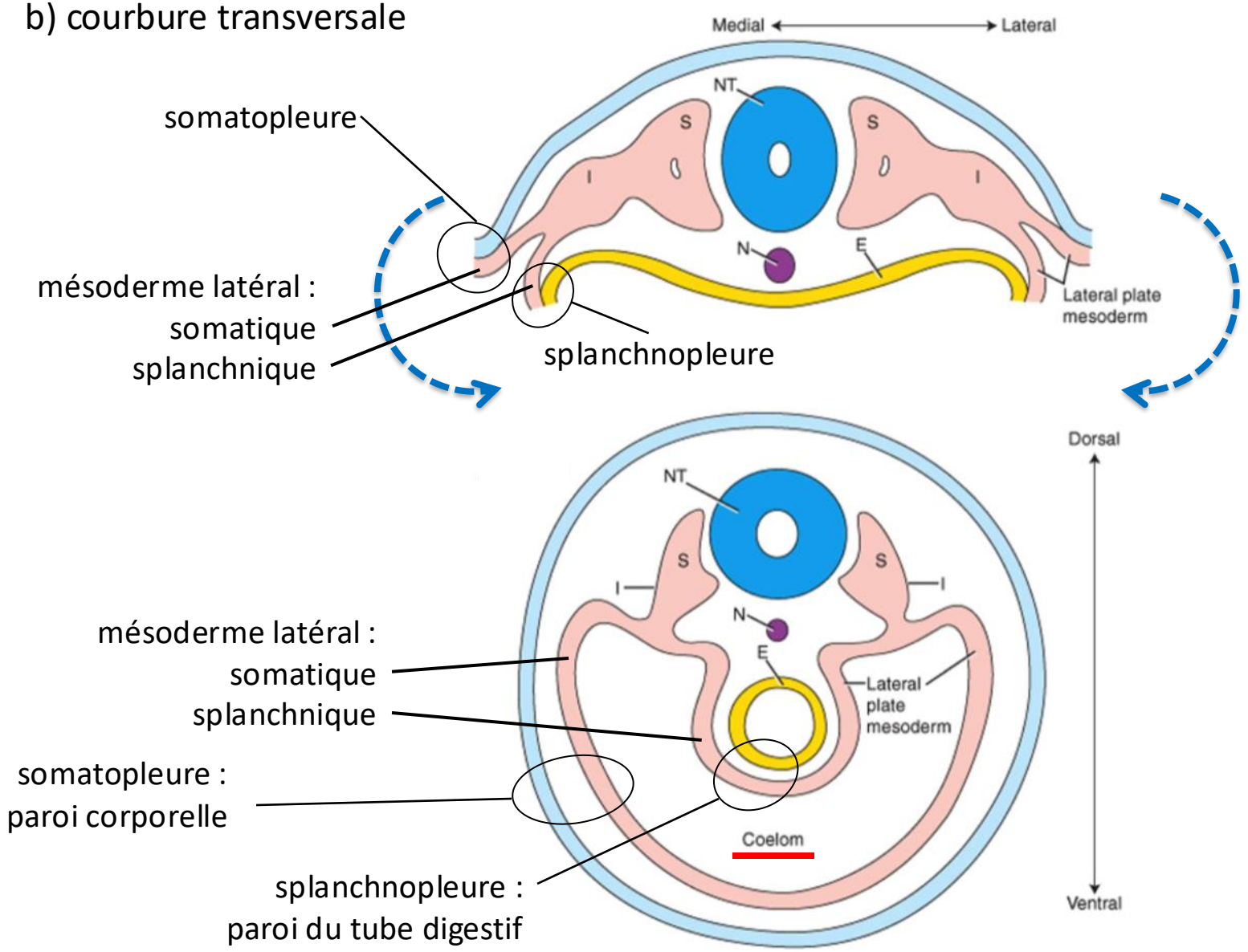


ammnios, mésoderme extraembryo. som. + visc.
+ pédicule abdominal, avec l'allantoïde distal
(+ vaisseaux) et sac (canal) vitellin

QUATRIEME SEMAINE

1. L'embryon prend une forme cylindrique

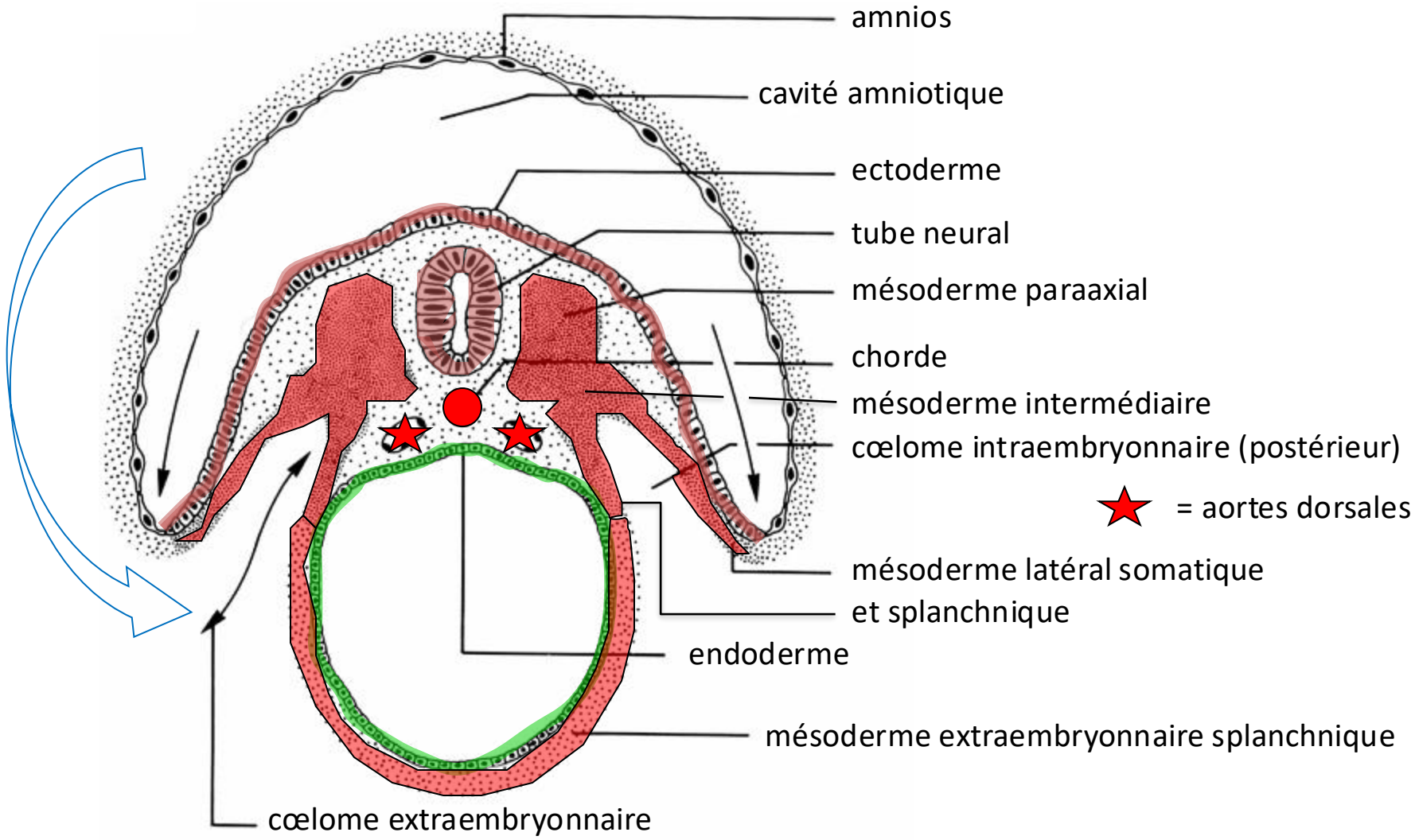
b) courbure transversale



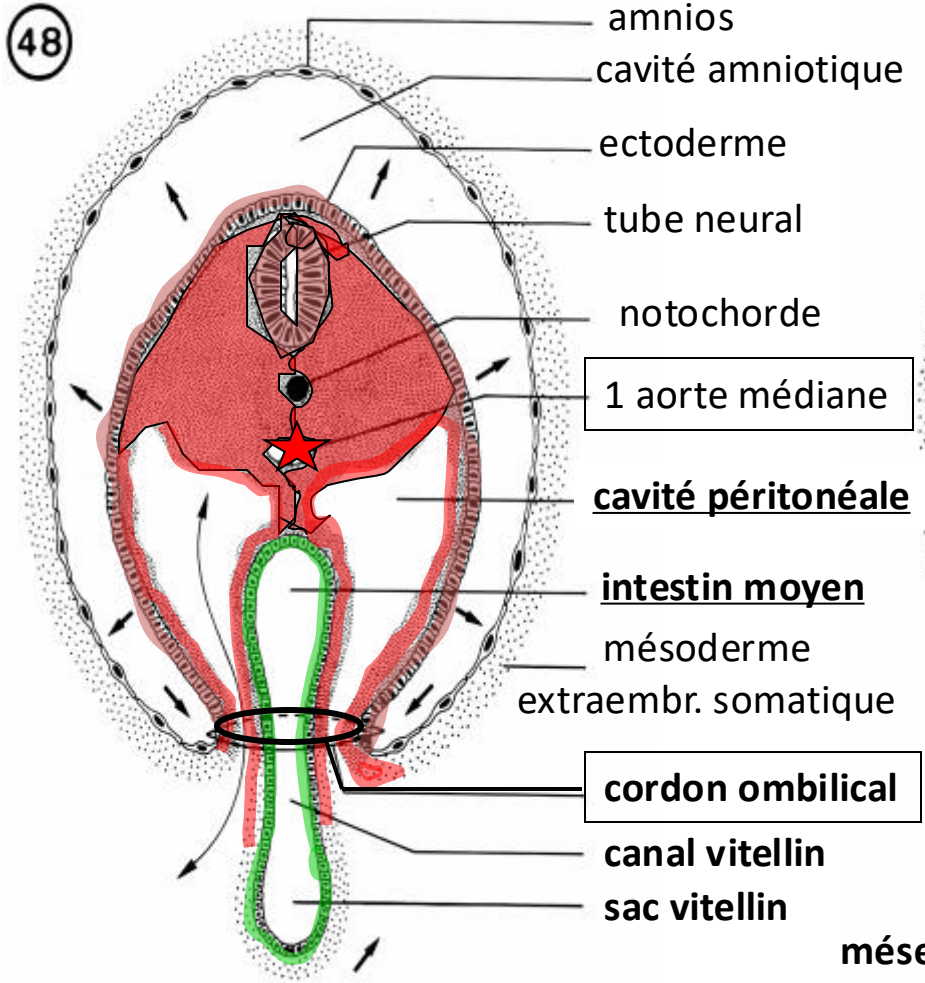
QUATRIEME SEMAINE

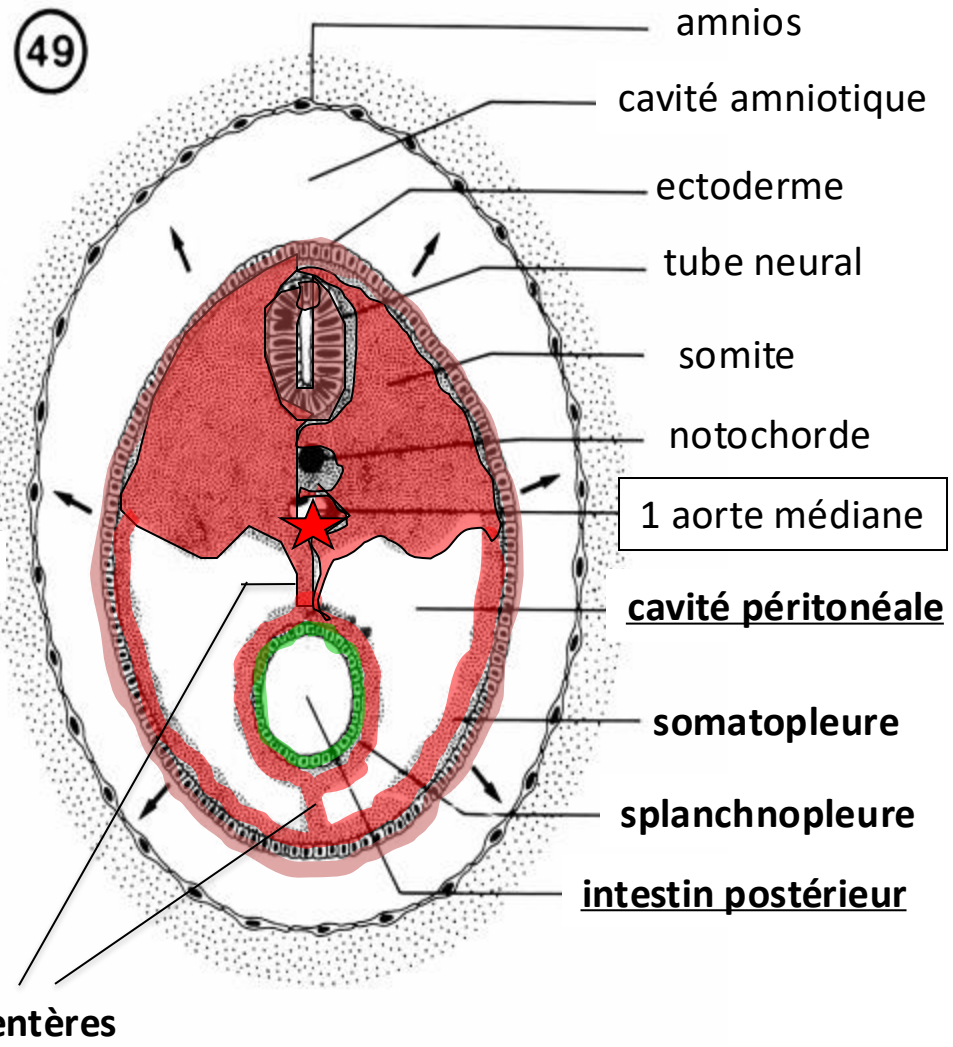
1. L'embryon prend une forme cylindrique

b) courbure transversale



COURBURE TRANSVERSALE
(milieu et partie postérieure du corps)

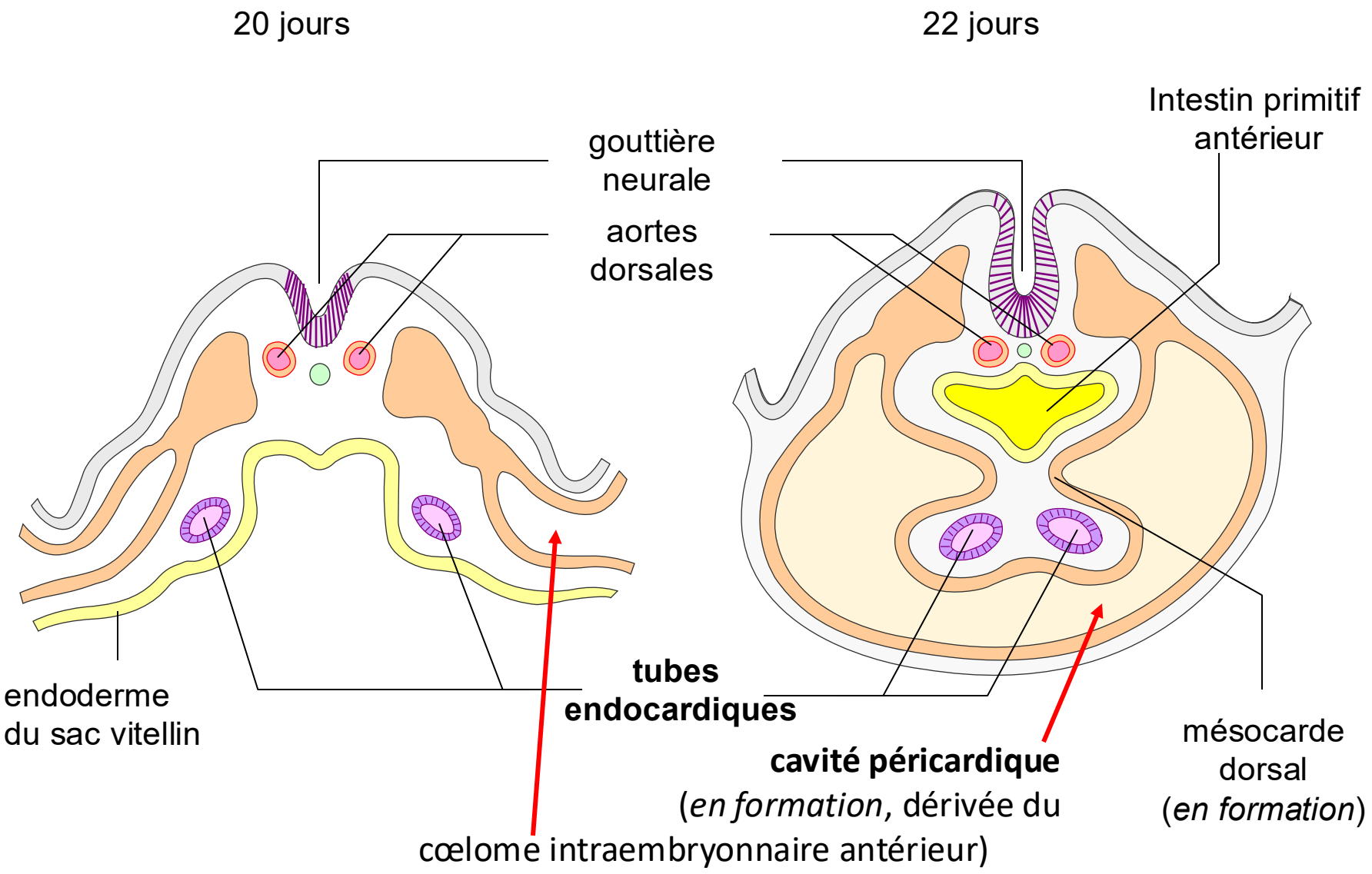


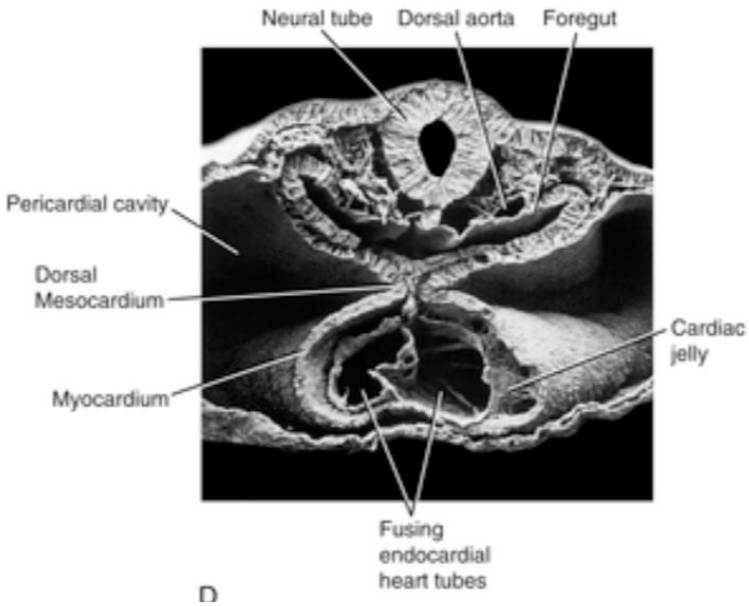


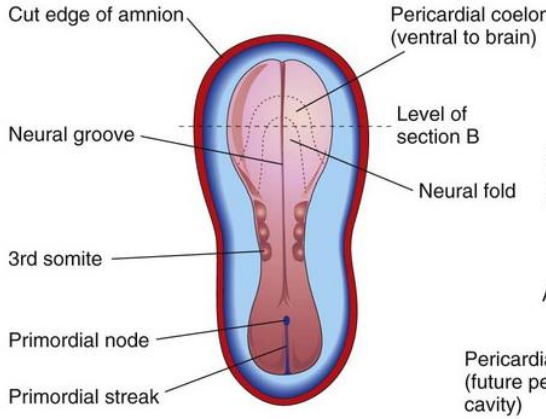
au niveau de l'intestin moyen

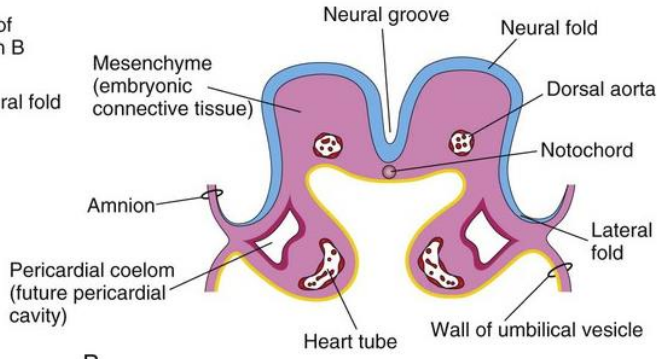
au niveau de l'intestin postérieur

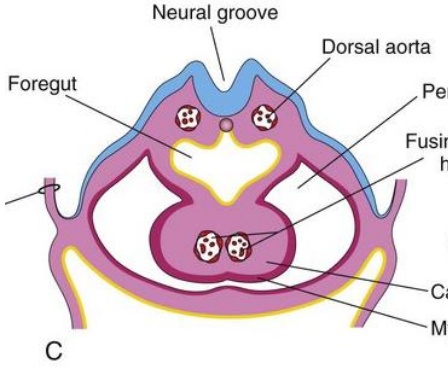
COURBURE TRANSVERSALE
(partie antérieure du corps)

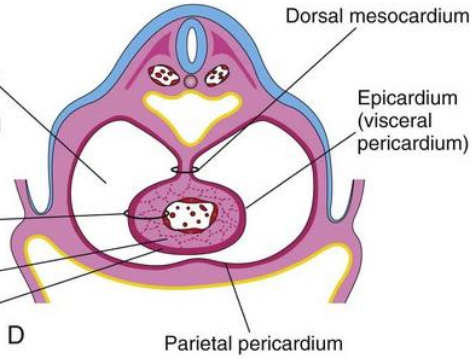


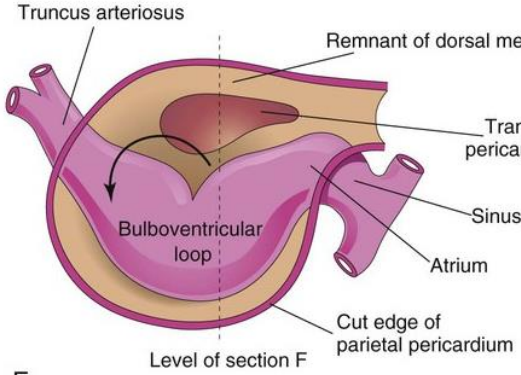

Neural tube
Dorsal aorta
Foregut
Pericardial cavity
Dorsal Mesocardium
Myocardium
Cardiac jelly
Fusing endocardial heart tubes
D

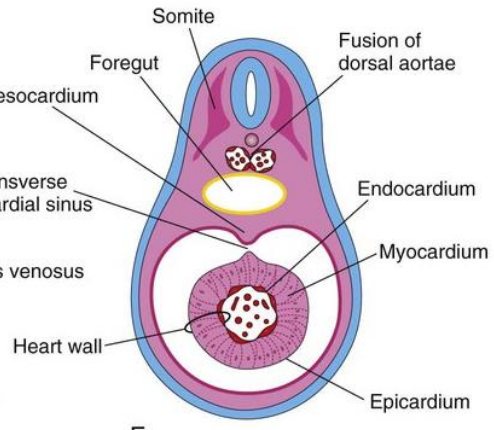

Cut edge of amnion
Pericardial coelom (ventral to brain)
Level of section B
Neural groove
Neural fold
3rd somite
Primordial node
Primordial streak


Neural groove
Neural fold
Mesenchyme (embryonic connective tissue)
Dorsal aorta
Notochord
Amnion
Lateral fold
Pericardial coelom (future pericardial cavity)
Heart tube
Wall of umbilical vesicle
B


Neural groove
Dorsal aorta
Foregut
Pericardial cavity
Fusing endocardial heart tubes
Cardiac jelly
Myocardium
C

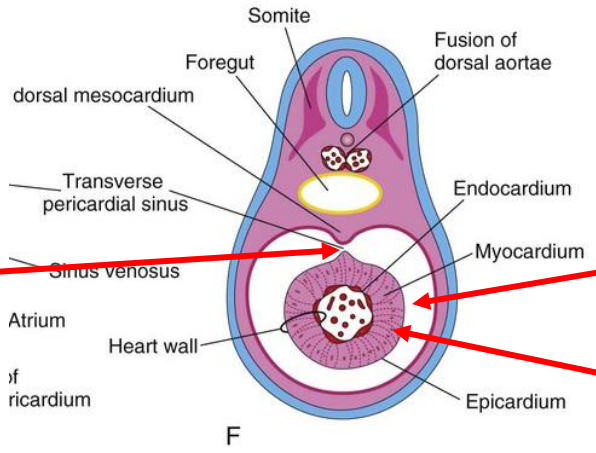

Dorsal mesocardium
Epicardium (visceral pericardium)
Wall of heart tube
Parietal pericardium
D


Truncus arteriosus
Remnant of dorsal mesocardium
Transverse pericardial sinus
Bulboventricular loop
Sinus venosus
Atrium
Cut edge of parietal pericardium
Level of section F
E


Somite
Fusion of dorsal aortae
Foregut
Endocardium
Myocardium
Heart wall
Epicardium
F

mésocarde dorsal

(dérivé du mésoderme latéral splanchnique)



cavité péricardique

(dérivée du cœlome intraembryonnaire antérieur)

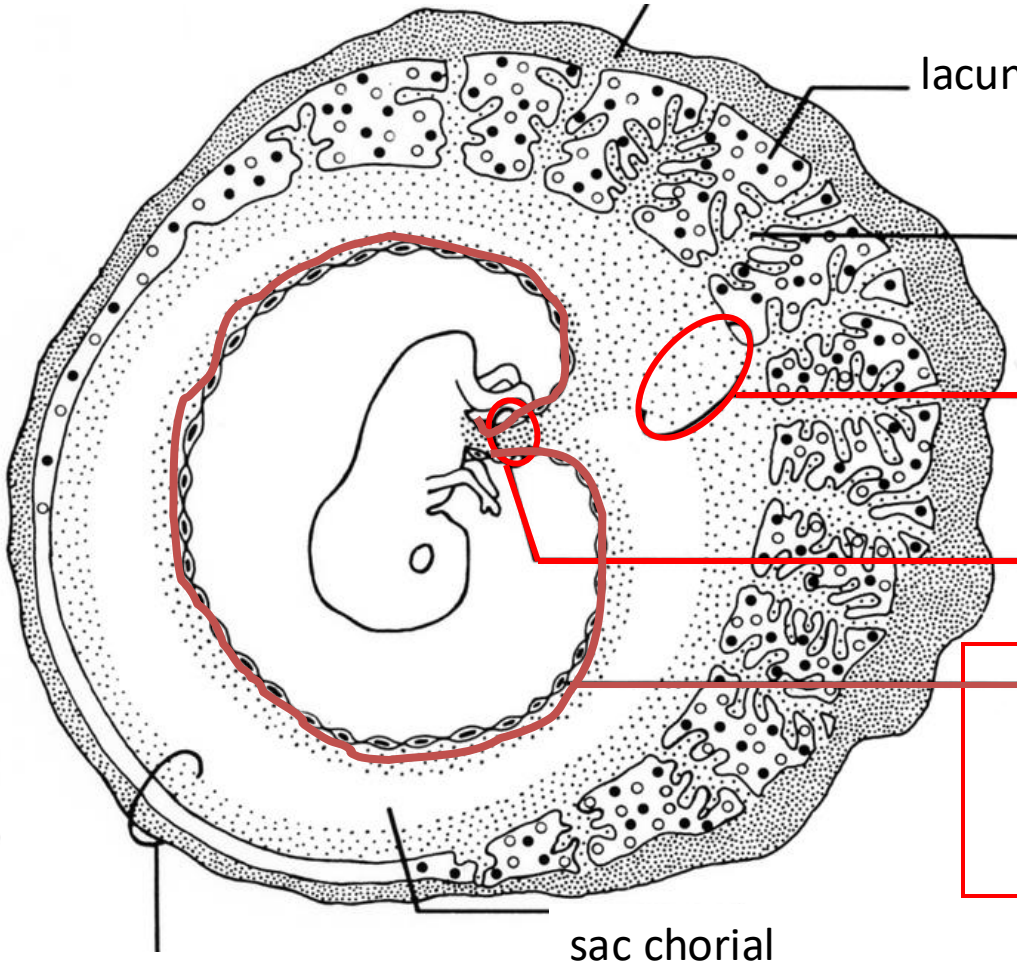
tube cardiaque (simple)

devient ventral par rapport au tube digestif

folding of the embryo movie

QUATRIEME SEMAINE

2. Le cordon ombilical est défini



décidue

lacune

villosité choriale

chorion <u>villeux</u> *(du côté du placenta)*

cordon ombilical:

amnios

pédicule abdominal
vaisseaux ombilicaux
canal vitellin
extrémité de l'allantoïde / allantoïs

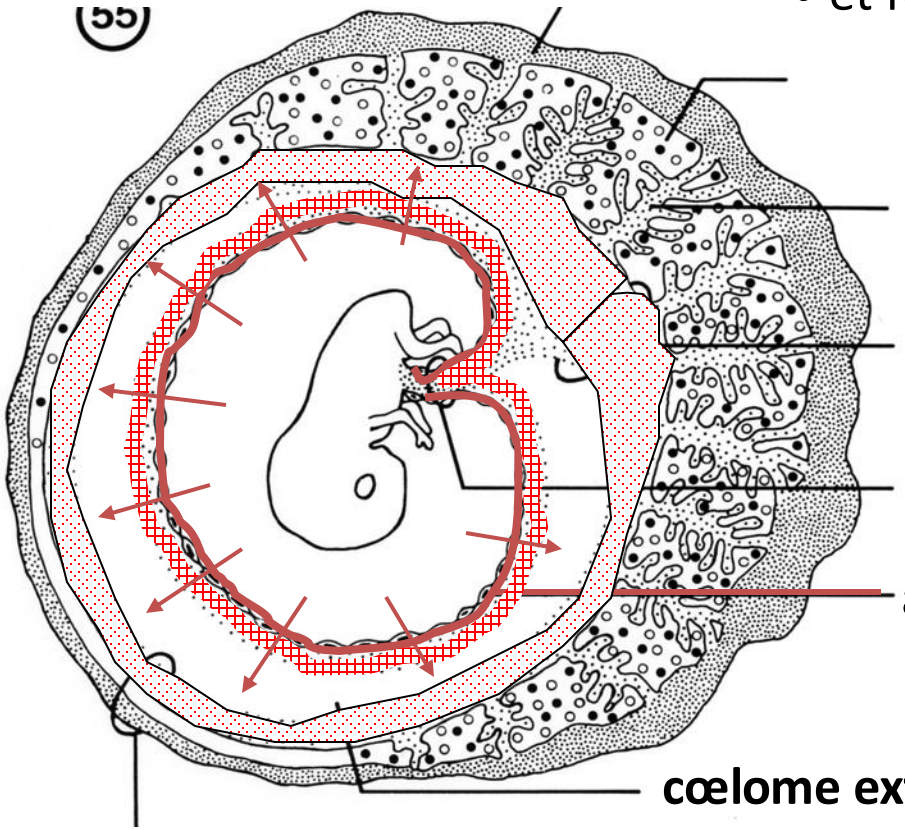
chorion <u>lisse</u>
(côté opposé)

sac chorial
(= cœlome extraembryonnaire)

QUATRIEME SEMAINE

3. Le cœlome extraembryonnaire (= cavité choriale)
est progressivement oblitéré

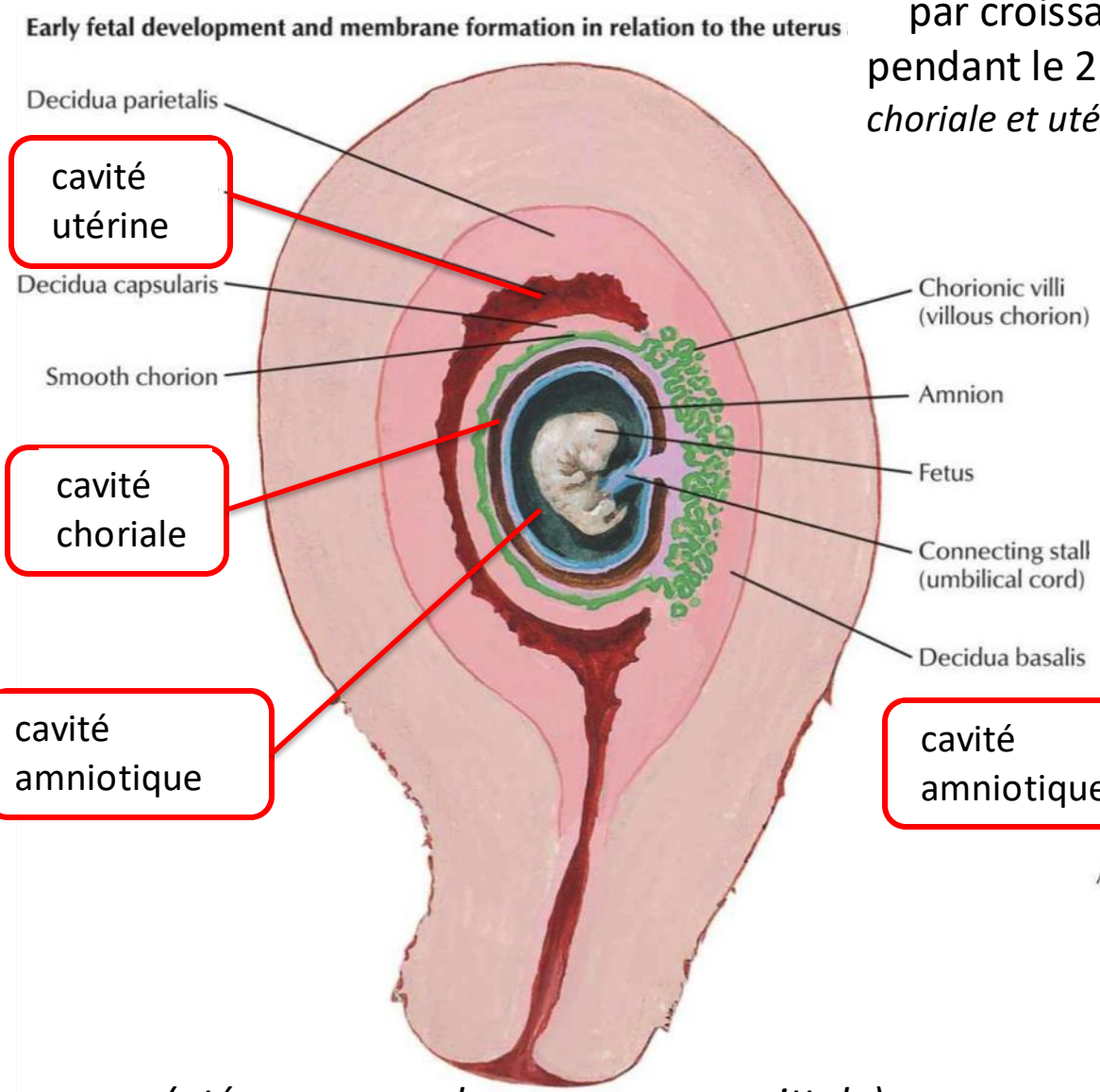
- par croissance de la cavité amniotique
- et fusion du mésoderme extraembryonnaire
  - somatique de l'amnios
  - somatique du chorion



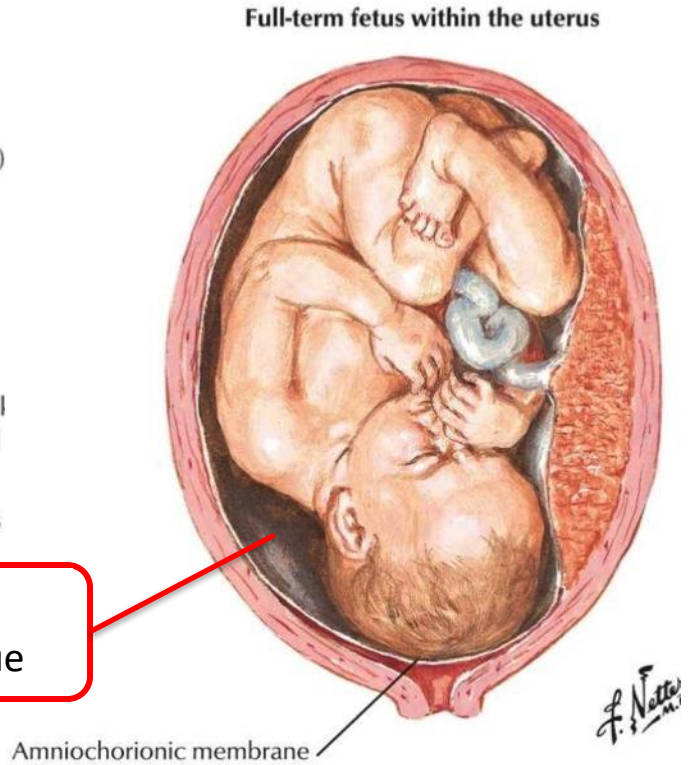
utérus et membranes fœtales

la cavité utérine est aussi progressivement oblitérée

par croissance de la cavité amniotique pendant le 2è mois *(l'effacement des cavités choriale et utérine est complet à la fin du 3è mois)*



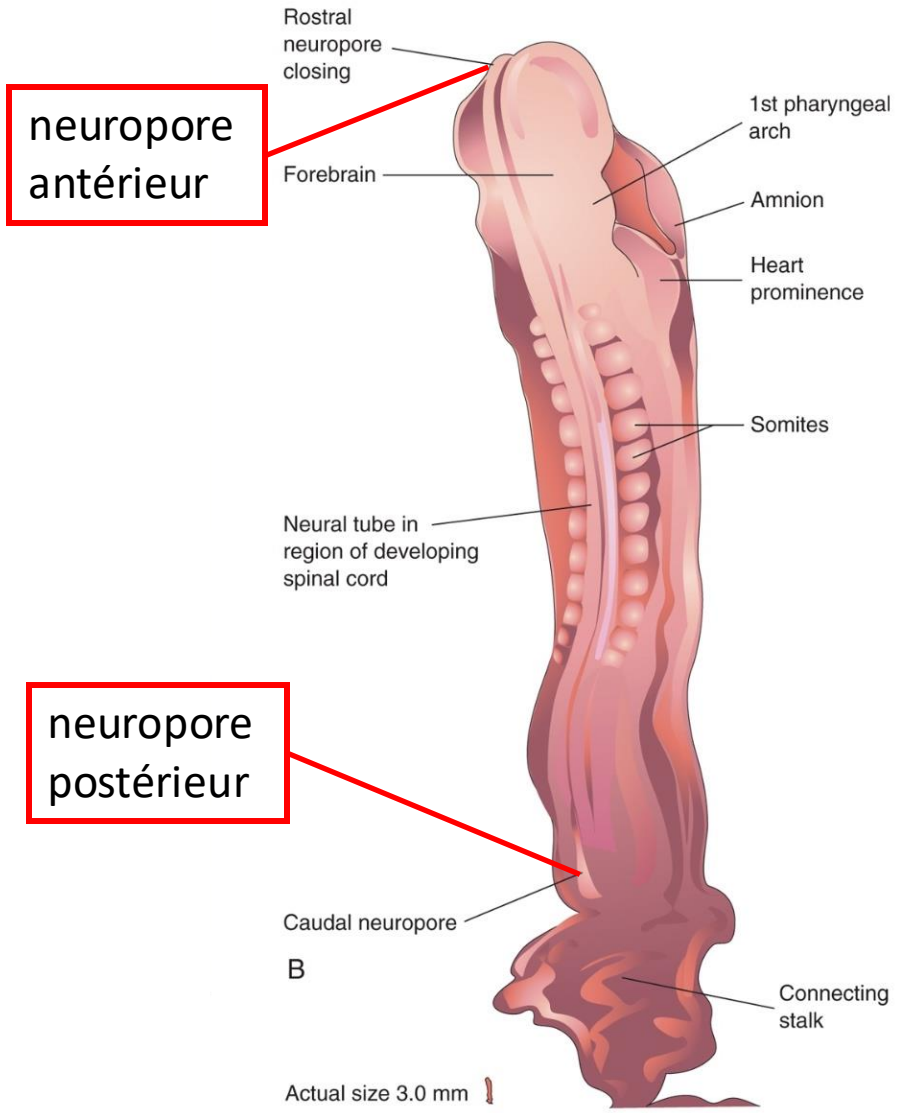
(utérus avec embryon ; coupe sagittale)

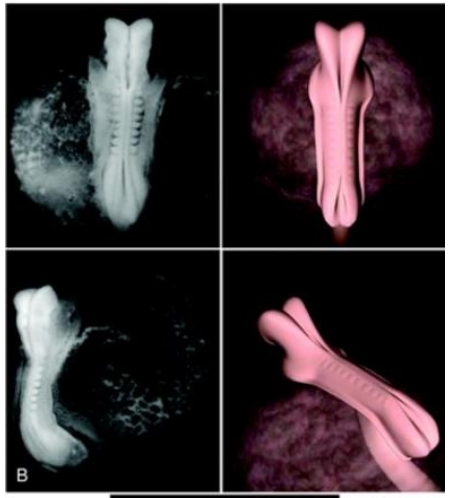


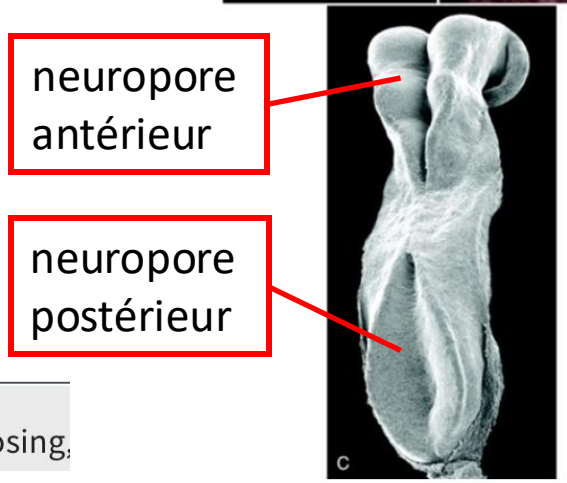
QUATRIEME SEMAINE

4. Fermeture du tube neural

- le neuropore antérieur (rostral) se ferme vers le 24ème-26ème jour.
- le neuropore postérieur (caudal) se ferme vers le 26ème-28ème jour.





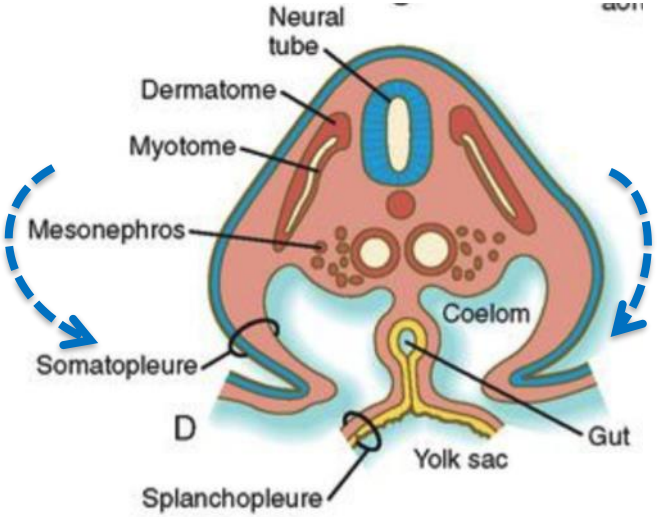


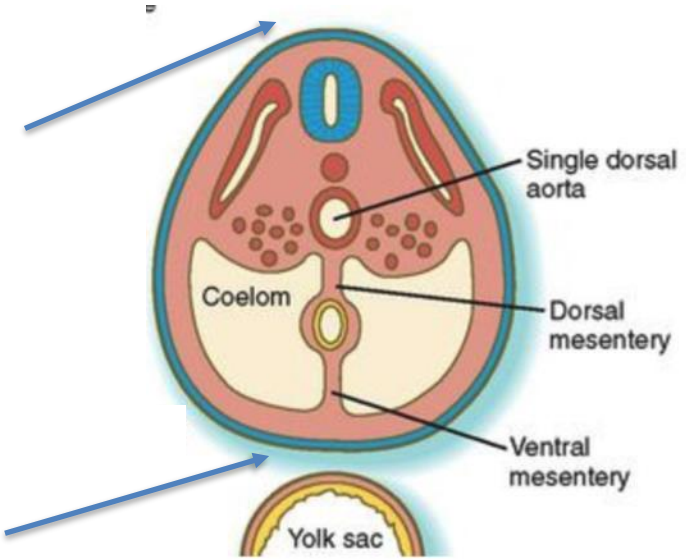
Carnegie stage 11, approximately 24 days. The rostral neuropore is closing,

QUATRIEME SEMAINE

5. Fermeture de l'épithélium de revêtement

- Face dorsale : à la fermeture du tube neural
- Face ventrale : en conséquence des courbures longitudinales et transversales

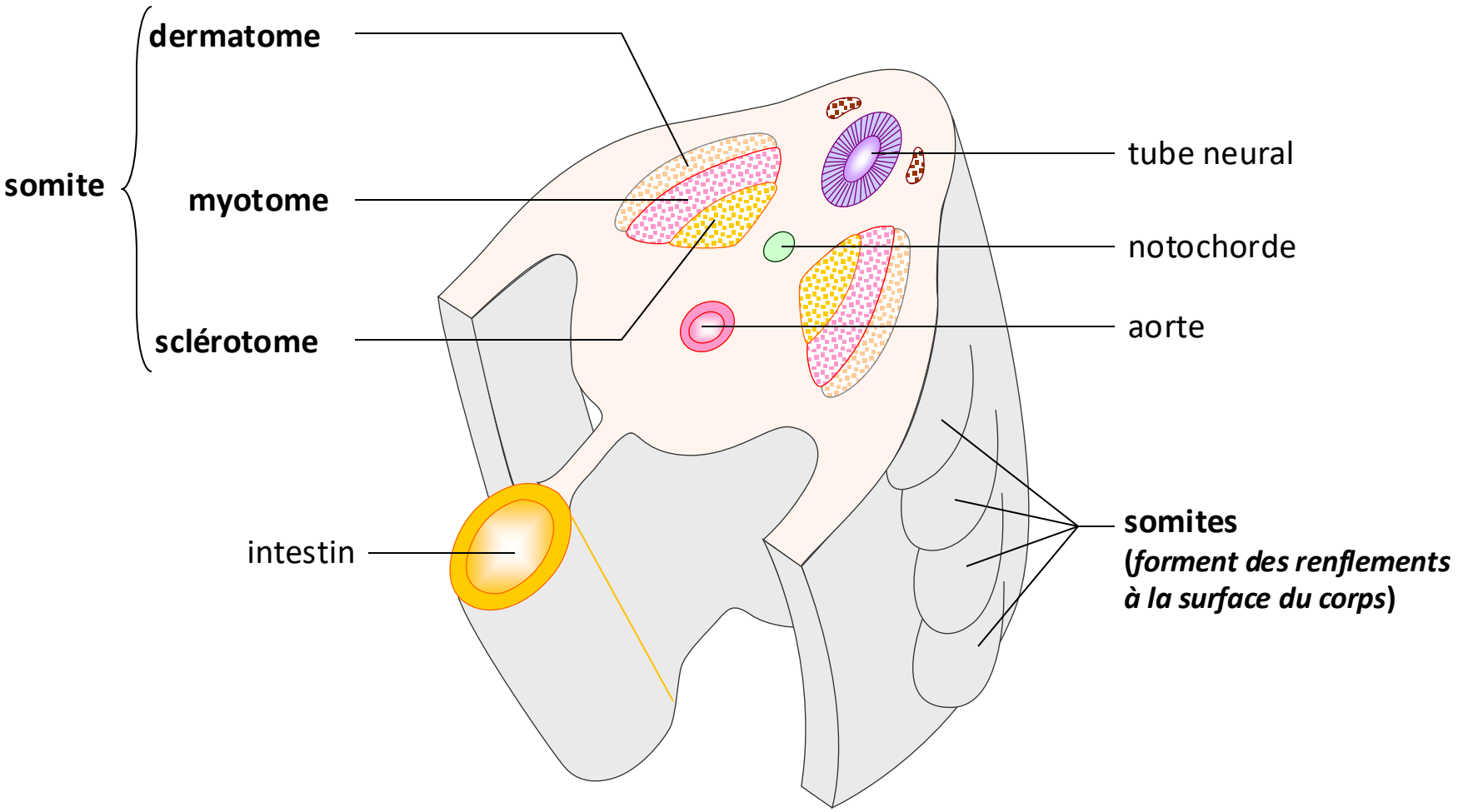




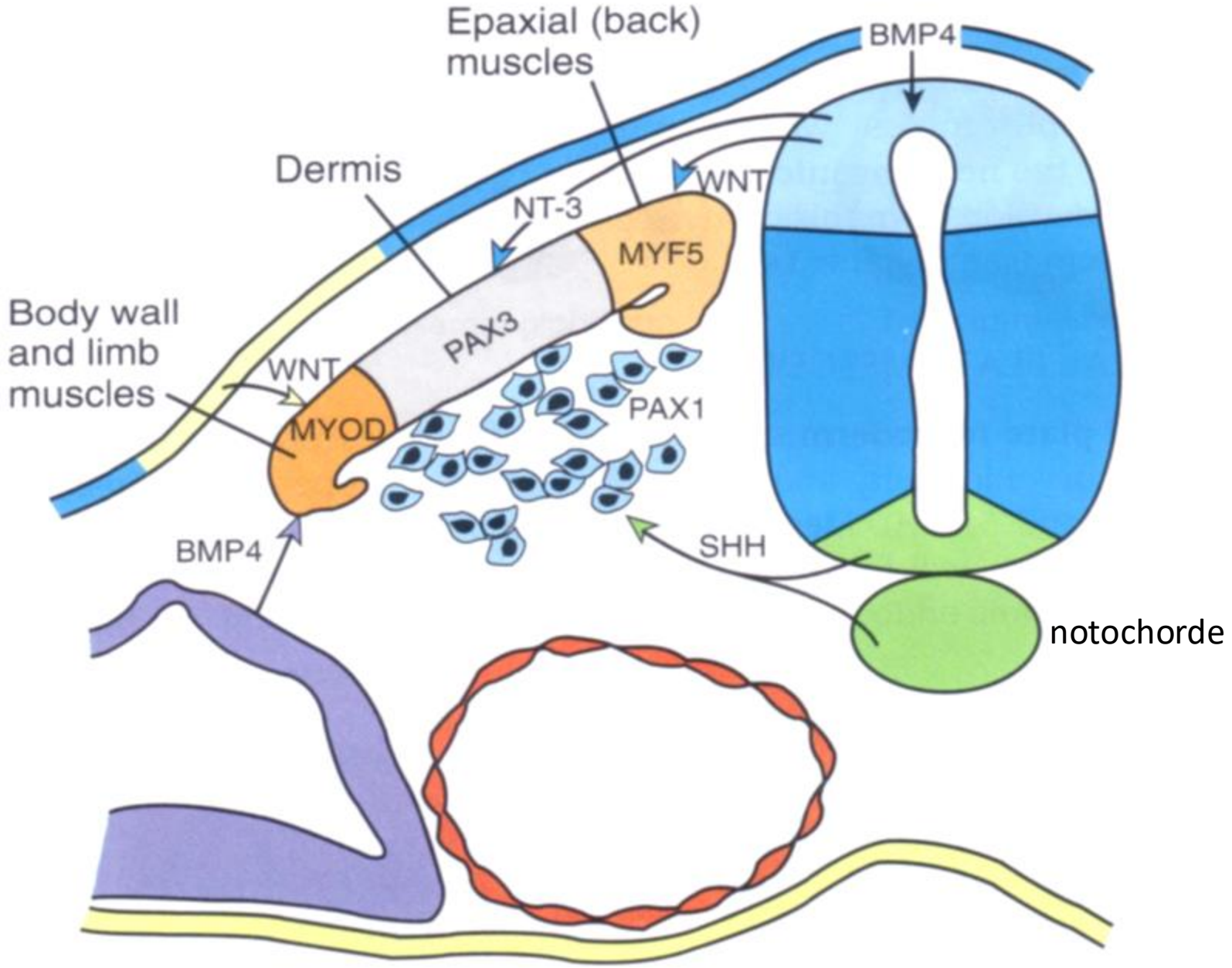
6. Différenciation des somites

- *Sclérotome* (en position médiane) formera le squelette axial (vertèbres + côtes)
- *Dermomyotome* (latéral) formera la musculature axiale et le derme

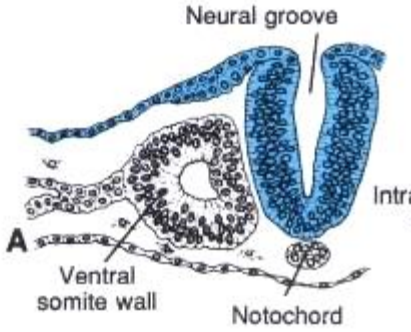
différenciation des somites

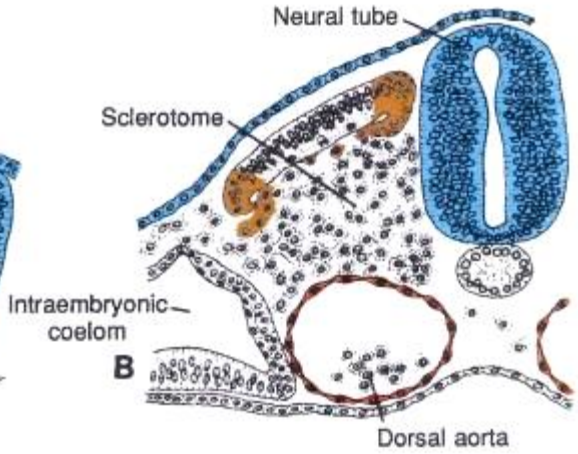


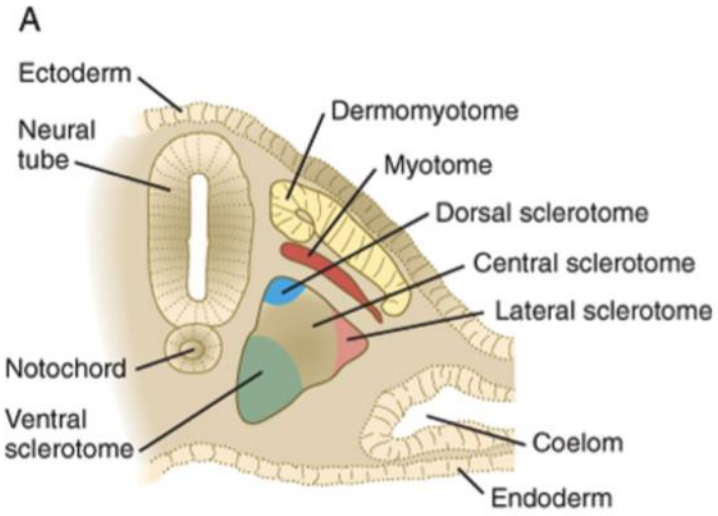
différenciation des somites



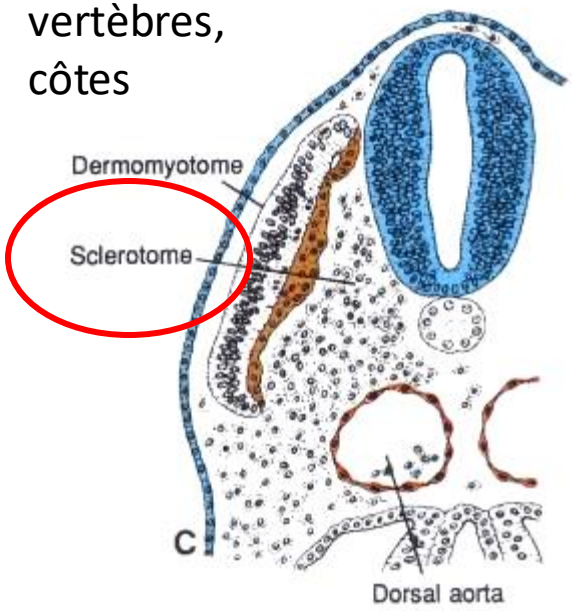
différenciation des somites : les vertèbres

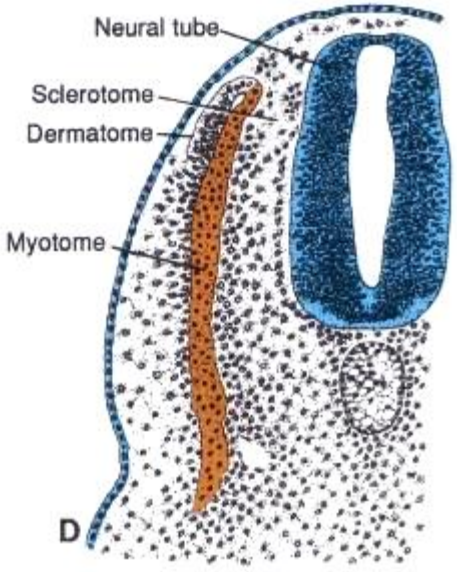


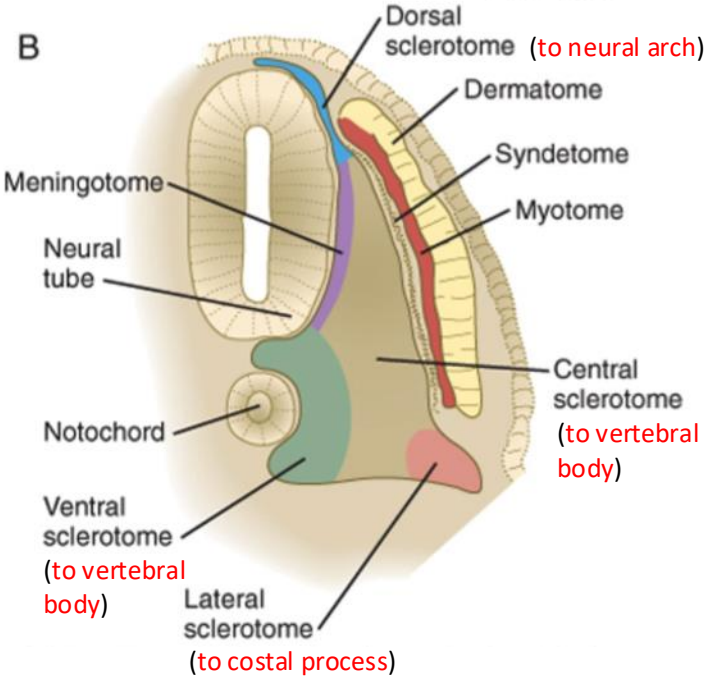




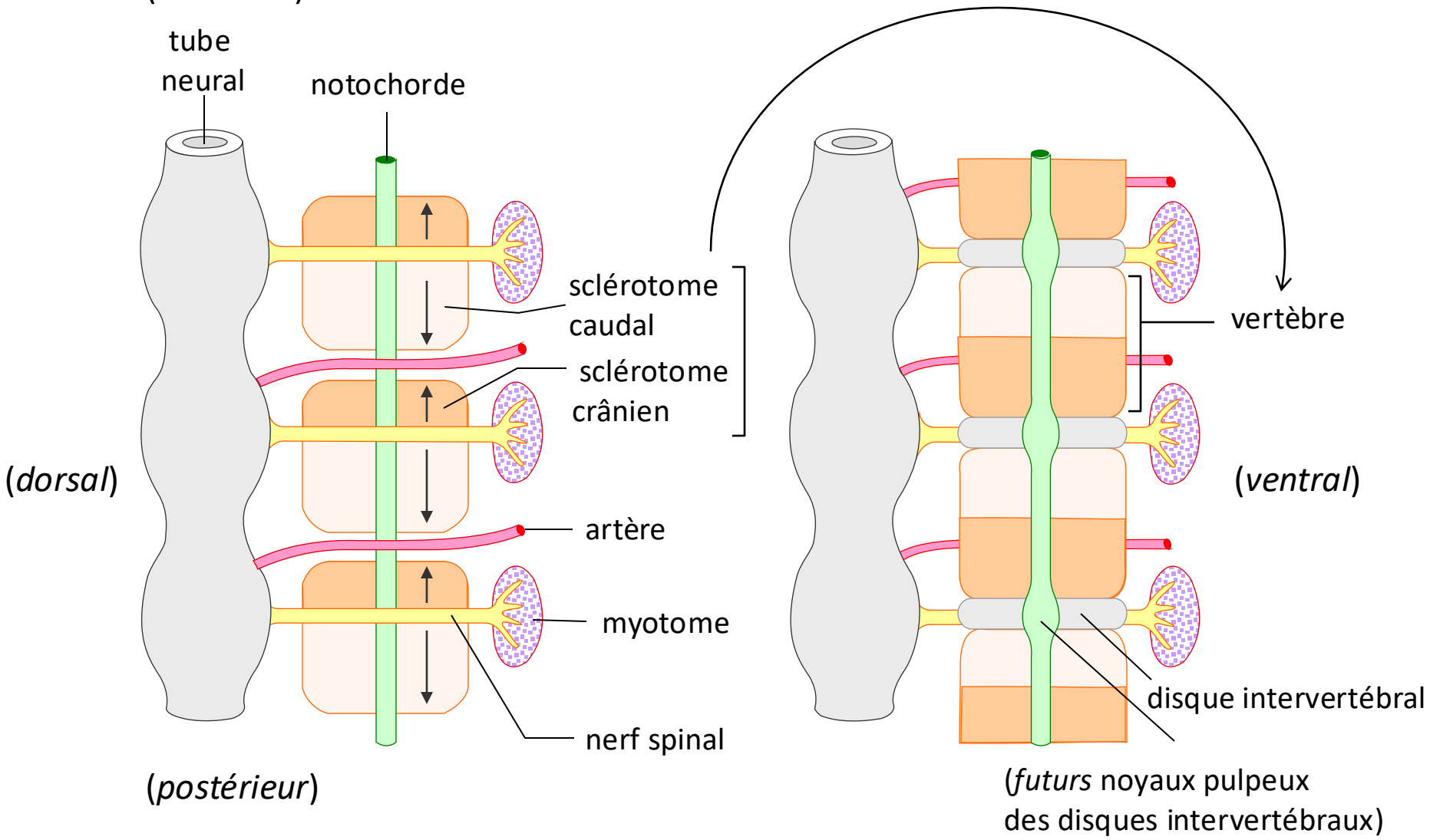
vertèbres, côtes







chaque vertèbre se forme avec la contribution de deux sclérotomes successifs

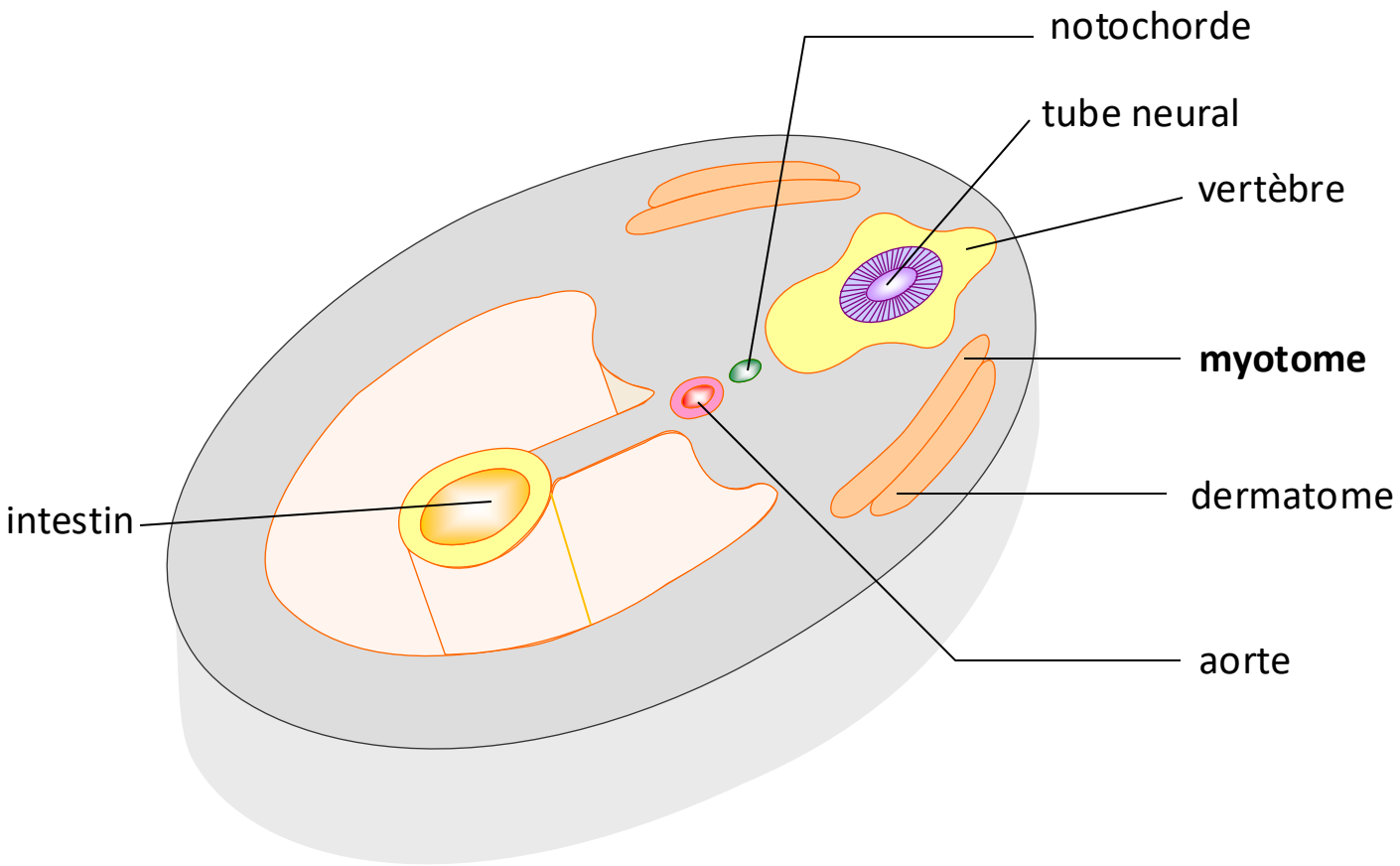


(vues latérales)

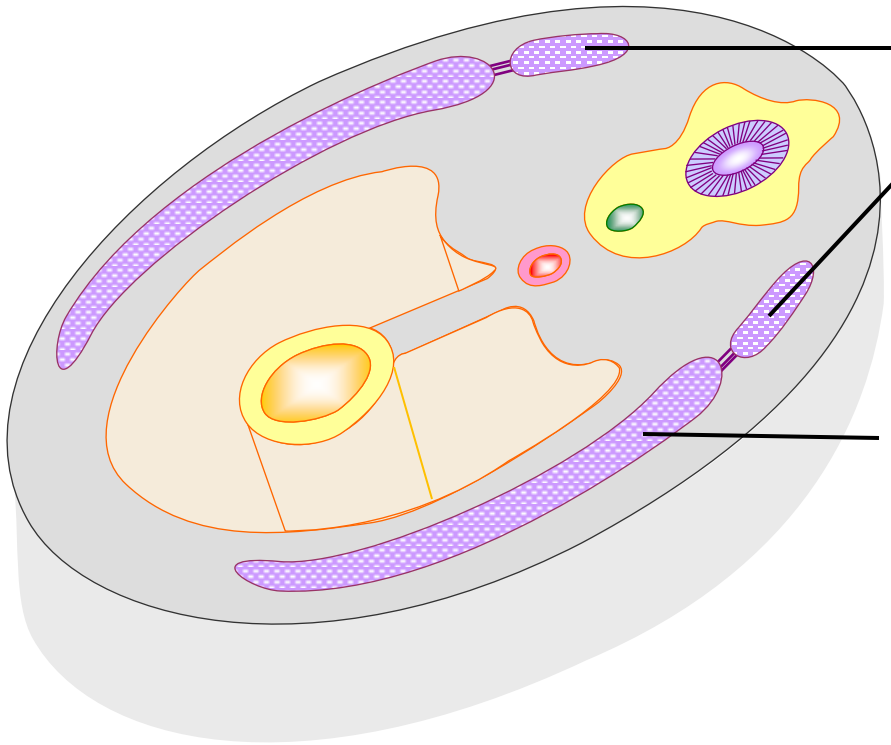
QUATRIEME SEMAINE

différenciation des somites : les muscles

les myotomes forment la musculature du tronc et des membres
les dermatomes forment le derme du tronc et des membres



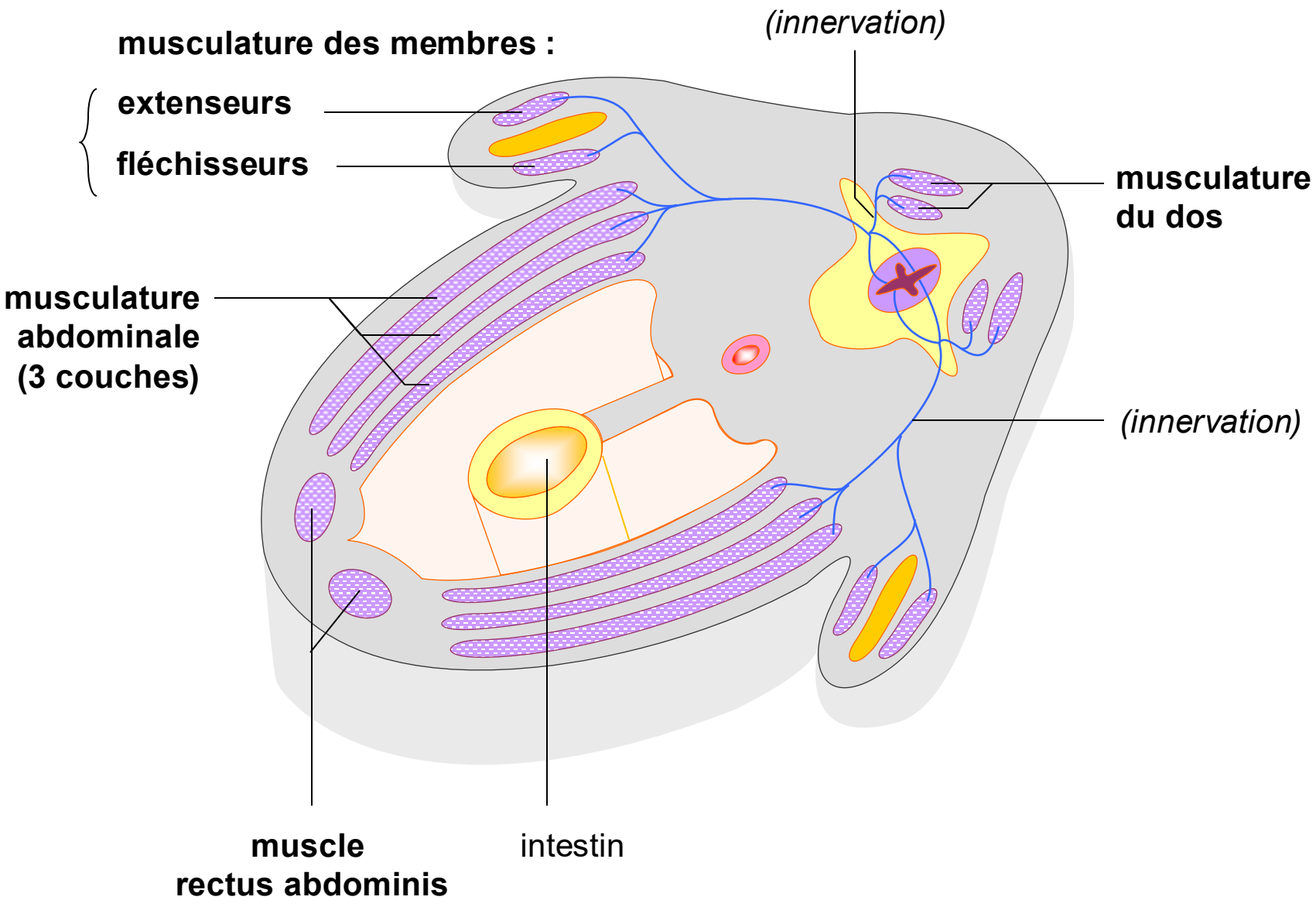
les myotomes forment la musculature du tronc et des membres (5 semaines)



épimère
(*primordium dorsal*
des muscles striés squelettiques :
musculature du dos)

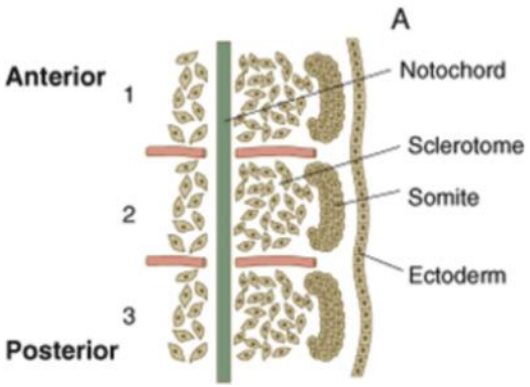
hypomère
(*primordium ventral*
des muscles striés squelettiques :
musculature abdominale et des membres)

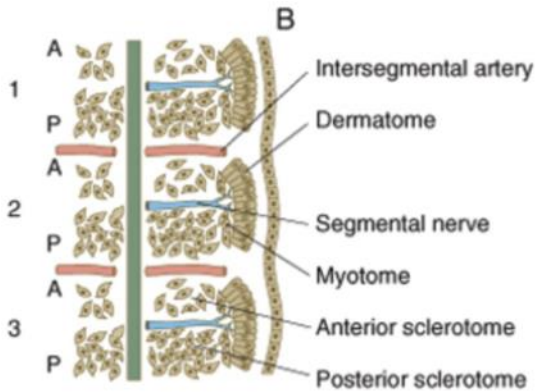
les myotomes forment la musculature du tronc et des membres (7 semaines)

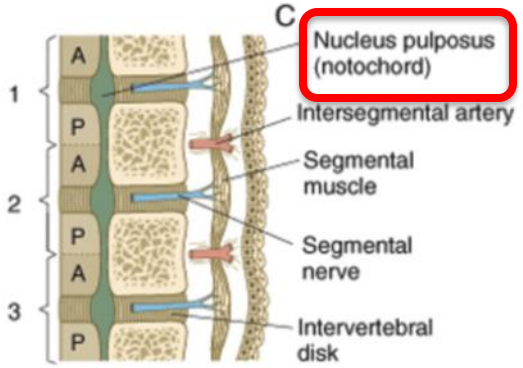


Devenir de la notochorde

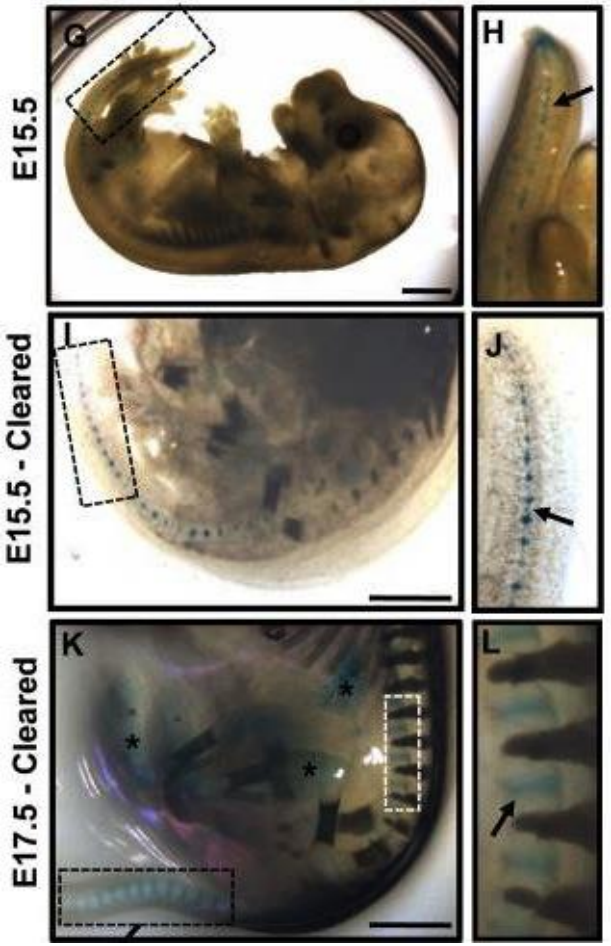
Traçage des lignages cellulaires chez des souris transgéniques “*Noto-Cre*”: “système Cre / loxP” (cf. 1er cours).

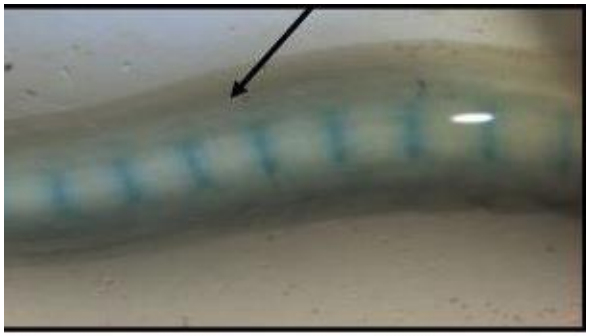






La notochorde,
tissu inducteur le plus important de l’embryon,
forme les **noyaux pulpeux** des disques intervertébraux.

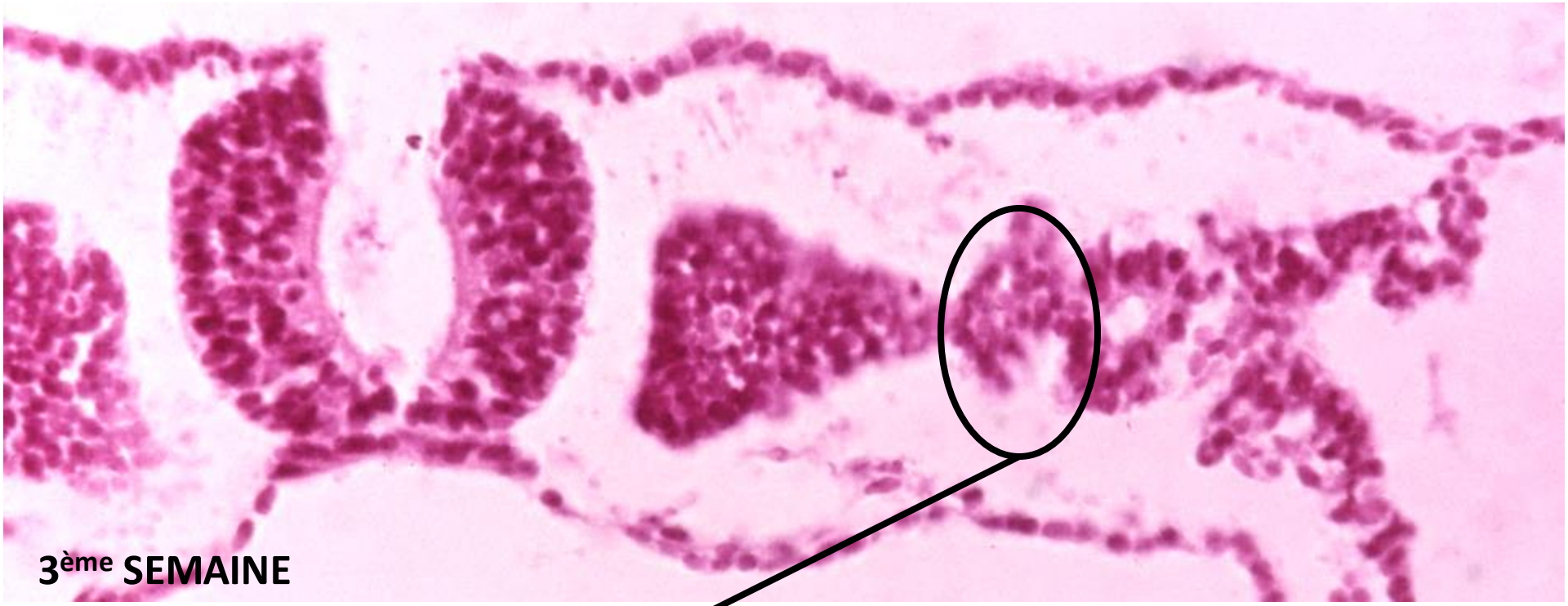




QUATRIEME SEMAINE

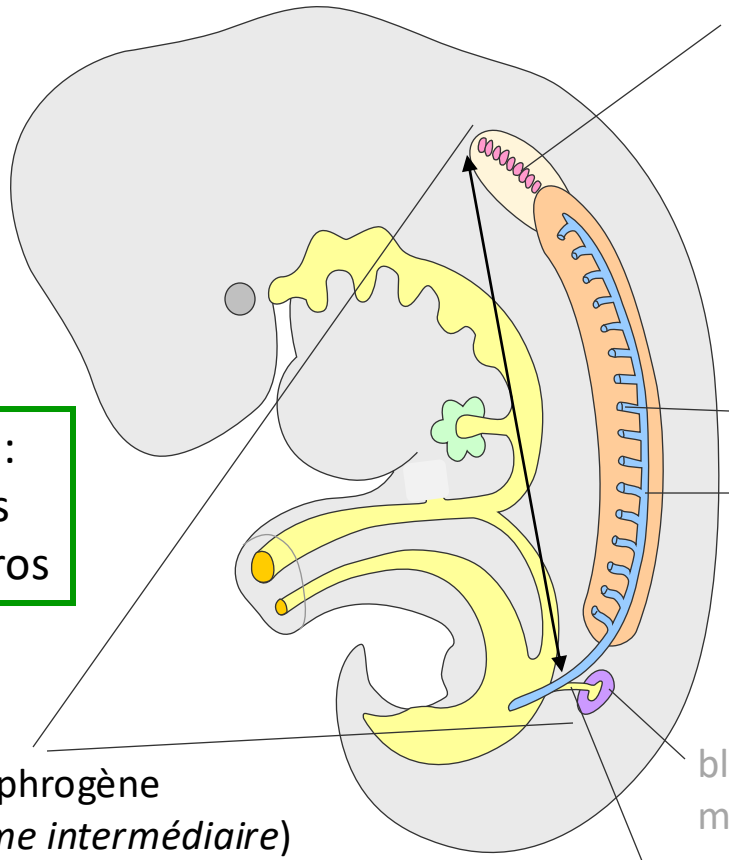
7. Différenciation du mésoderme intermédiaire

- Formera les appareils excréteurs (pronéphros, mésonéphros et finalement métanéphros)
- Formera également la partie somatique des gonades



QUATRIEME SEMAINE

7. Mésoderme intermédiaire: début de la différenciation du mésonéphros



néphrons
non fonctionnels
et canal pronéphrique

Pronéphros

4è semaine :
-pronéphros
-mésonéphros

néphrons fonctionnels

canal mésonéphrique

Mésonéphros

cordon néphrogène
(*mésoderme intermédiaire*)

blastème
métanéphrogène

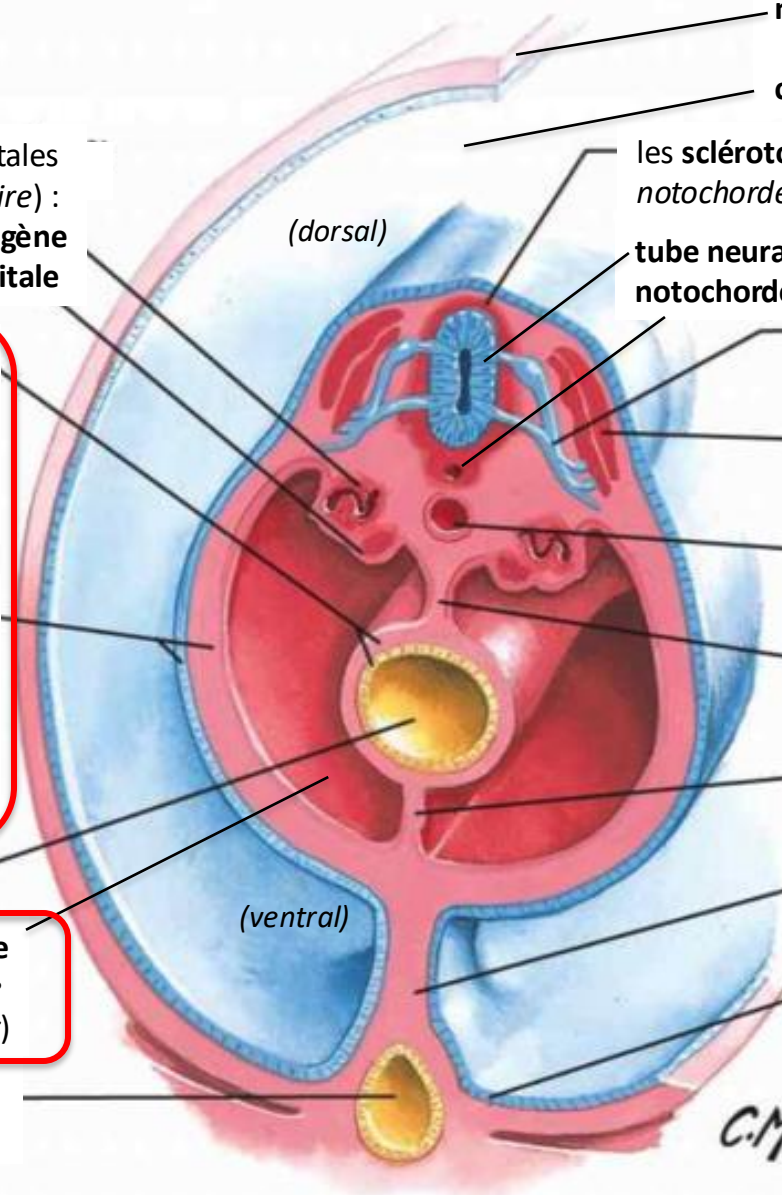
bourgeon urétéral

Métanéphros

les trois types successifs de reins

mésonéphros: rein fonctionnel <u>jusqu'à la fin du 3è mois</u>

plan corporel à la fin de la 4è semaine *(partie postérieure du corps)*



mésoderme extraembryonnaire

cavité amniotique

les **sclérotomes** *des **somites** entourent le tube neural et la notochorde, pour former les corps des vertèbres*

tube neural
notochorde

nerf spinal (rachidien)

les **dermomyotomes** *des **somites** forment la musculature et le derme de la peau*

aorte dorsale

crêtes urogénitales (*mésoderme intermédiaire*) :
- **cordon néphrogène**
- **crête génitale**

splanchnopleure (*endoderme + mésoderme latéral splanchnique*) : *paroi du tube digestif*

somatopleure (*ectoderme + mésoderme latéral somatique*) : *paroi corporelle, avec le derme des somites*

mésentère dorsal

mésentère ventral

dérivés du mésoderme latéral splanchnique

tube digestif

cavité péritonéale (*dérivée du cœlome intraembryonnaire postérieur*)

cordon ombilical (*coupe tangentielle, sans passer par les vaisseaux ni le canal vitellin*)

amnios

reste du **sac vitellin**

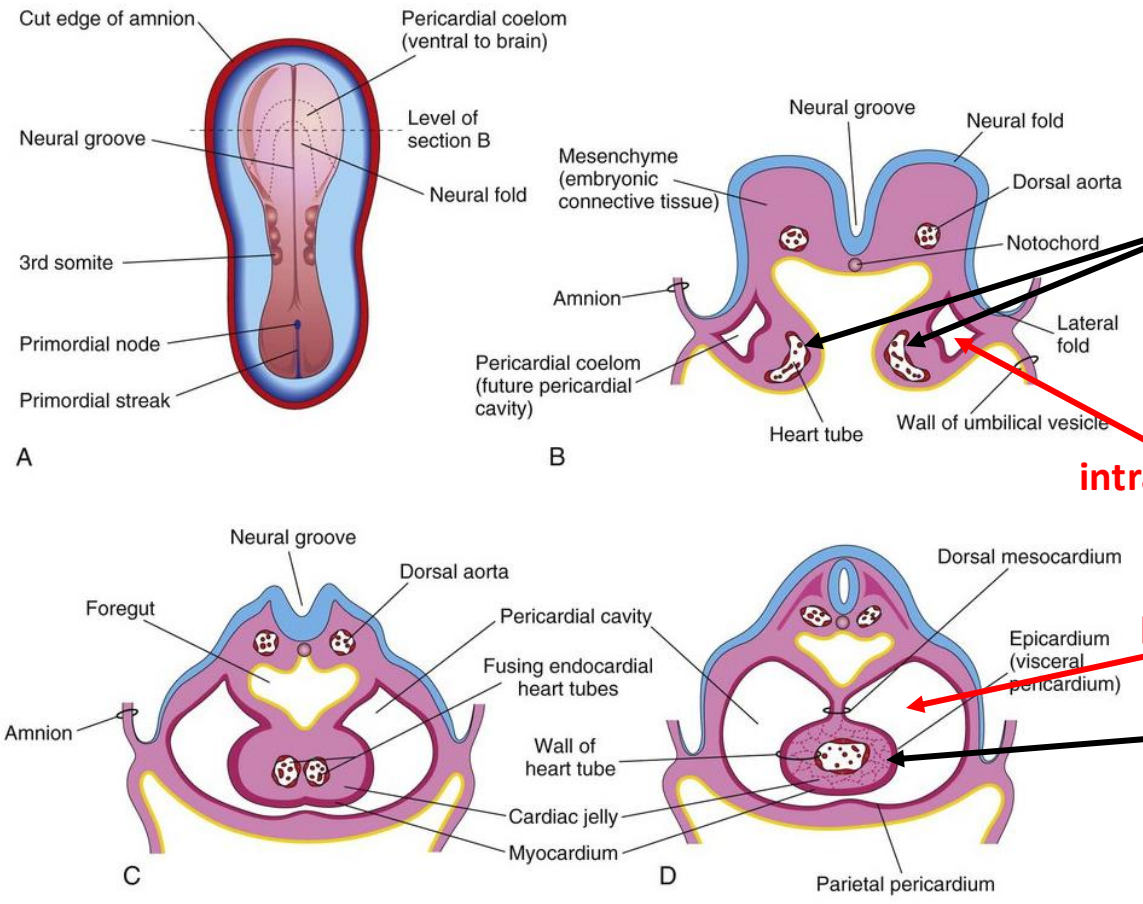
QUATRIEME SEMAINE

heart development movie

up to the folding

8. Système cardiovasculaire

- De double, devient simple, par fusion, au moment de la courbure transversale



Les tubes cardiaques

cœlome intraembryonnaire

devient

cavité péricardique

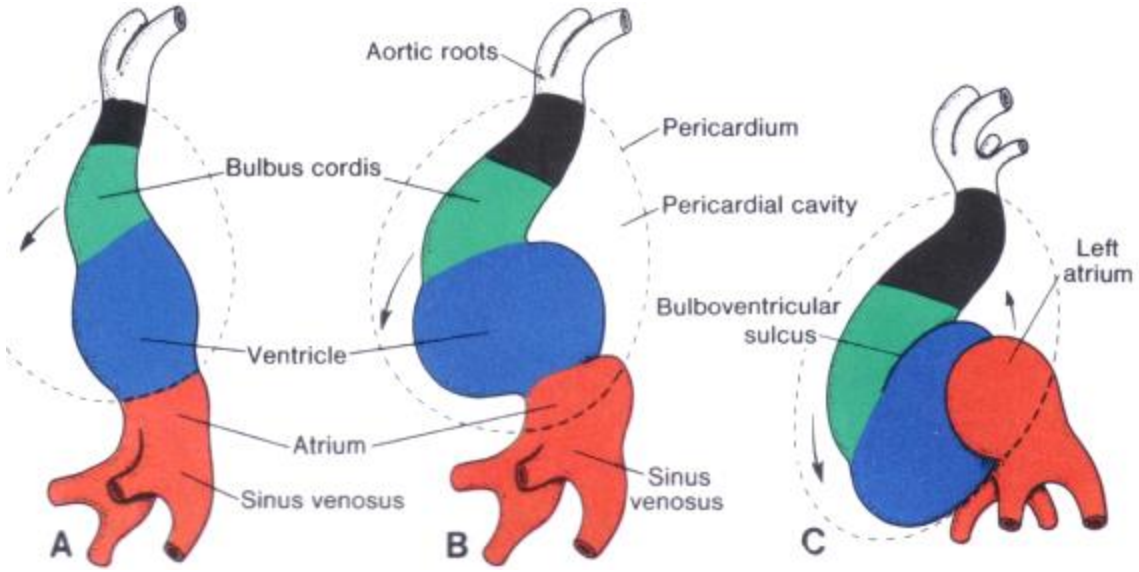
forment

le coeur primitif

- Les aortes dorsales fusionnent en une aorte médiane (partie postérieure)

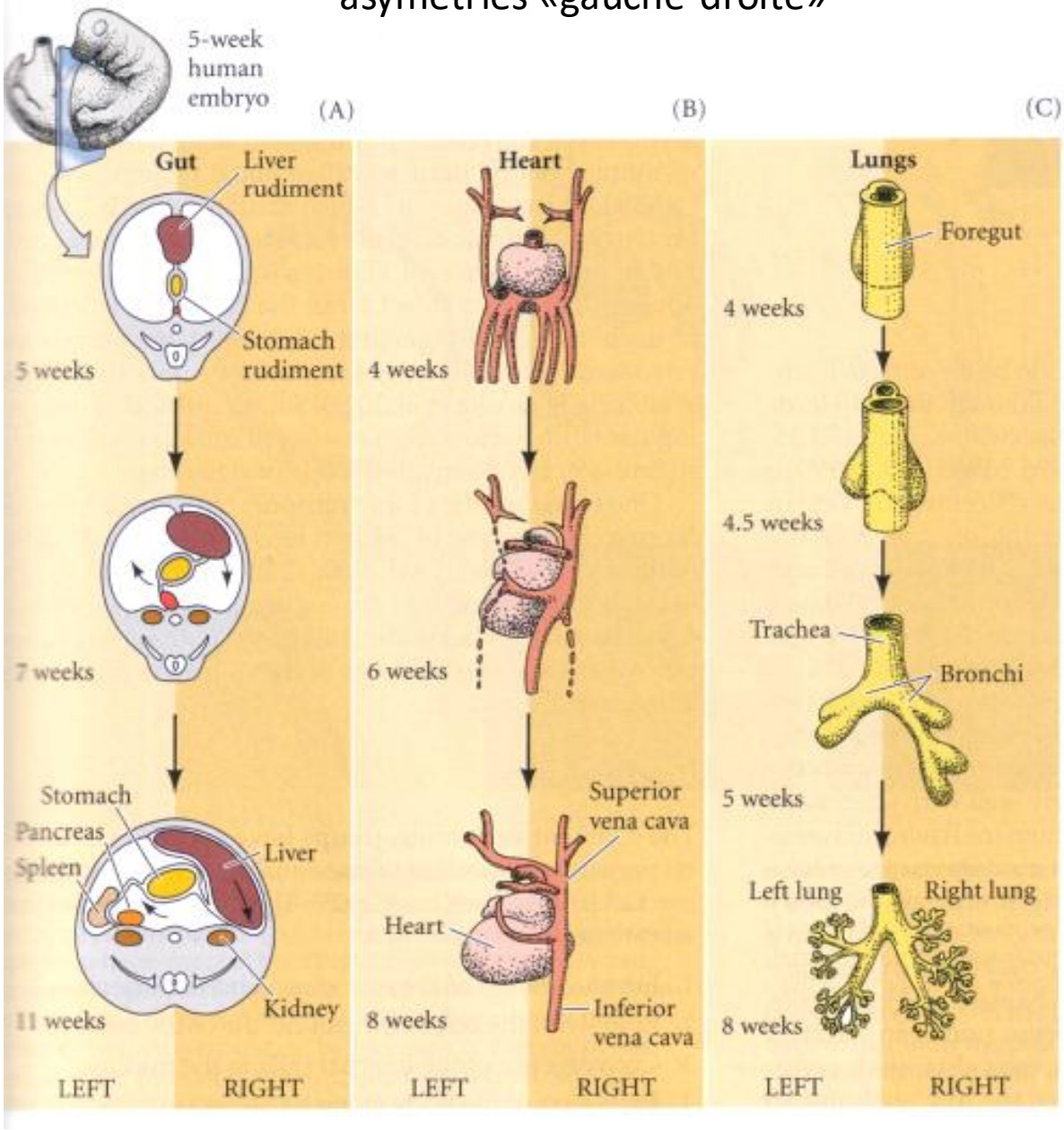
ASYMETRIE CARDIAQUE

- Première manifestation morphologique de l'asymétrie gauche / droite: la courbure cardiaque



- La courbure cardiaque débute au cours de la 4ème semaine
- Autres asymétries gauche-droite:
  - poumons
  - foie
  - rate
  - intestins

asymétries «gauche-droite»



ANOMALIES DE L'ASYMETRIE GAUCHE – DROITE :
SITUS INVERSUS
HETEROTAXIE (malformation congénitale)

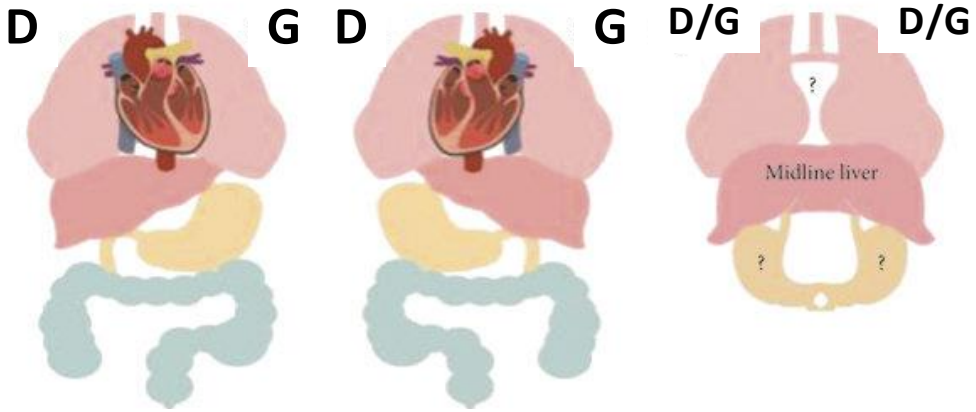
- Situs solitus, disposition asymétrique normale des organes à l'intérieur du corps

- Situs inversus, inversion complète (c.-à-d. placement des organes «en miroir») par rapport à l'axe de symétrie gauche – droite (1/10'000)

- Hétérotaxie, mauvais placement des organes par rapport à l'axe de symétrie bilatérale : *situs ambiguus (= situs inversus partiel), dextrocardie, isomérisme* (disposition symétrique, anormale)

situs inversus :

dextrocardie
rotation intestinale inversée
foie à gauche
estomac et rate à droite

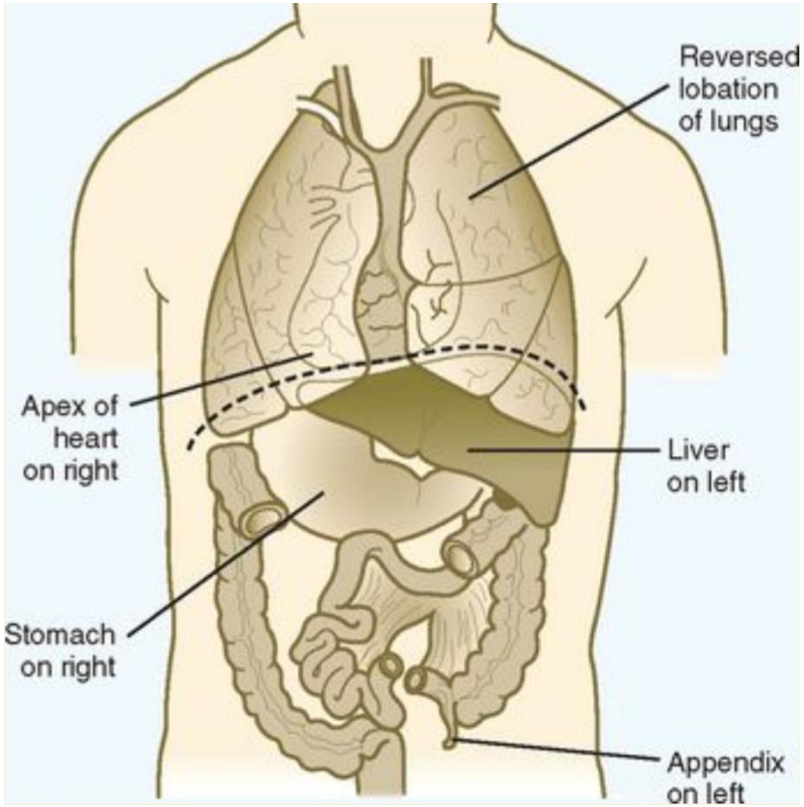


situs solitus (***disposition normale***)

situs inversus

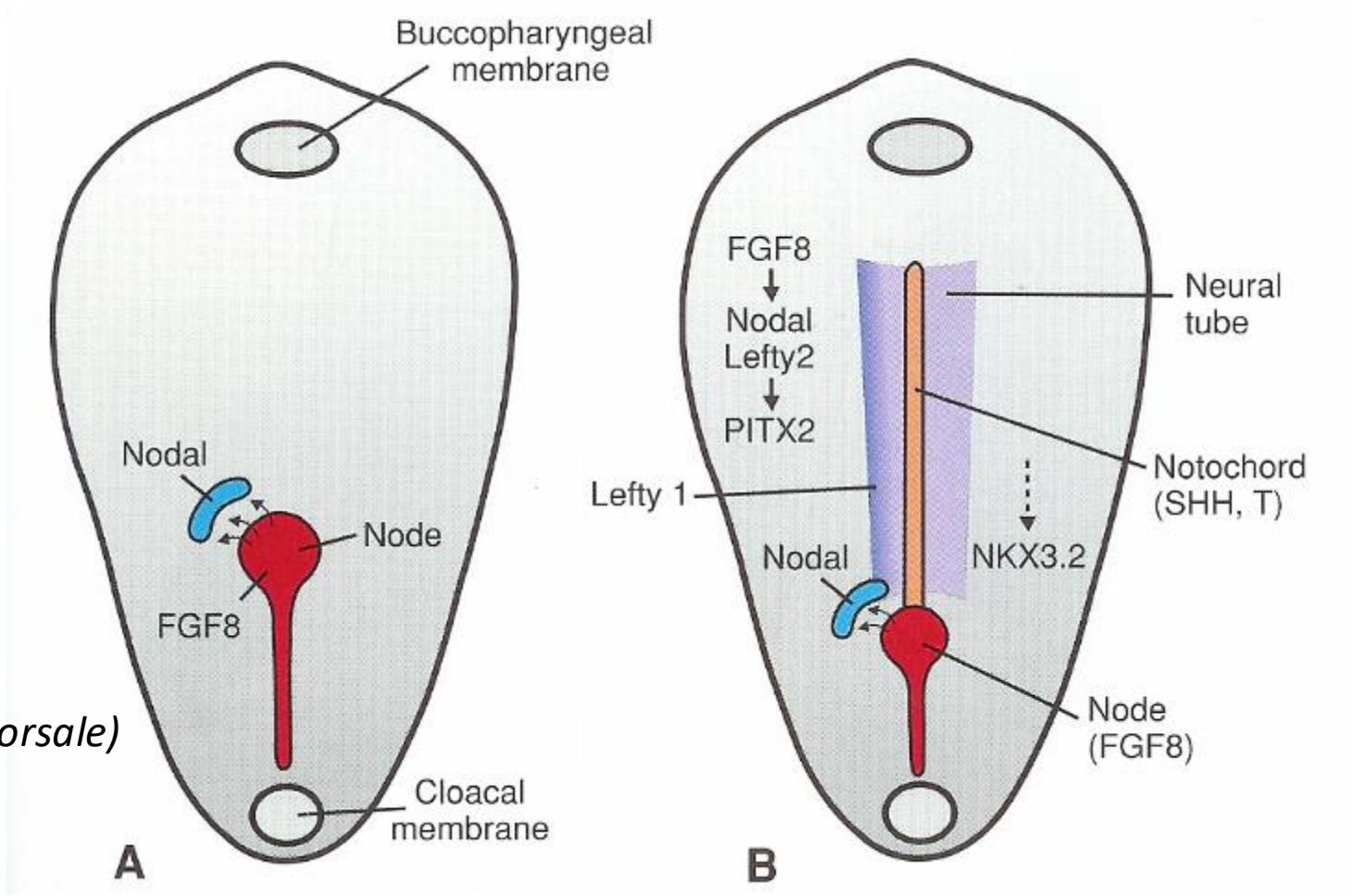
hétérotaxie (***isomérisme***)

situs inversus totalis



TROISIEME SEMAINE

MECANISME DE L'ASYMETRIE GAUCHE - DROITE



(vue dorsale)

…où comment sait une cellule si elle se trouve à gauche ou à droite du nœud et la ligne primitive!?

MECANISME DE L'ASYMETRIE GAUCHE - DROITE

Syndrome de Kartagener : mutations du gène de la dynéine

- syndrome du “cil immobile”
- fertilité diminuée (*spermatozoïdes*)
- sensibilité aux infections bronchiques
- hétérotaxie

- KIF3B
  - protéine de la superfamille de la kinésine (KIF)
  - protéine motrice (transport de molécules entre organelles via les microtubules)
  - impliquée dans la ciliogenèse
  - KIF3B exprimé dans neurones & autres tissus

Souris manquant KIF3B ("Kif3B KO")

- Asymétrie G-D au hasard
- Malformations cardiaques et de la colonne vertébrale
- Mortalité vers le milieu de la gestation

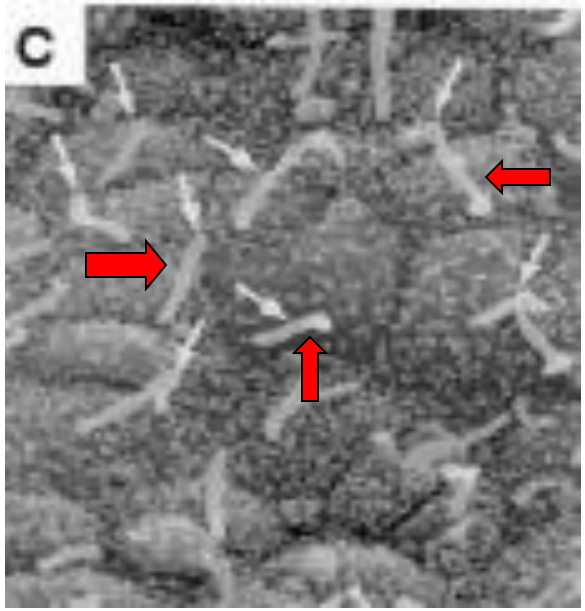
Hétérozygotes (KIf3B+/-) → développement normal

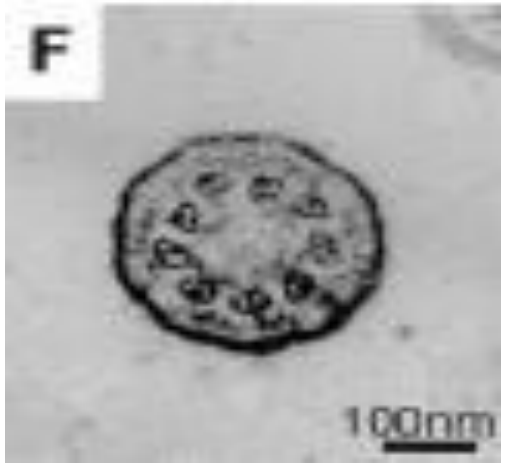
MECANISME DE L'ASYMETRIE GAUCHE - DROITE

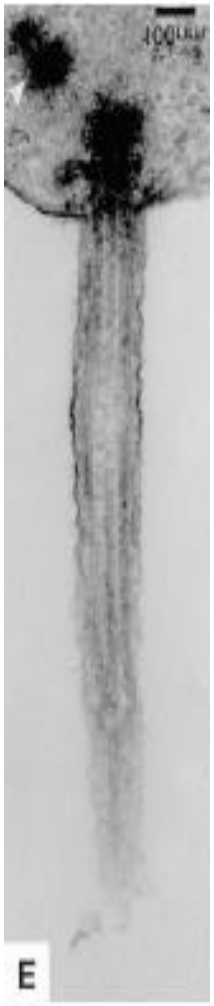
Les cellules du nœud primitif

ont un cil chacune:

- des kinocils (intérieur du nœud)
- des stéréocils (immobiles, cellules en périphérie)

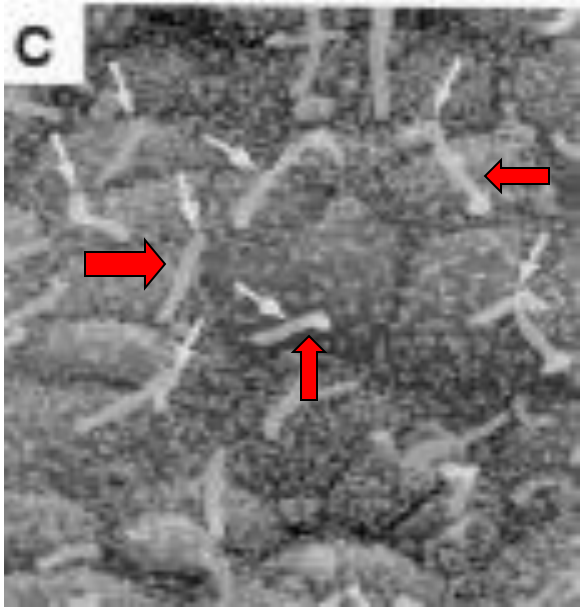


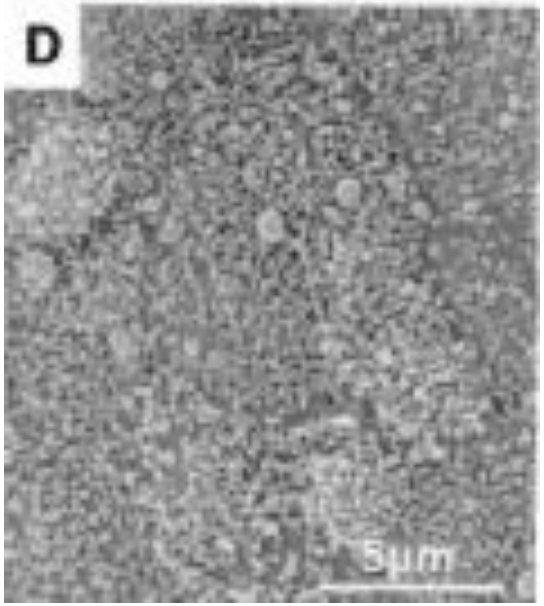




Résultat #1

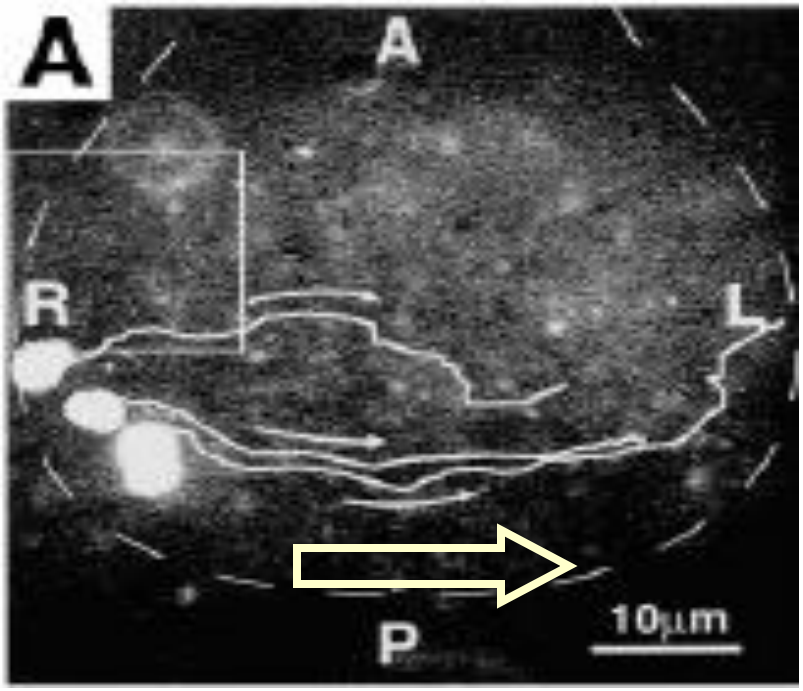
- Wild-type (KIF3B+/+) had normal “short single cilium on each nodal cell”
- Mutant (KIF3B-/-) had no cilia extending from basal body in nodal cells

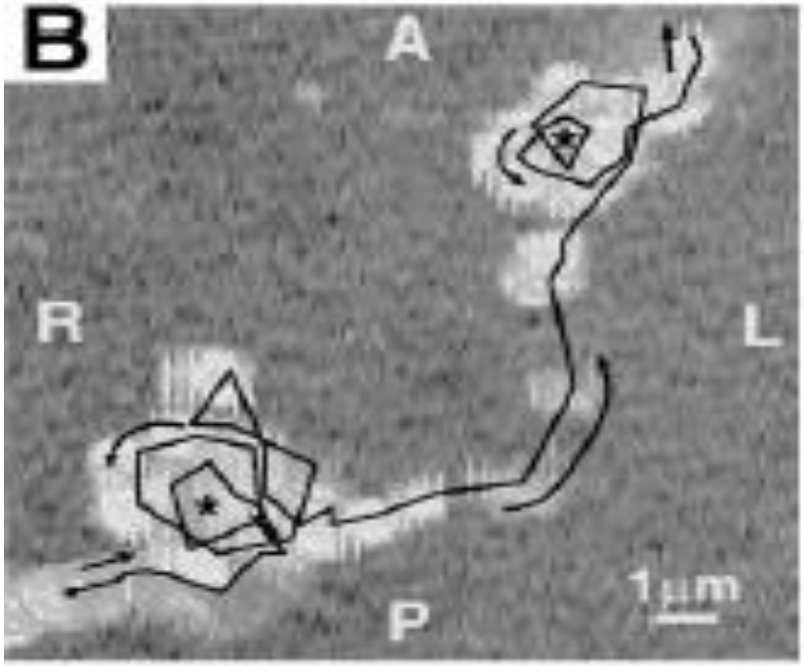




Résultat #2

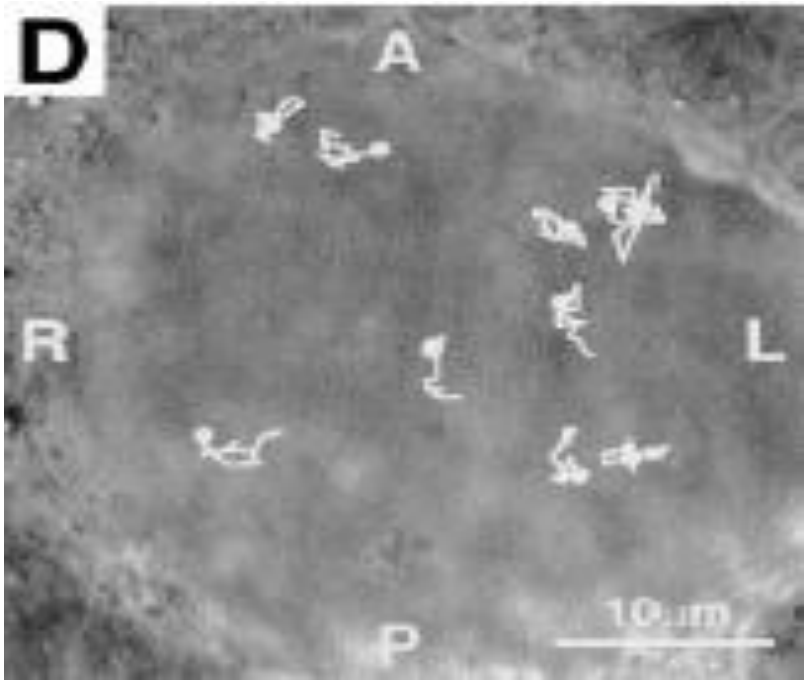
- In wild-type (KIF3B+/+) beads moved leftward across the node
- Beads exhibited counterclockwise rotation around cilia





Résultat #3

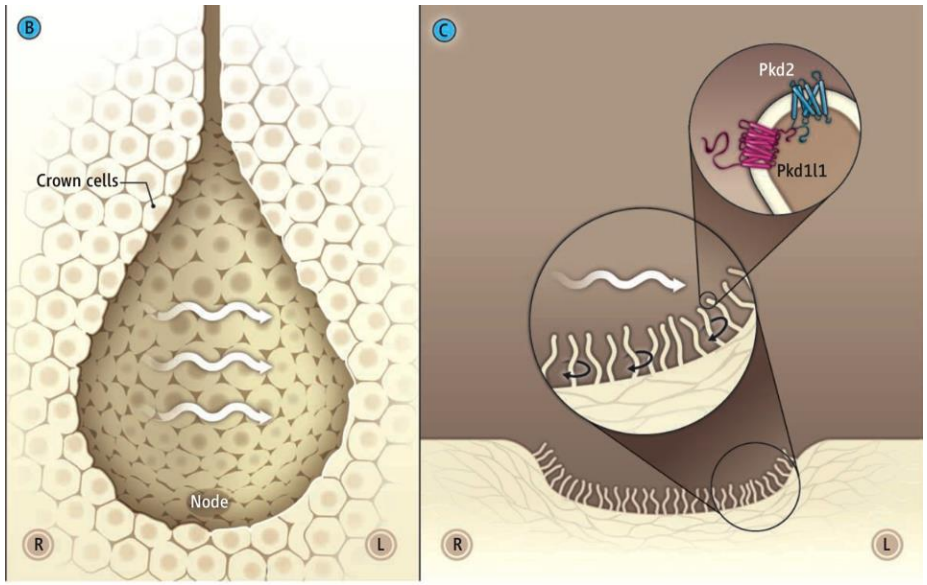
- Mutants (KIF3B-/-)
  - Movement resembled Brownian motion
  - Beads did not move a considerable distance across node
  - Direction of movement was random



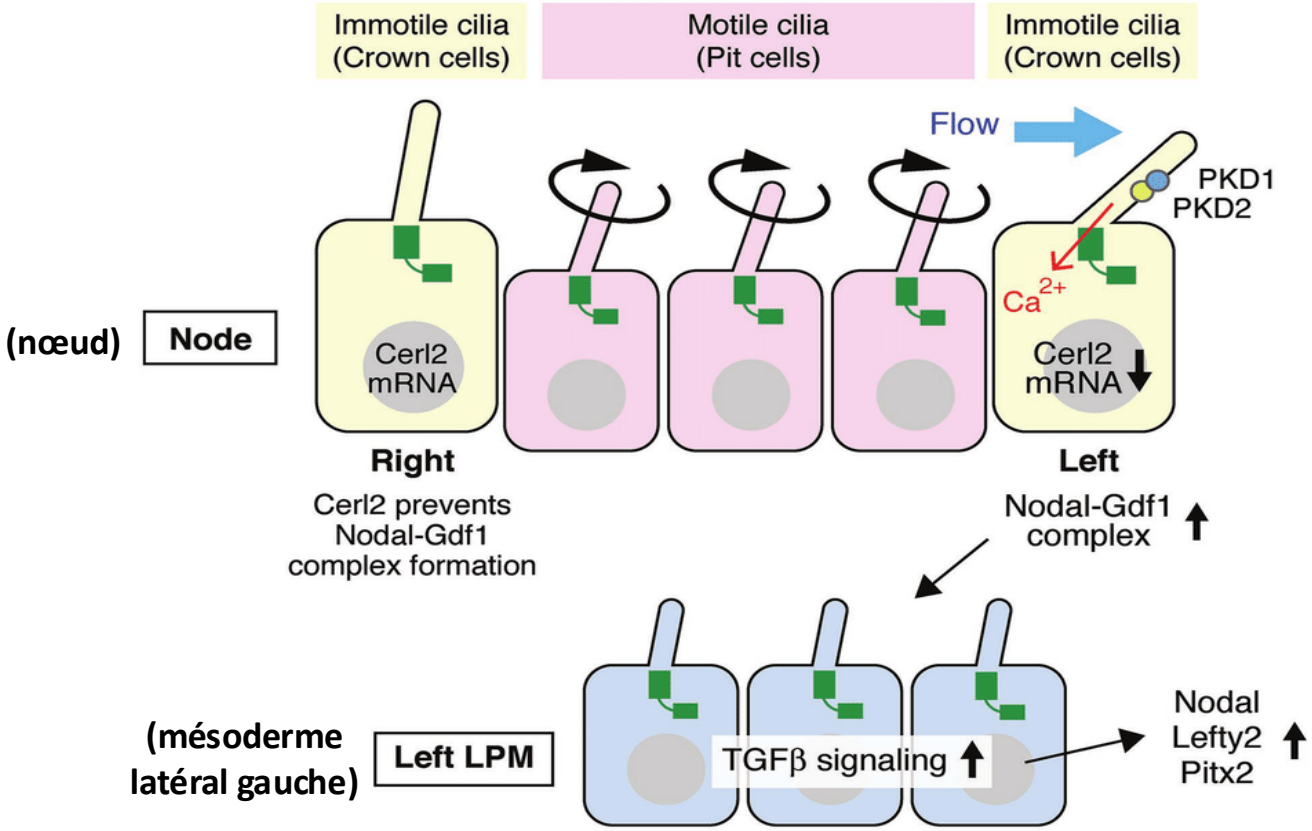
Modèle pour l'établissement du plan Gauche-Droite

- KIF3B est nécessaire pour la formation des cils → produisent un courant dans le nœud
- Ceci entraine l'accumulation au côté gauche du nœud de facteurs sécrétés (Ca^{++}, FGF…)
- Ce gradient déclenche une cascade de signalisation (=expression génique) asymétrique (côté gauche seulement)
- signalisation au calcium:

Pkd2, un canal Ca^{2+}, est présent sur les stéréocils des cellules en *périphérie* du nœud primitif



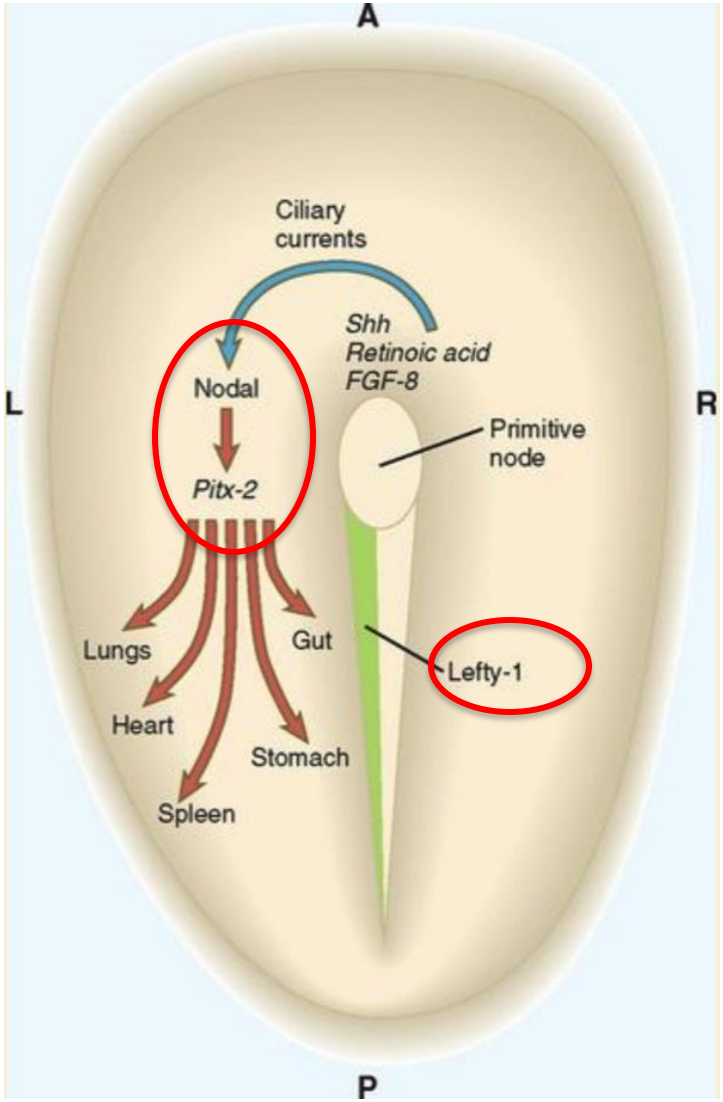
nœud (organisateur, ou organisateur gauche-droite)



MECANISME DE L'ASYMETRIE GAUCHE - DROITE

Les cascades d'expression génique sont différentes à gauche et à droite de la ligne primitive

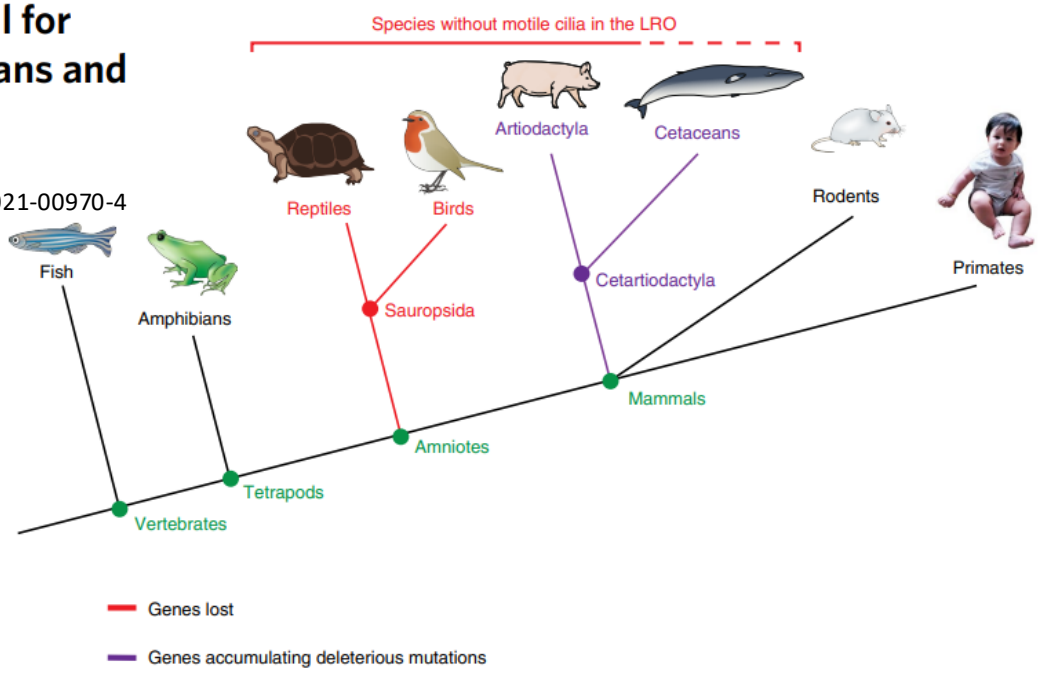
expression génique "asymétrique"



Discovery of a genetic module essential for assigning left-right asymmetry in humans and ancestral vertebrates

Szenker-Ravi, E., Ott, T., Khatoo, M. *et al.*

Nat Genet **54,** 62–72 (2022). https://doi.org/10.1038/s41588-021-00970-4



- reptiles, oiseaux et *cétacés/artiodactyles* (mammifères) : <u>ont perdu les cils dans le nœud</u> !
- ces espèces ont aussi perdu 5 gènes fonctionnellement imbriqués dans un groupe transcriptionnel coordonné, un «opéron fonctionnel» pour la détermination gauche-droite (chez les cétartiodactyles ils sont devenus des pseudogènes)

	Gene
Genes present only in species with motile cilia at their LRO	*CIROP*
	C1orf127
	MMP21
	PKD1L1
	DAND5

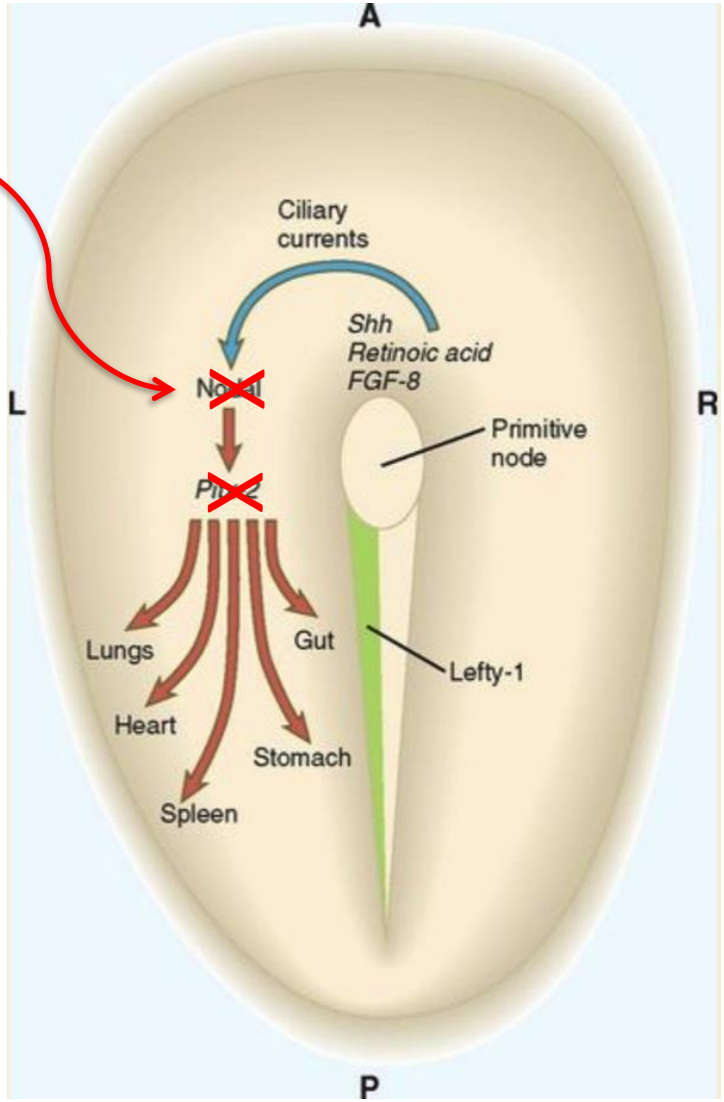
le gène CIROP est exprimé seulement pendant 2 heures dans le nœud !!!

ALTERATIONS DE L'ASYMETRIE GAUCHE - DROITE

mère diabétique : hétérotaxie fréquente

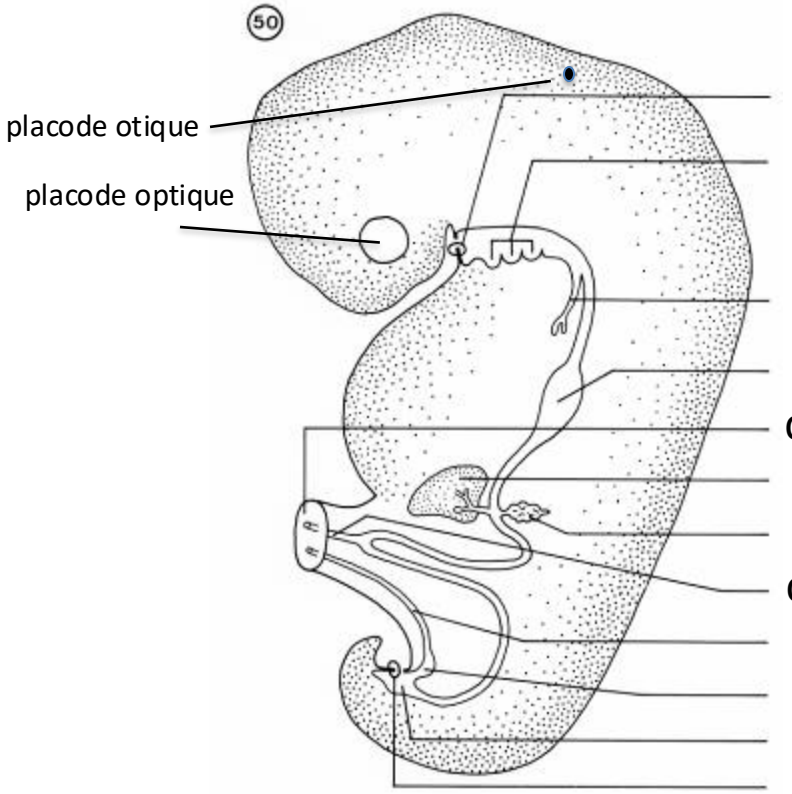
hyperglycémie chronique

(inhibition de la voie de signalisation de Notch)



QUATRIEME SEMAINE

9. Le **tube digestif** donne, par évaginations et bourgeonnements



membrane oropharyngée

poches branchiales endodermiques

système respiratoire (trachée, bronches)

estomac

cordon ombilical

foie

pancréas

canal vitellin (dérivé du sac vitellin)

vessie (dérivé de l'allantoïde)

sinus uro-génital

rectum

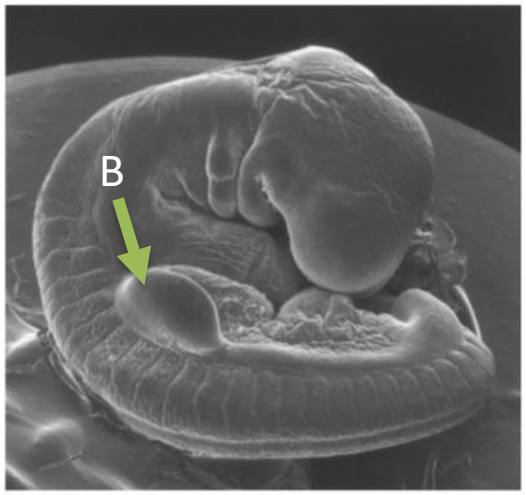
membrane cloacale

10. Apparition des bourgeons des bras et des jambes (26ème-28ème jour)

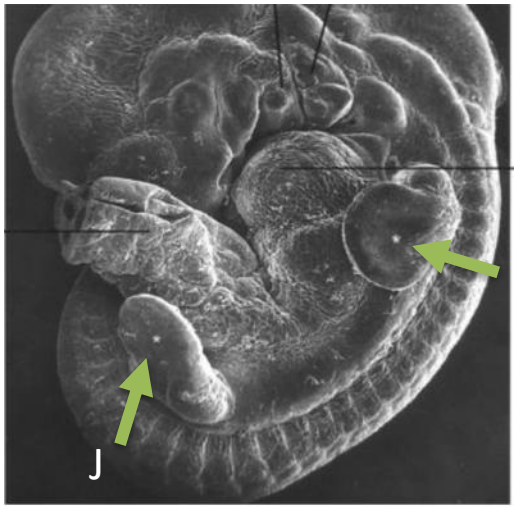
11. Apparition des placodes otiques et optiques

QUATRIEME SEMAINE

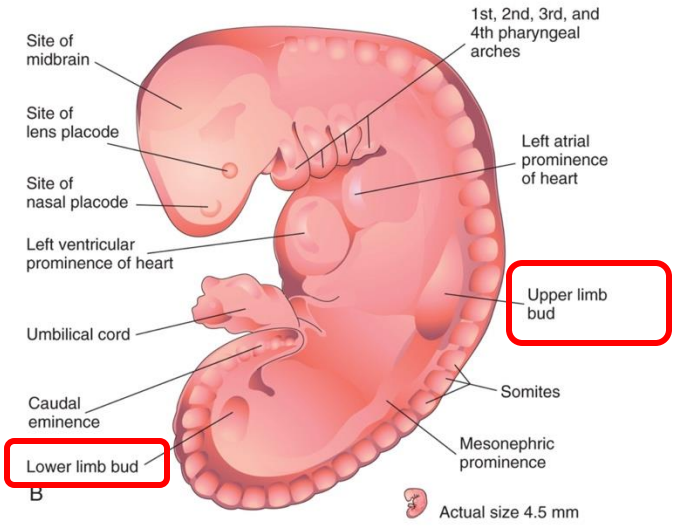
10. Début du bourgeonnement des bras (dès 28è j.: des jambes aussi)



4è sem. (34 paires de somites, 5mm) :
bourgeons des bras



5è sem. (10mm) :
bourgeons des bras et des jambes
(palettes distales)

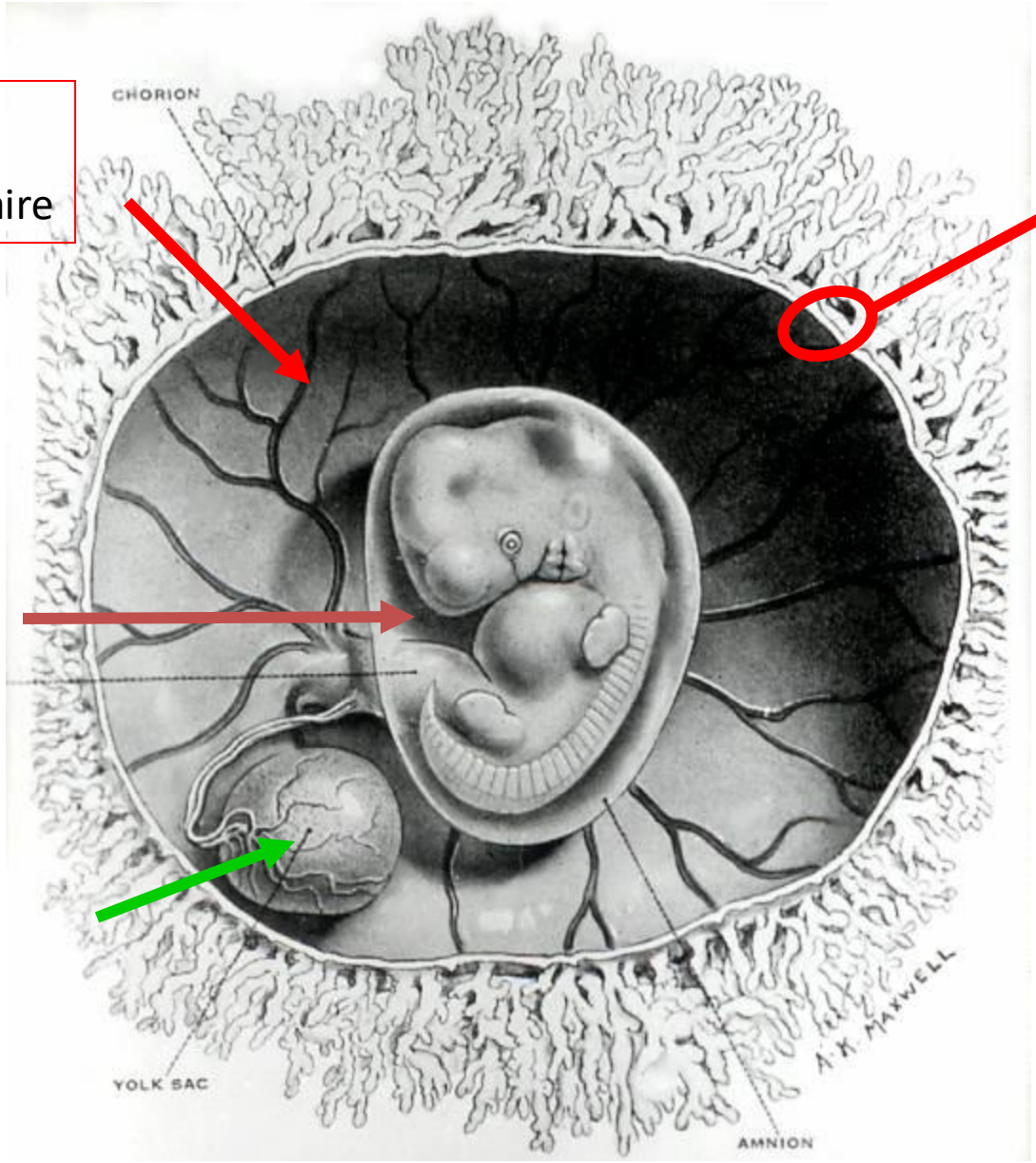


L'embryon dans le « sac chorial »

célome extra-embryonnaire

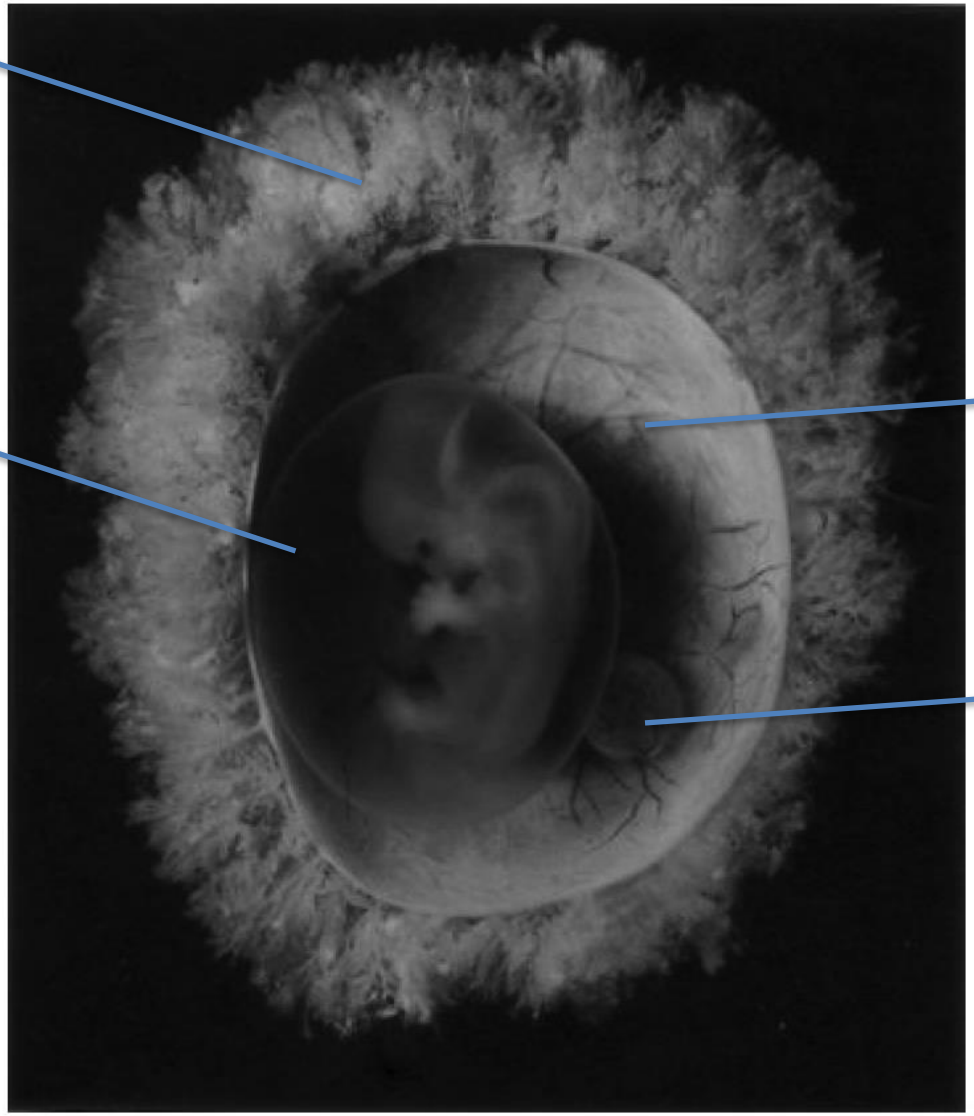
cavité amniotique

vésicule vitelline



chorion

villosités choriales (= *cyto + syncytiotrophoblaste + mésoderme extraembryonnaire*) du placenta



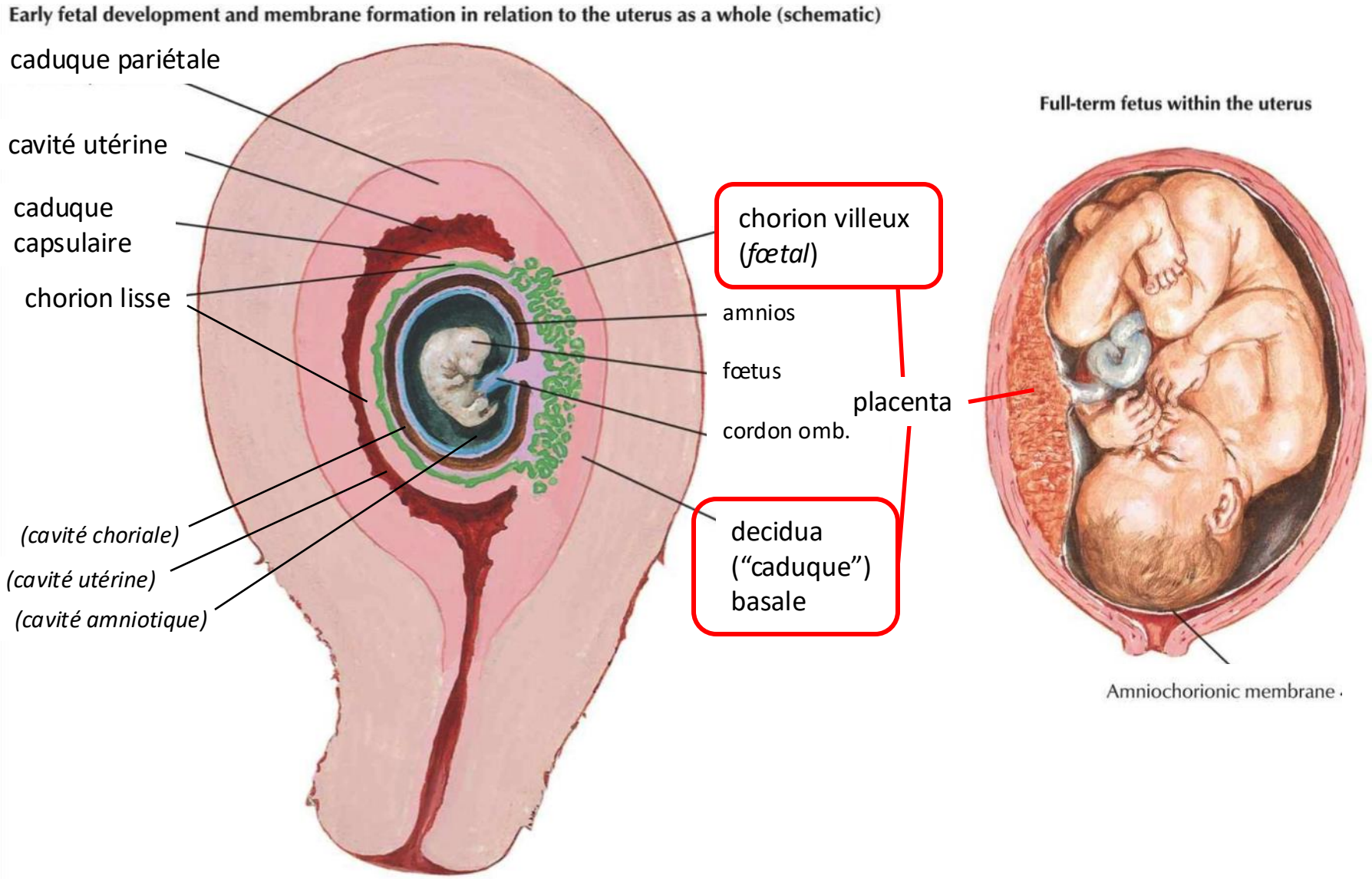
cavité amniotique

célome extraembryonnaire

sac vitellin

FIGURE 7-3 A 7-week-old human embryo surrounded by its amnion. The embryo was exposed by cutting open the chorion. The small sphere to the right of the embryo is the yolk sac.

Membranes fœtales



(utérus avec embryon ; coupe sagittale)

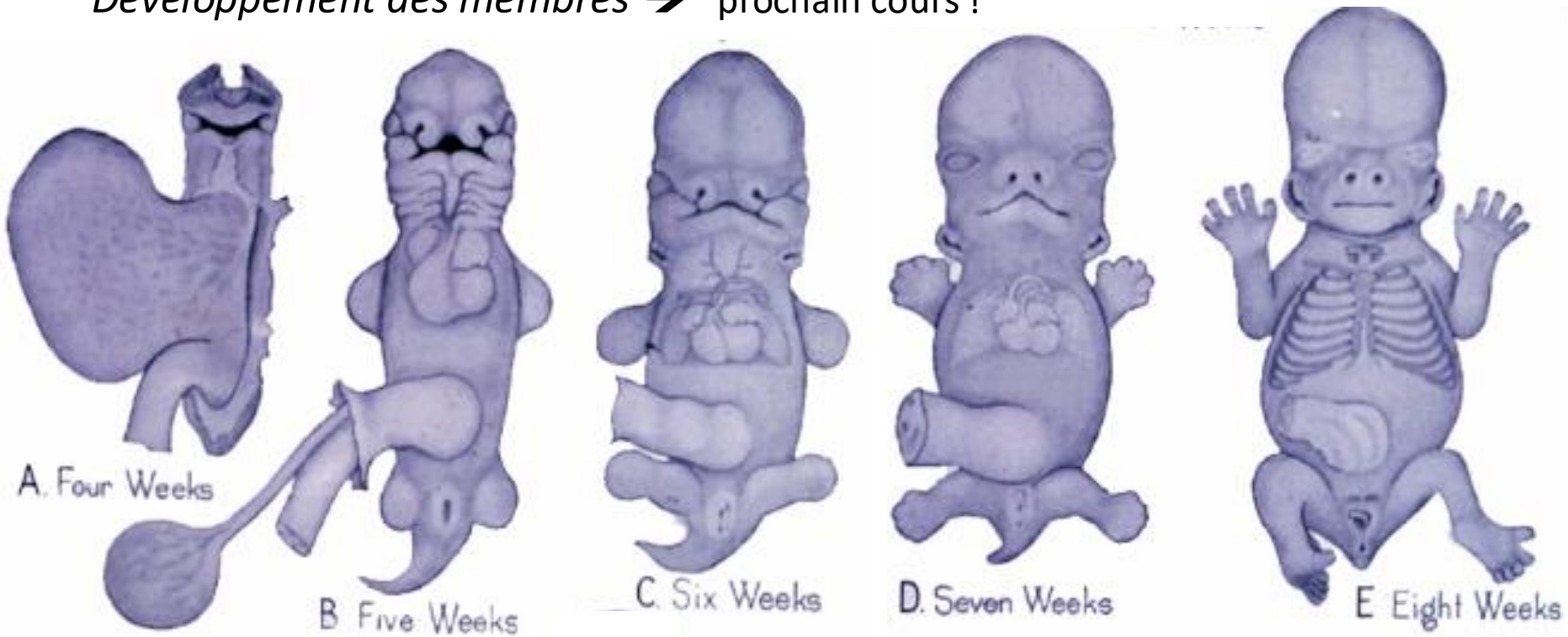
DEUXIEME MOIS

- acquisition de la forme humaine et croissance (*morphogenèse*)
- formation et agencement des organes (*organogenèse)*

début du développement des systèmes : génital, nerveux (profs. Nef et Altaba), *cardivasculaire, digestif, urinaire, respiratoire, et dév. de la face et des membres*

➔ «embryologie spéciale»

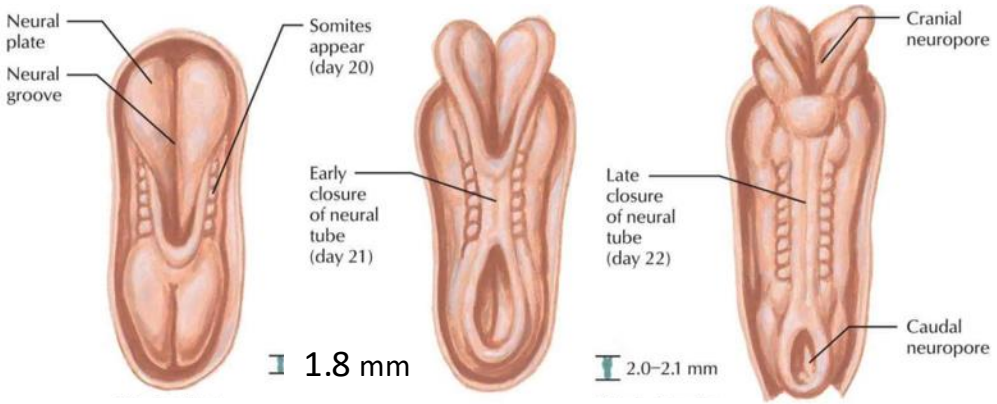
Développement des membres ➔ prochain cours !



période fœtale (du 3ème au 9ème mois) : *histogenèse (maturation des systèmes) et croissance*

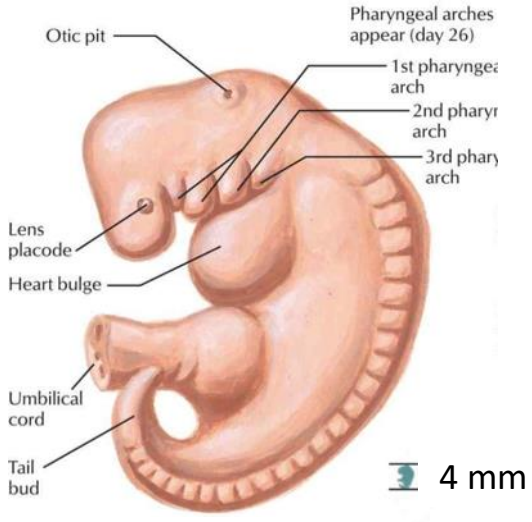
LA FORME EXTERNE DU CORPS DE L'EMBRYON (1)

- PREMIERE SEMAINE : MASSE CELLULAIRE ("masse cellulaire interne")
- DEUXIEME SEMAINE : DISQUE BILAMINAIRE
- TROISIEME SEMAINE : DISQUE TRILAMINAIRE *(gastrulation)*
- QUATRIEME SEMAINE : DISQUE trilaminaire <u>allongé</u> ➔➔ CYLINDRE
  (neurulation et somitogenèse) *(plicatures)*



fin 3è sem. début 4è sem.

(vues dorsales)

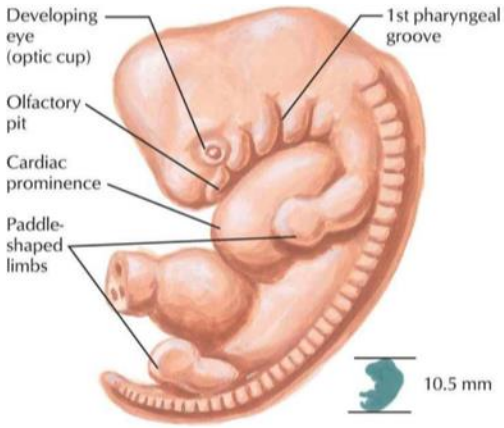


fin 4è sem.

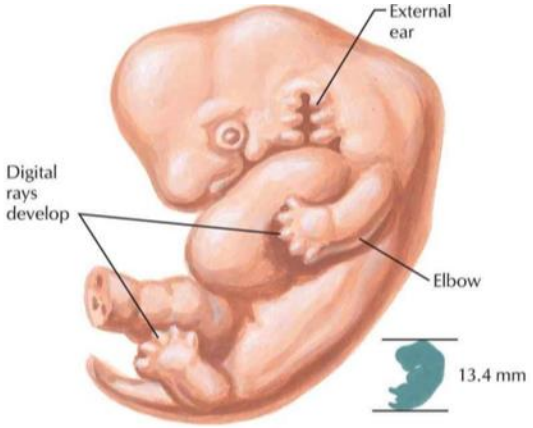
(vue latérale)

LA FORME EXTERNE DU CORPS DE L'EMBRYON (2)

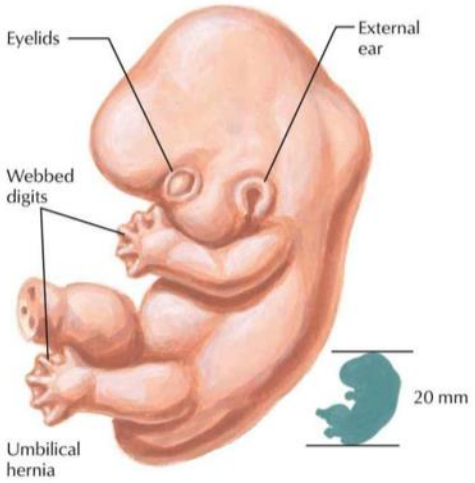
- DEUXIEME MOIS : "hominisation"



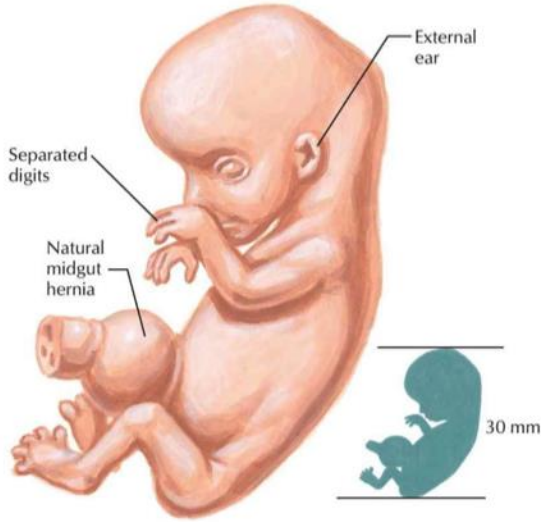
fin 5è sem.



6è sem.

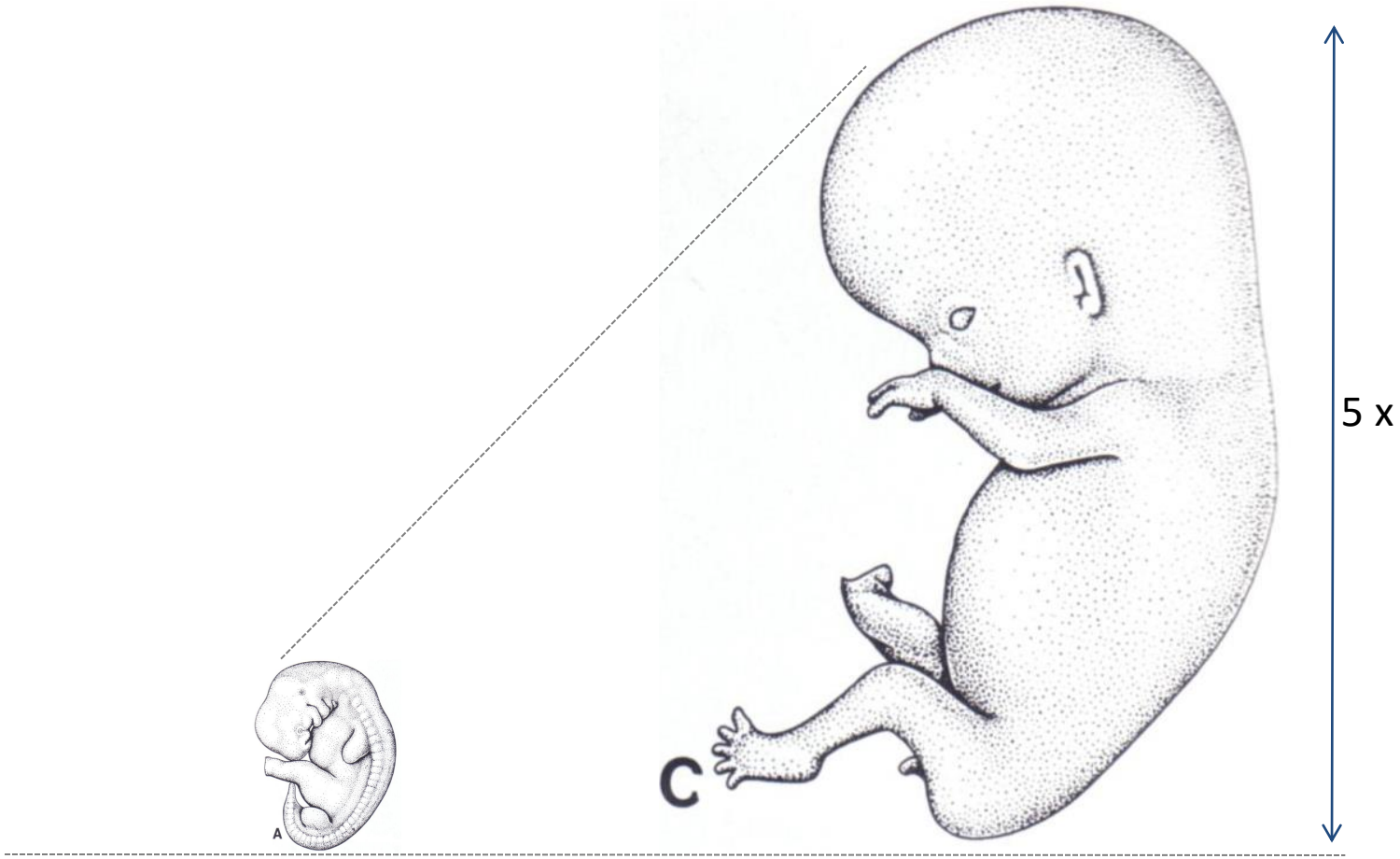


7è sem.



8è sem.

DEUXIEME MOIS - *morphogenèse externe :* croissance en taille ; acquisition de la forme humaine

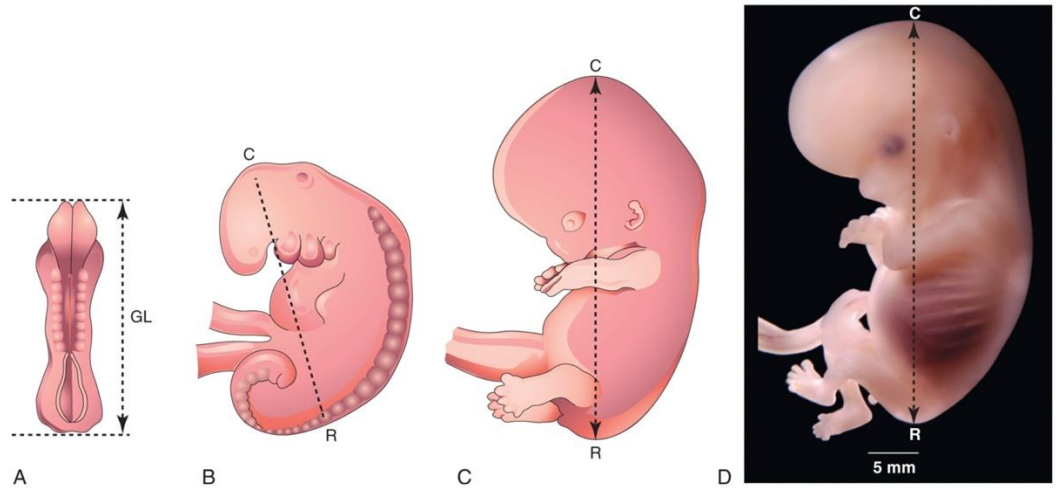


5 semaines (6mm)

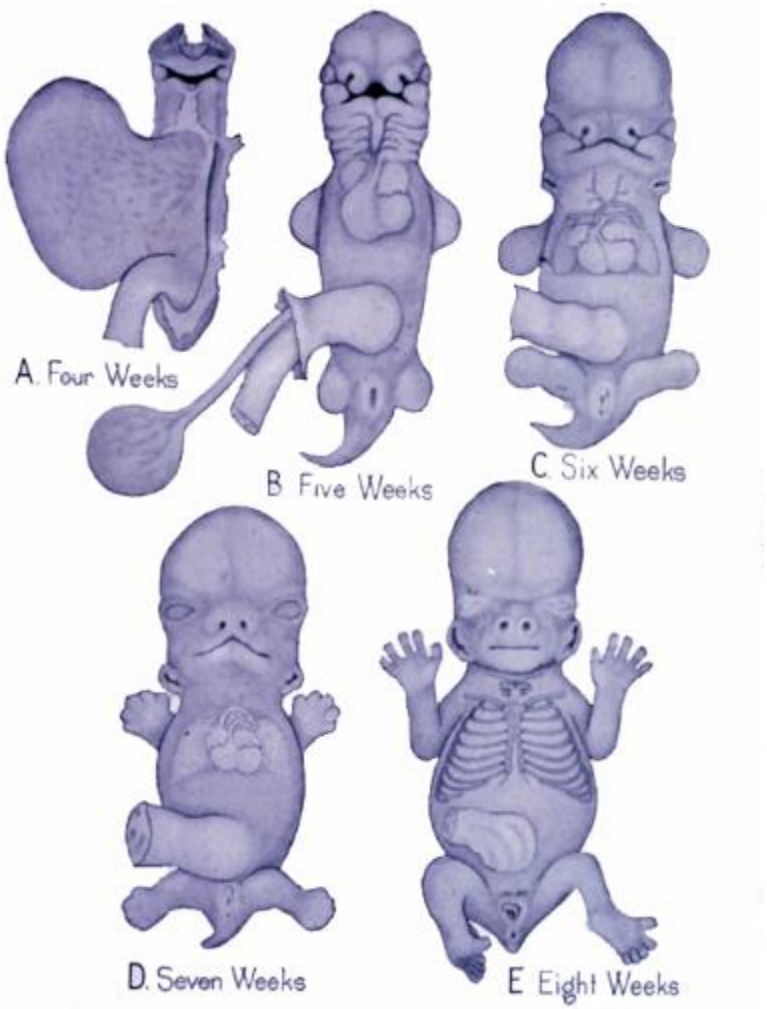
8 semaines (3cm)

DEUXIEME MOIS

- Croissance en taille : la longueur passe de 5-6mm à 30mm (*facteur 5 !*)
- Acquisition de la forme humaine



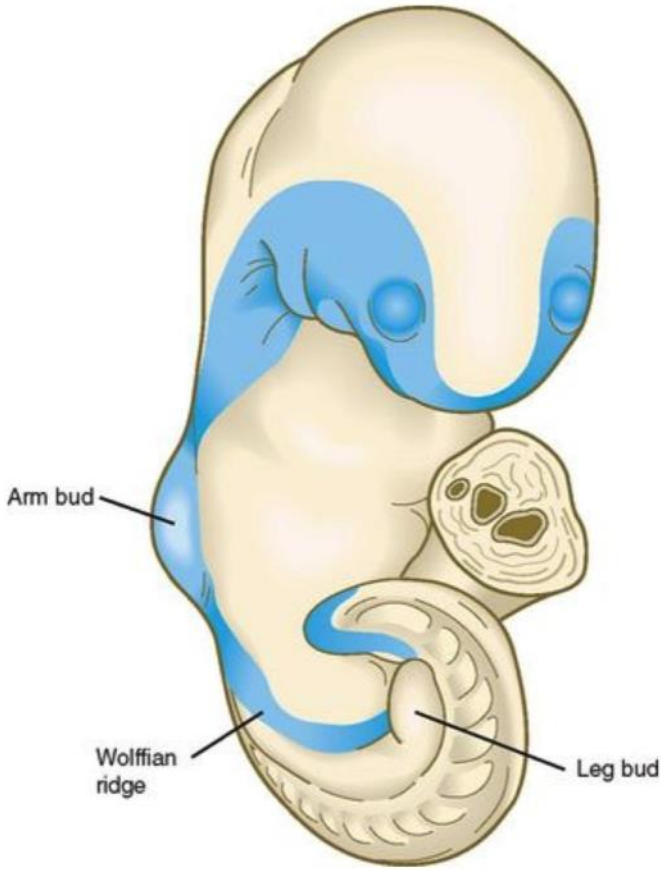
(4 sem.) *(5 semaines)* *(7-8 sem.)* *(8 semaines)*



Morphologiquement (externe) il y a trois changements majeurs :

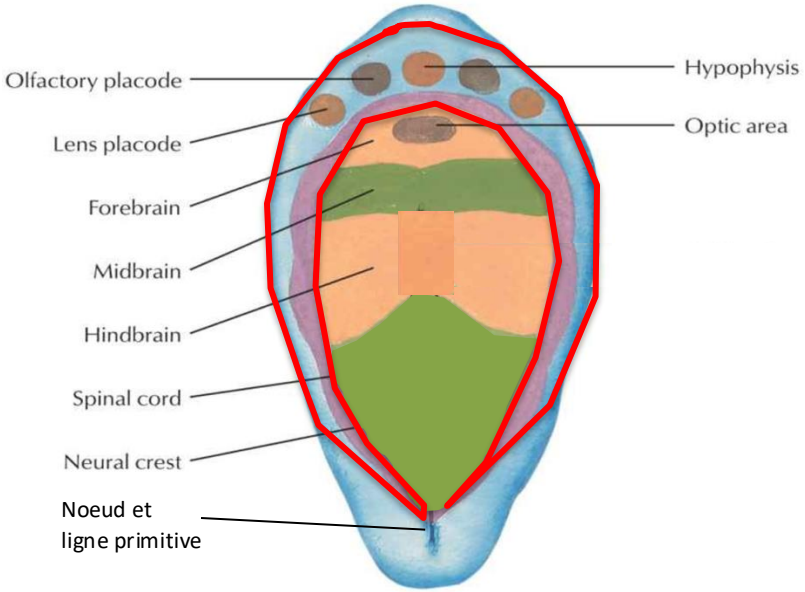
- disparition (*par différenciation*) des <u>somites</u> et de l'appendice <u>caudal</u>
- développement du <u>visage</u>
- formation des <u>membres</u>

pendant le 2ème mois, les bourgeons de nombreuses structures (nez, yeux, oreilles, arcs branchiaux, et les membres) se forment a partir d'une région de l'ectoderme, épaissie, qui forme une sorte de bande latérale tout autour du corps de l'embryon



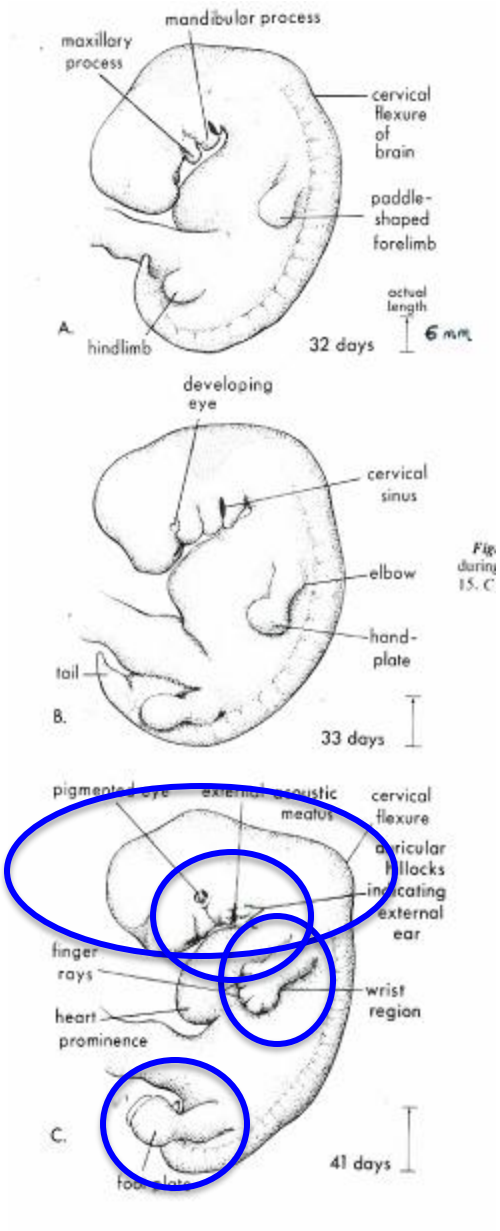
Ventrolateral view of a 30-somite (4.2-mm) human embryo showing the thickened ectodermal ring (*blue*).

territoires présomptifs de l'épiblaste



DEUXIEME MOIS

(0.6 – 3 cm de longueur: x5)



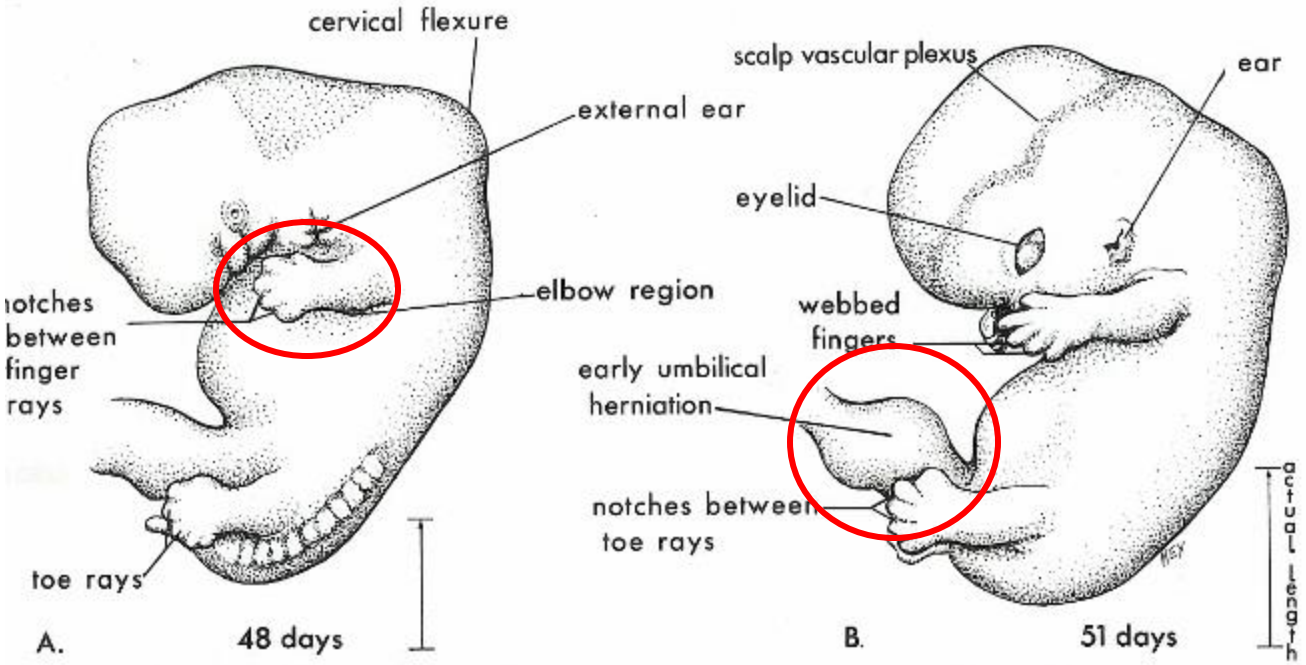
~ 6 mm

5ème - 6ème semaines

- croissance de la région céphalique
- croissance des membres:
  le membre supérieur (antérieur) se différencie
  avant le membre inférieur (postérieur)
- développement de l'œil
  et de l'oreille externe

DEUXIEME MOIS

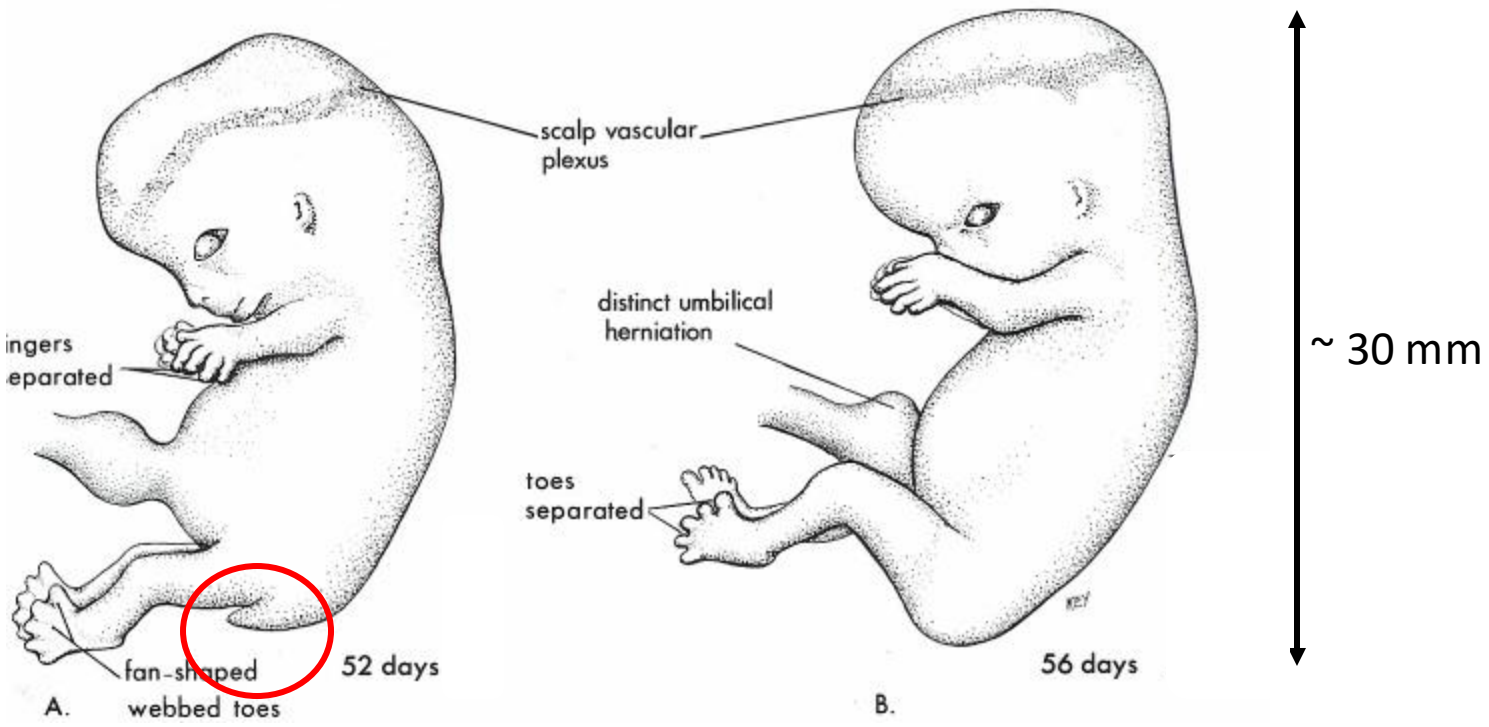
7ème semaine



- développement des doigts:
  rayons digitaux et encoches entre les rayons digitaux
- anses intestinales extra-abdominales, dans le cordon ombilical
  = hernie ombilicale physiologique (jusqu'à 10ème semaine)
- développement de la face:
  fusion des massifs dérivés des arcs branchiaux

DEUXIEME MOIS

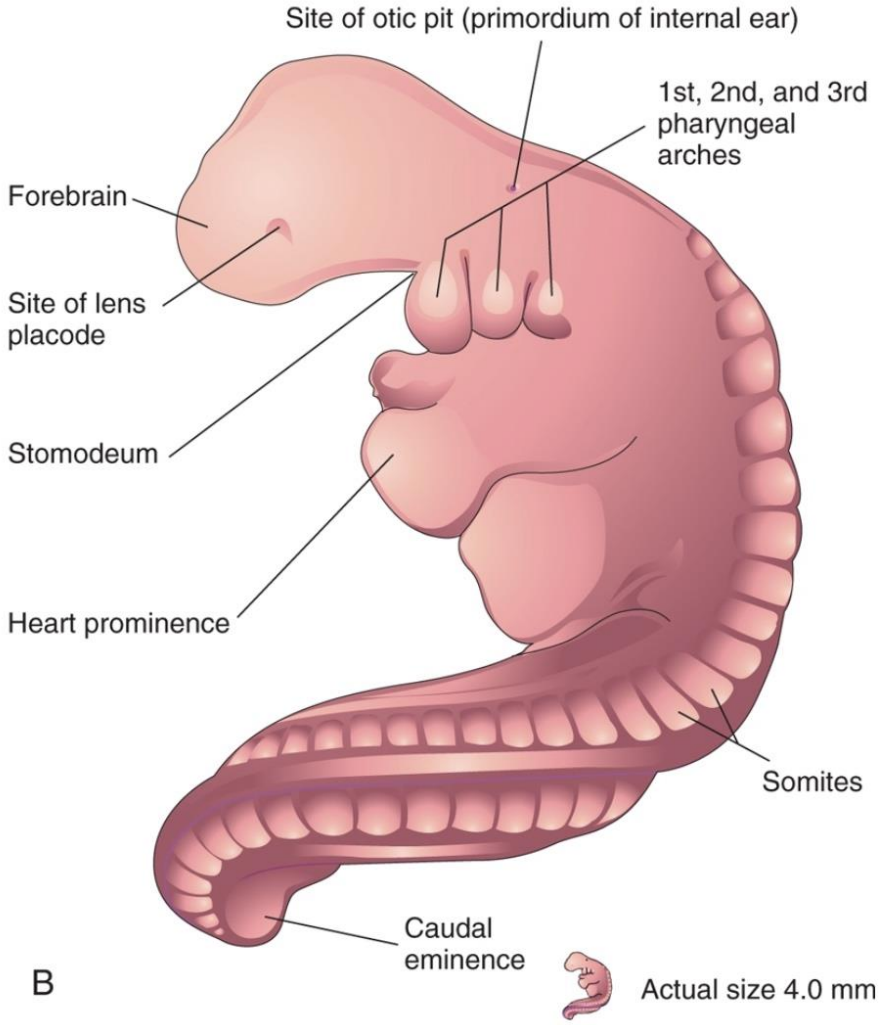
8ème semaine



- doigts et orteils séparés
- queue disparaît
- yeux ouverts
- organes génitaux externes
  "masculins" et "féminins" identiques

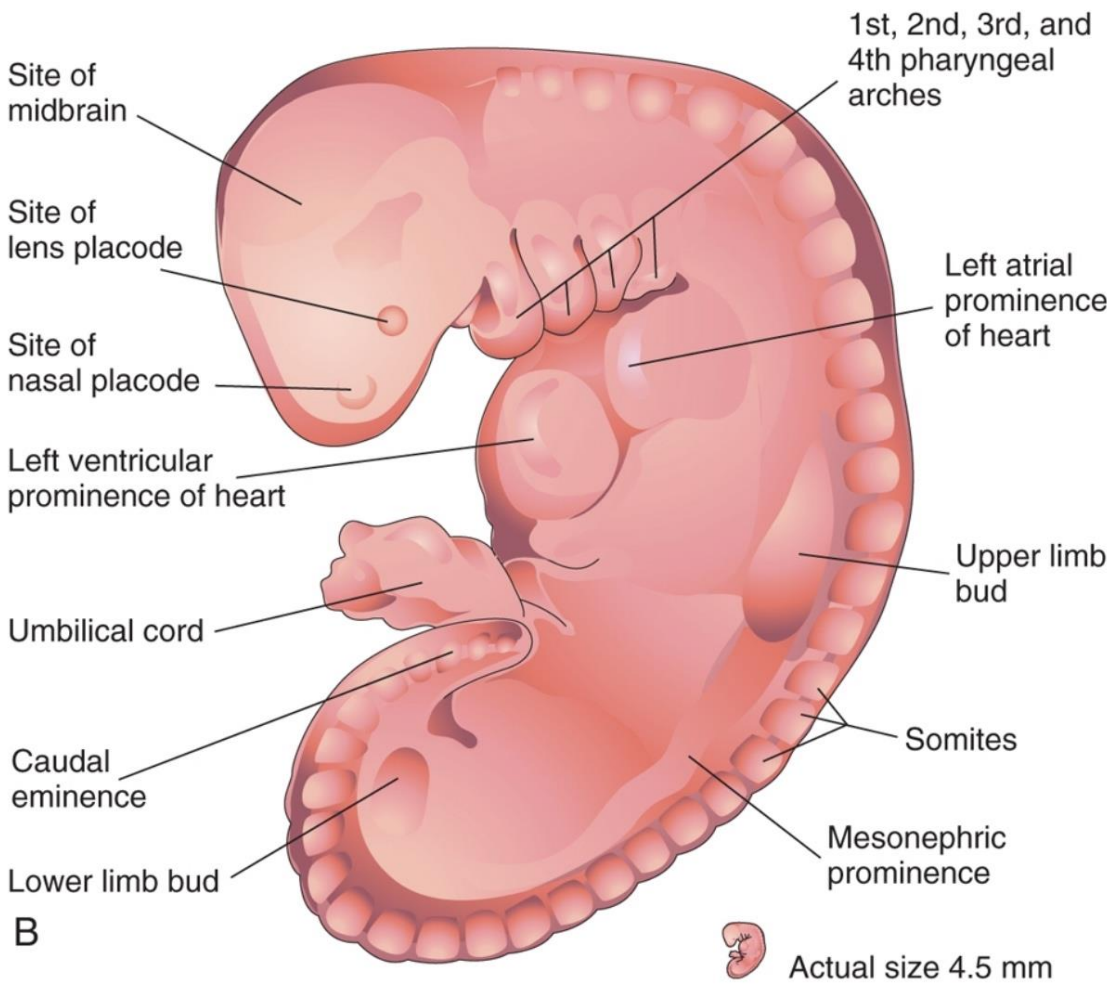
26 jours Carnegie 12 (stade de 27 somites)

- neuropore rostral fermé
- 3 paires d'arcs branchiaux sont visibles
- placodes optiques et otiques apparentes
- bourgeon de la queue long et courbe



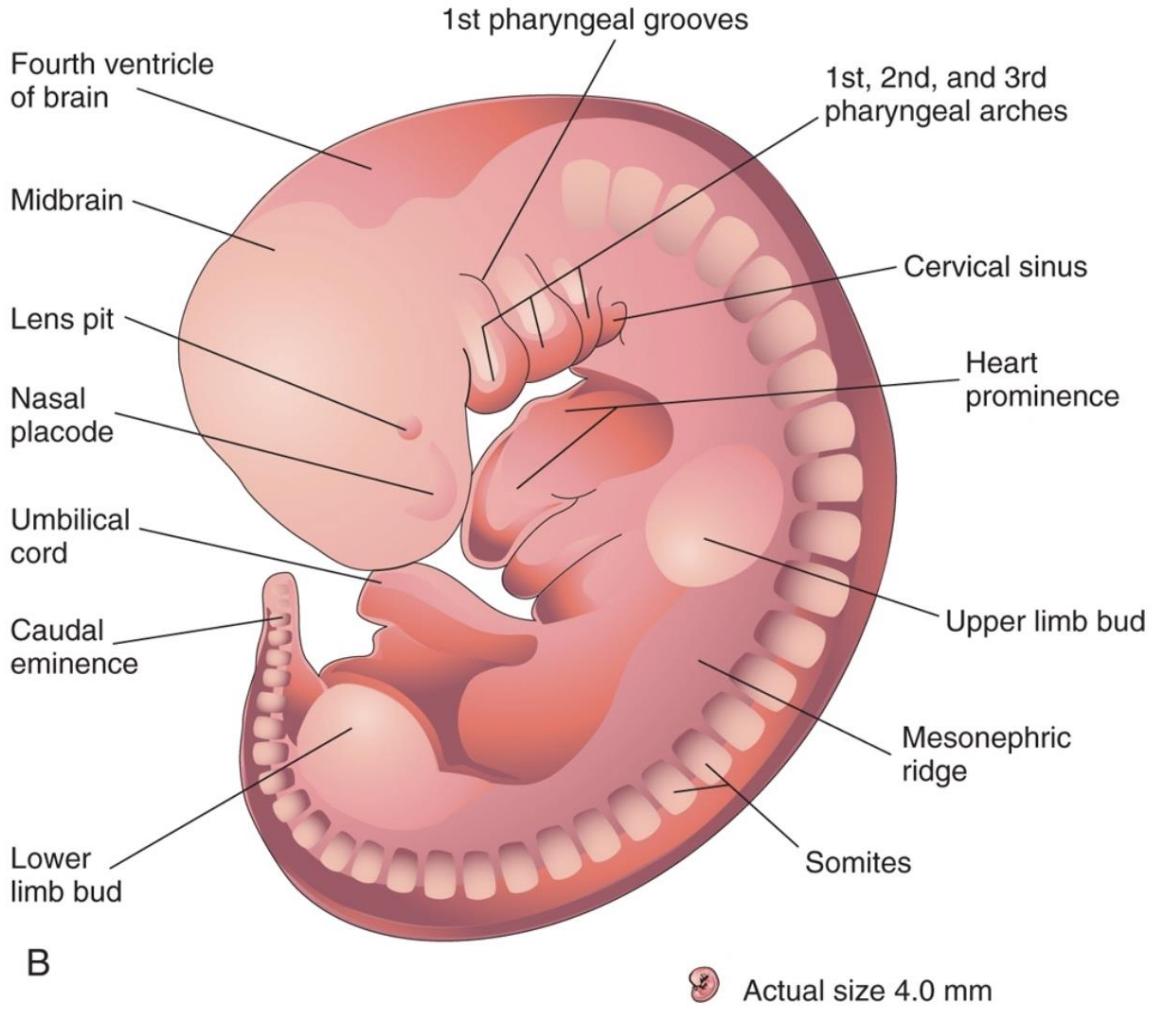
fin de la 4ème semaine Carnegie 13 (~28 jours)

- les neuropores sont fermés
- 4 arcs branchiaux sont visibles
- le bourgeon du cœur est proéminent, avec oreillette et ventricule bien distincts
- bourgeons des bras



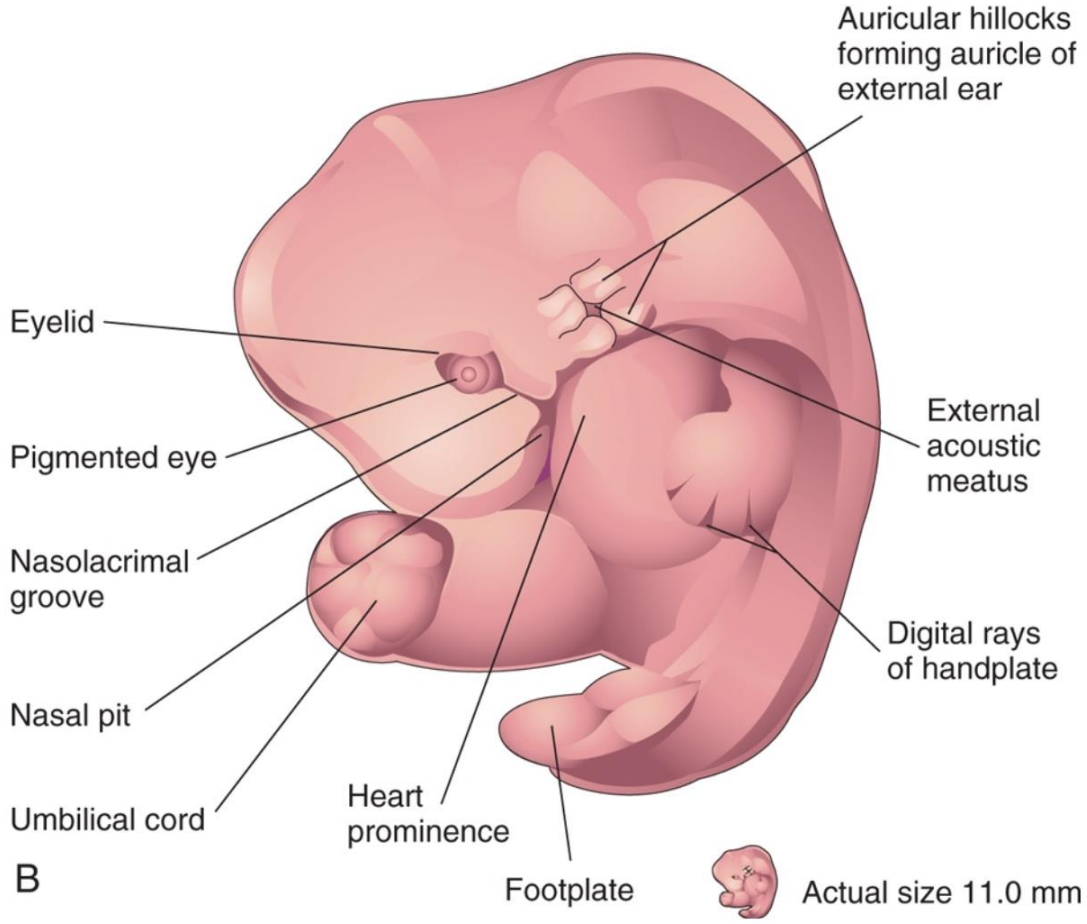
5ème semaine Carnegie 14 (~32 jours)

- croissance céphalique;
- bourgeonnements des membres postérieurs visibles
- développement de l'œil



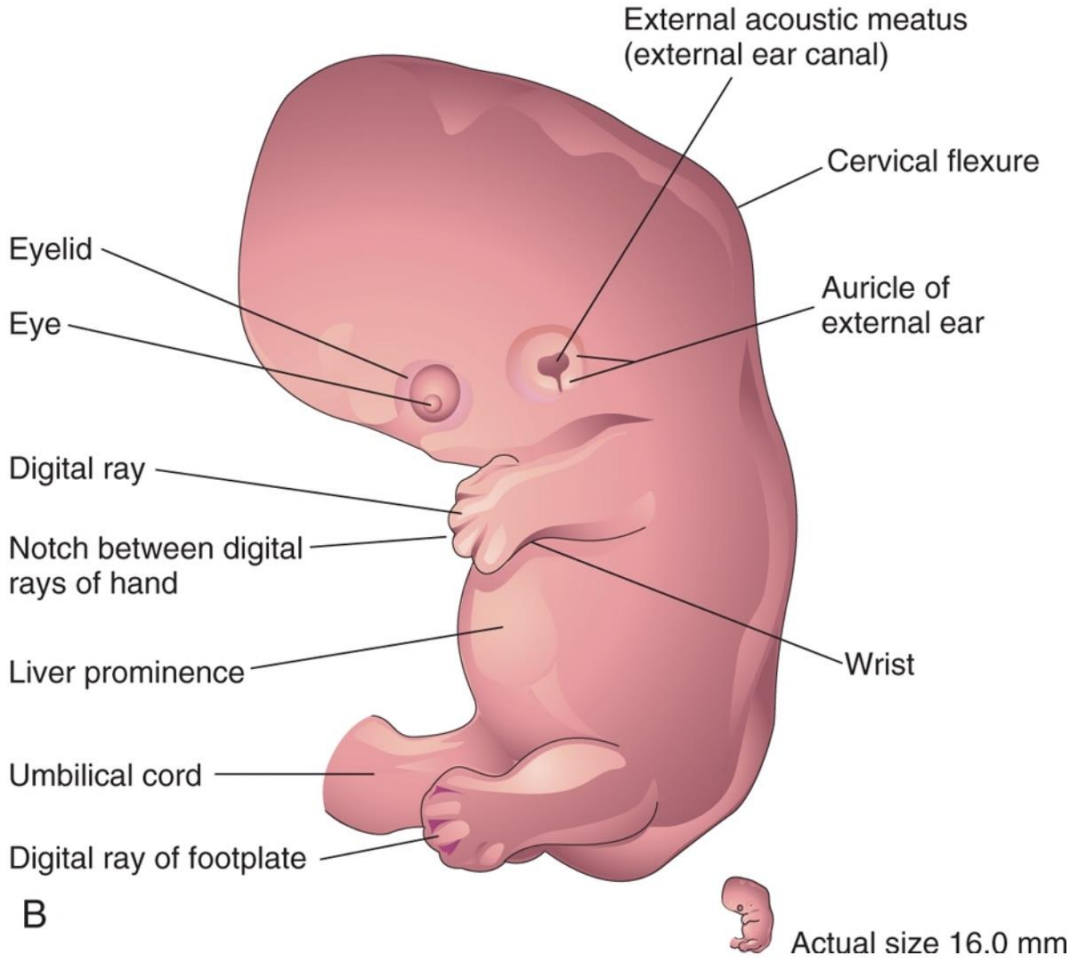
fin de la 6ème semaine Carnegie 17 (~42 jours)

- développement de l'oreille externe (bourrelets des pavillons auriculaires)
- dév. de la palette de la main, avec les rayons des doigts
- anses intestinales commencent a se former a l'extérieur du corps, a la base du cordon ombilical
- les somites ne sont plus distingables exterieurement



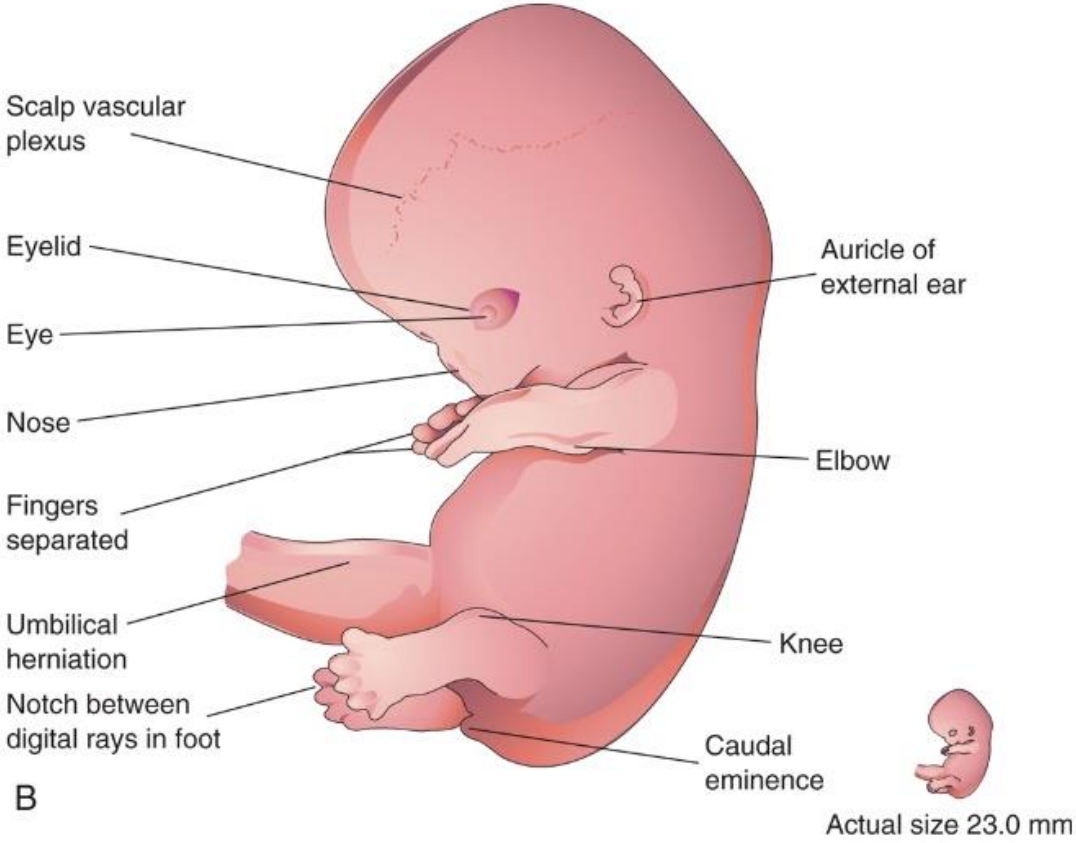
fin de la 7ème semaine (Carnegie 19)

- encoches entre les doigts de la main ; dév. de la palette des pieds, avec rayons des orteils
- développement de la face: fusions des massifs dérivés des arcs branchiaux
- conduit auditif et pavillon de l'oreille sont visibles ; développement du foie



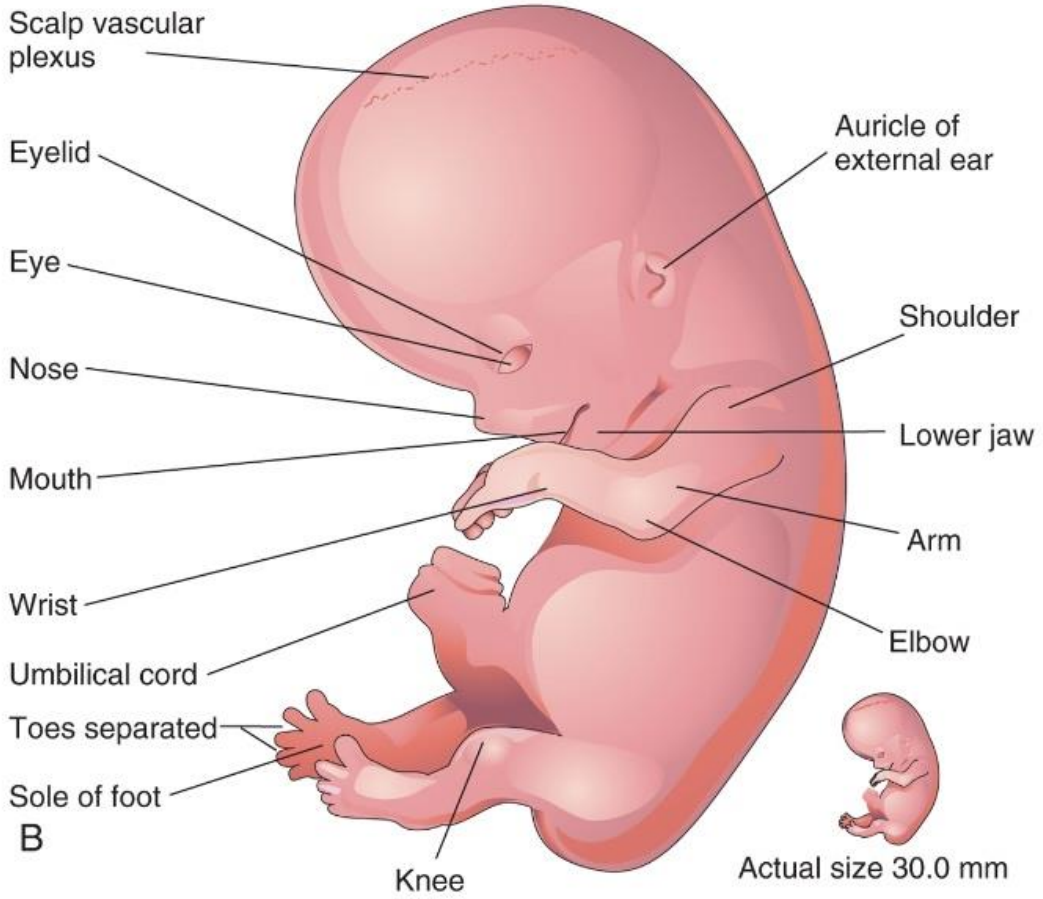
8ème semaine Carnegie 21

- orteils séparés
- la proéminence caudale (queue) persiste, mais en train de régresser
- les yeux sont ouverts et pigmentés



fin de la 8ème semaine Carnegie 23 (~56 jours)

- la queue disparaît complétement
- les organes génitaux externes restent indifférenciés

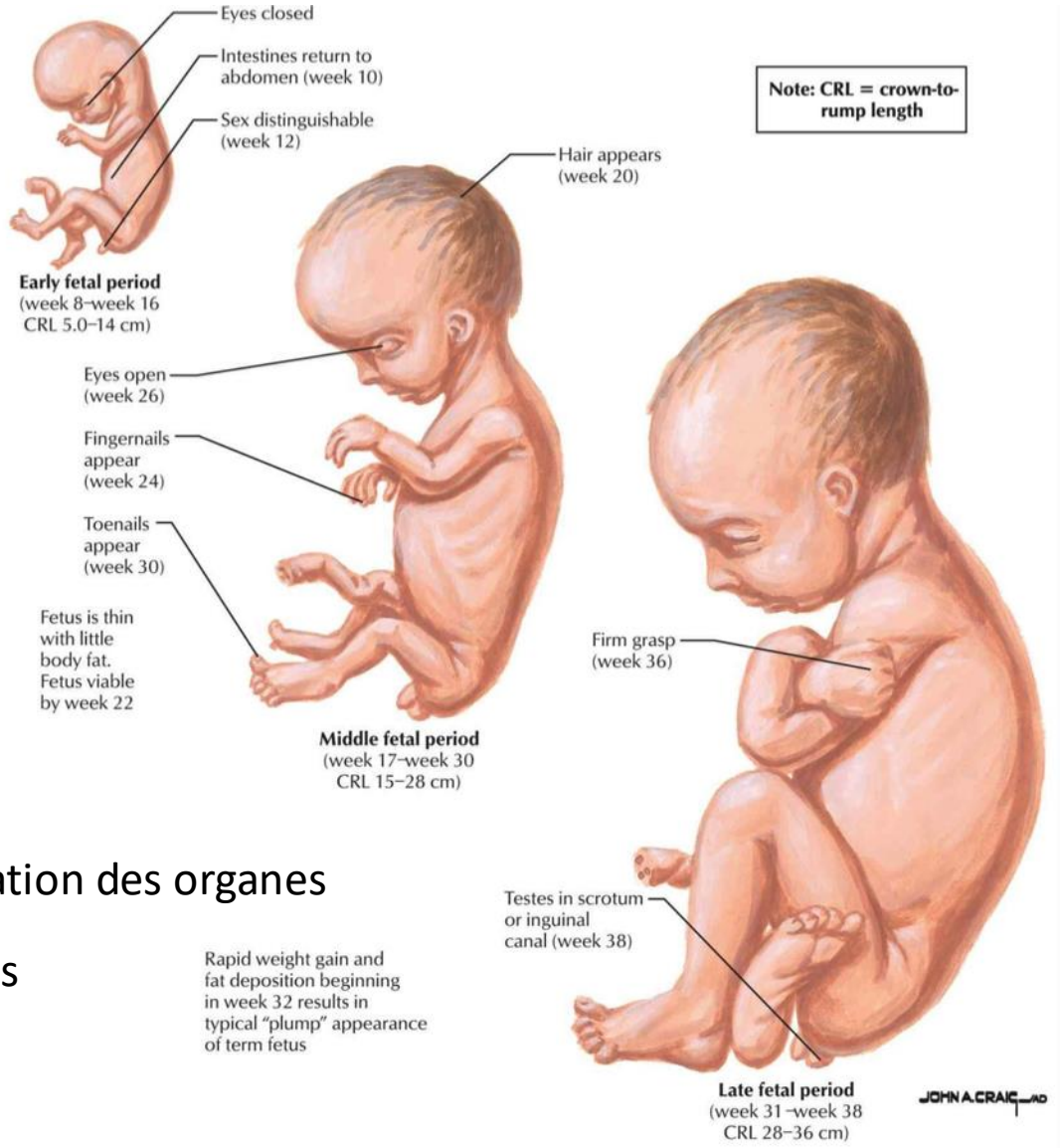


Période fœtale (semaines 9 à 38)

Malgré sa courte durée, la *période embryonnaire* est fondamentale puisque l'embryon acquiert sa forme presque définitive (*morphogenèse*) et édifie ses principales ébauches organiques (*organogenèse*).

Pendant la longue *période fœtale* qui suit, les organes ne subiront pratiquement plus que des phénomènes de maturation à l'échelle histologique (*histogenèse*).

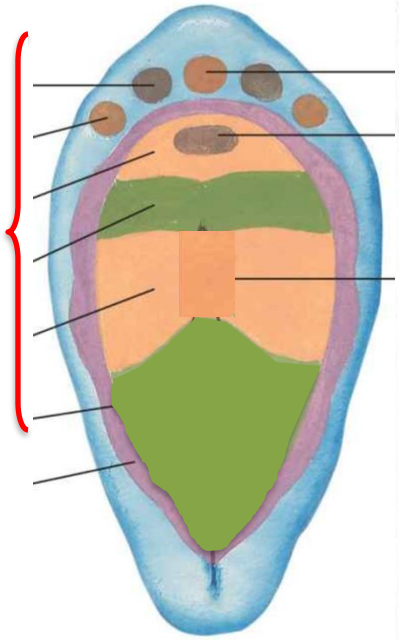
Période fœtale (semaines 9 à 38)



- Croissance et différenciation des organes
- Maturation des systèmes

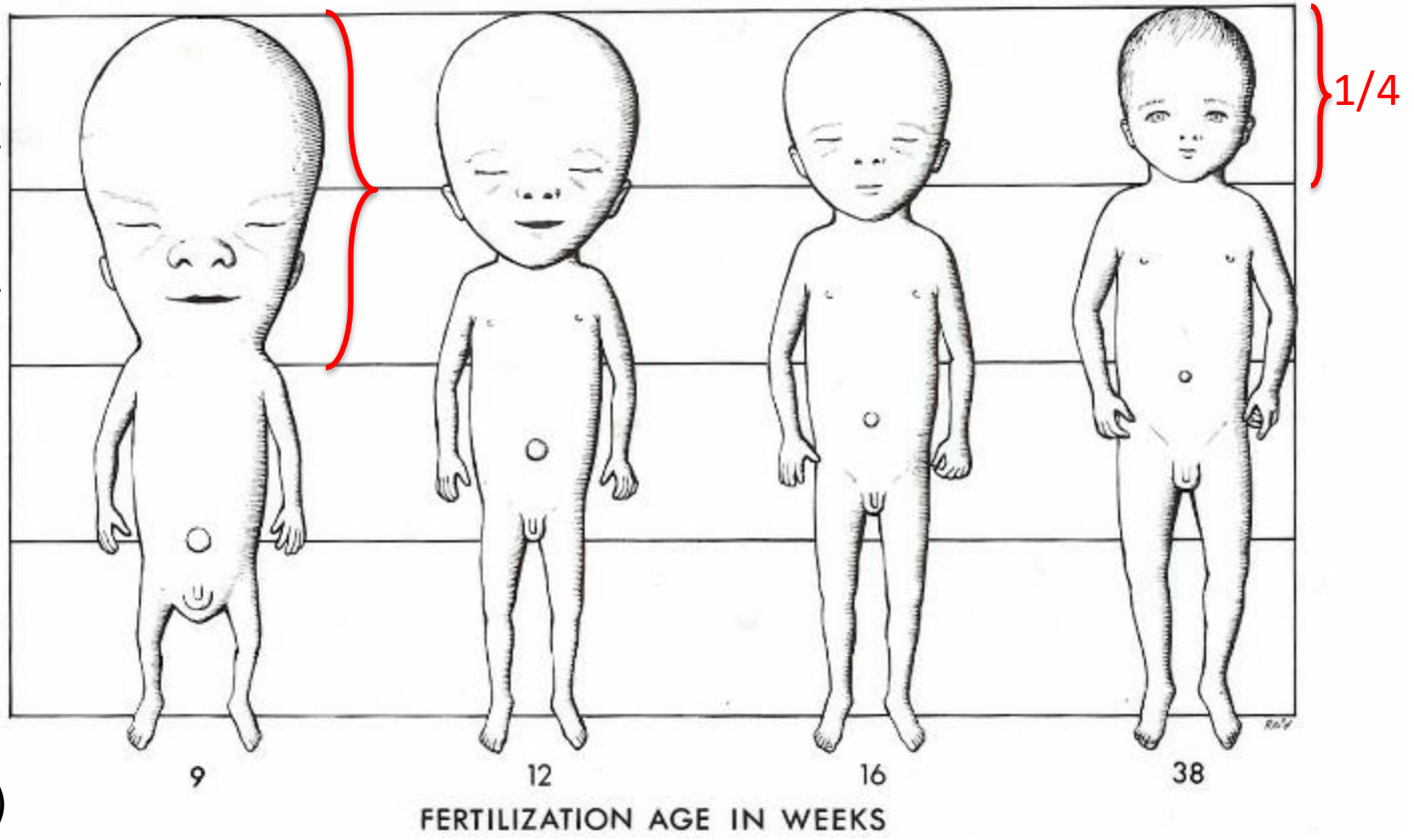
croissance : facteur 10 !!!

PERIODE FŒTALE



TÊTE (2/3 !!!)

GASTRULA
(disque trilaminaire)
(*3 semaines*)



la croissance des différentes parties du corps est *allométrique*

Carnegie Stages of Early Human Embryonic Development (Weeks 1 to 8)

Age (days)	External Features	Carnegie Stage	Crown-Rump Length (mm)	Pairs of Somites
1	Fertilized oocyte	1	0.1	
2 to 3	Morula (4 to 16 cells)	2	0.1	
4 to 5	Free blastocyst	3	0.1	
6	Attachment of blastocyst to endometrium	4	0.1	
7 to 12	Implantation, bilaminar embryo with primary yolk sac	5	0.1 to 0.2	
17	Trilaminar embryo with primitive streak, chorionic villi	6	0.2 to 0.3	
19	Gastrulation, formation of notochordal process	7	0.4	
23	Hensen's node and primitive pit, notochord and neurenteric canal, appearance of neural plate, neural folds, and blood islands	8	1 to 1.5	
25	Appearance of first somites, deep neural groove, elevation of cranial neural folds, early heart tubes	9	1.5 to 2.5	1 to 3
28	Beginning of fusion of neural folds, formation of optic sulci, presence of first two pharyngeal arches, beginning heart beat, curving of embryo	10	2 to 3.5	4 to 12
29	Closure of cranial neuropore, formation of optic vesicles, rupture of oropharyngeal membrane	11	2.5 to 4.5	13 to 20
30	Closure of caudal neuropore, formation of pharyngeal arches 3 and 4, appearance of upper limb buds and tail bud, formation of otic vesicle	12	3 to 5	21 to 29
32	Appearance of lower limb buds, lens placode, separation of otic vesicle from surface ectoderm	13	4 to 6	30 to 31
33	Formation of lens vesicle, optic cup, and nasal pits	14	5 to 7	
36	Development of hand plates, primary urogenital sinus, prominent nasal pits, evidence of cerebral hemispheres	15	7 to 9	
38	Development of foot plates, visible retinal pigment, development of auricular hillocks, formation of upper lip	16	8 to 11	
41	Appearance of finger rays, rapid head enlargement, six auricular hillocks, formation of nasolacrimal groove	17	11 to 14	
44	Appearance of toe rays and elbow regions, beginning of formation of eyelids, tip of nose distinct, presence of nipples	18	13 to 17	
46	Elongation and straightening of trunk, beginning of herniation of midgut into umbilical cord	19	16 to 18	
49	Bending of arms at elbows, distinct but webbed fingers, appearance of scalp vascular plexus, degeneration of anal and urogenital membranes	20	18 to 22	
51	Longer and free fingers, distinct but webbed toes, indifferent external genitalia	21	22 to 24	
53	Longer and free toes, better development of eyelids and external ear	22	23 to 28	
56	More rounded head, fusion of eyelids	23	27 to 31	

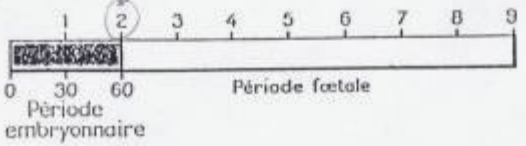
Major Developmental Events During the Fetal Period

External Features	Internal Features
8 Weeks	
Head is almost half the total length of fetus	Midgut herniation into umbilical cord occurs
Cervical flexure is about 30 degrees	Extraembryonic portion of allantois has degenerated
Indifferent external genitalia are present	Ducts and alveoli of lacrimal glands form
Eyes are converging	Paramesonephric ducts begin to regress in males
Eyelids are unfused	Recanalization of lumen of gut tube occurs
Tail disappears	Lungs are becoming glandlike
Nostrils are closed by epithelial plugs	Diaphragm is completed
Eyebrows appear	First ossification begins in skeleton
Urine is released into amniotic fluid	Definitive aortic arch system takes shape
9 Weeks	
Neck develops and chin rises from thorax	Intestines are herniated into umbilical cord
Cranial flexure is about 22 degrees	Early muscular movements occur
Chorion is divided into chorion laeve and chorion frondosum	Adrenocorticotropic hormone and gonadotropins are produced by pituitary
Eyelids meet and fuse	Corticosteroids are produced by adrenal cortex
External genitalia begin to become gender specific	Semilunar valves in heart are completed
Amniotic fluid is swallowed	Fused paramesonephric ducts join vaginal plate
Thumb sucking and grasping begin	Urethral folds begin to fuse in males
10 Weeks	
Cervical flexure is about 15 degrees	Intestines return into body cavity from umbilical cord
Gender differences are apparent in external genitalia	Bile is secreted
Fingernails appear	Blood islands are established in spleen
Eyelids are fused	Thymus is infiltrated by lymphoid stem cells
Fetal yawning occurs	Prolactin production by pituitary occurs
	First permanent tooth buds form
	Deciduous teeth are in early bell stage
	Epidermis has three layers

11 Weeks	
Cervical flexure is about 8 degrees	Stomach musculature can contract
Nose begins to develop bridge	T lymphocytes emigrate into bloodstream
Taste buds cover inside of mouth	Colloid appears in thyroid follicles
	Intestinal absorption begins
12 weeks	
Head is erect	Ovaries descend below pelvic rim
Neck is almost straight and well defined	Parathyroid hormone is produced
External ear is taking form and has moved close to its definitive position in the head	Blood can coagulate
Yolk sac has shrunk	
Fetus can respond to skin stimulation	
Bowel movements begin (meconium expelled)	
4 Months	
Skin is thin; blood vessels can easily be seen through it	Seminal vesicle forms
Nostrils are almost formed	Transverse grooves appear on dorsal surface of cerebellum
Eyes have moved to front of face	Bile is produced by liver and stains meconium green
Legs are longer than arms	Gastric glands bud off from gastric pits
Fine lanugo hairs appear on head	Brown fat begins to form
Fingernails are well formed; toenails are forming	Pyramidal tracts begin to form in brain
Epidermal ridges appear on fingers and palms of hand	Hematopoiesis begins in bone marrow
Enough amniotic fluid is present to permit amniocentesis	Ovaries contain primordial follicles
Mother can feel fetal movements	

External Features	Internal Features
5 Months	
Epidermal ridges form on toes and soles of feet	Myelination of spinal cord begins
Vernix caseosa begins to be deposited on skin	Sebaceous glands begin to function
Abdomen begins to fill out	Thyroid-stimulating hormone is released by pituitary
Eyelids and eyebrows develop	Testes begin to descend
Lanugo hairs cover most of body	
6 Months	
Skin is wrinkled and red	Surfactant begins to be secreted
Decidua capsularis degenerates because of reduced blood supply	Tip of spinal cord is at S1 level
Lanugo hairs darken	
Odor detection and taste occur	
7 Months	
Eyelids begin to open	Sulci and gyri begin to appear on brain
Eyelashes are well developed	Subcutaneous fat storage begins
Scalp hairs are lengthening (longer than lanugo)	Testes are descending into scrotum
Skin is slightly wrinkled	Termination of splenic erythropoiesis occurs
Breathing movements are common	
8 Months	
Skin is pink and smooth	Regression of hyaloid vessels from lens occurs
Eyes are capable of pupillary light reflex	Testes enter scrotum
Fingernails have reached tips of fingers	
9 Months	
Toenails have reached tips of toes	Larger amounts of pulmonary surfactant are secreted
Most lanugo hairs are shed	Ovaries are still above brim of pelvis
Skin is covered with vernix caseosa	Testes have descended into scrotum
Attachment of umbilical cord becomes central in abdomen	Tip of spinal cord is at L3
About 1 L of amniotic fluid is present	Myelination of brain begins
Placenta weighs about 500 g	
Fingernails extend beyond fingertips	
Breasts protrude and secrete "witch's milk"	

PRINCIPALES ETAPES DU DEVELOPPEMENT DE LA PERIODE EMBRYONNAIRE



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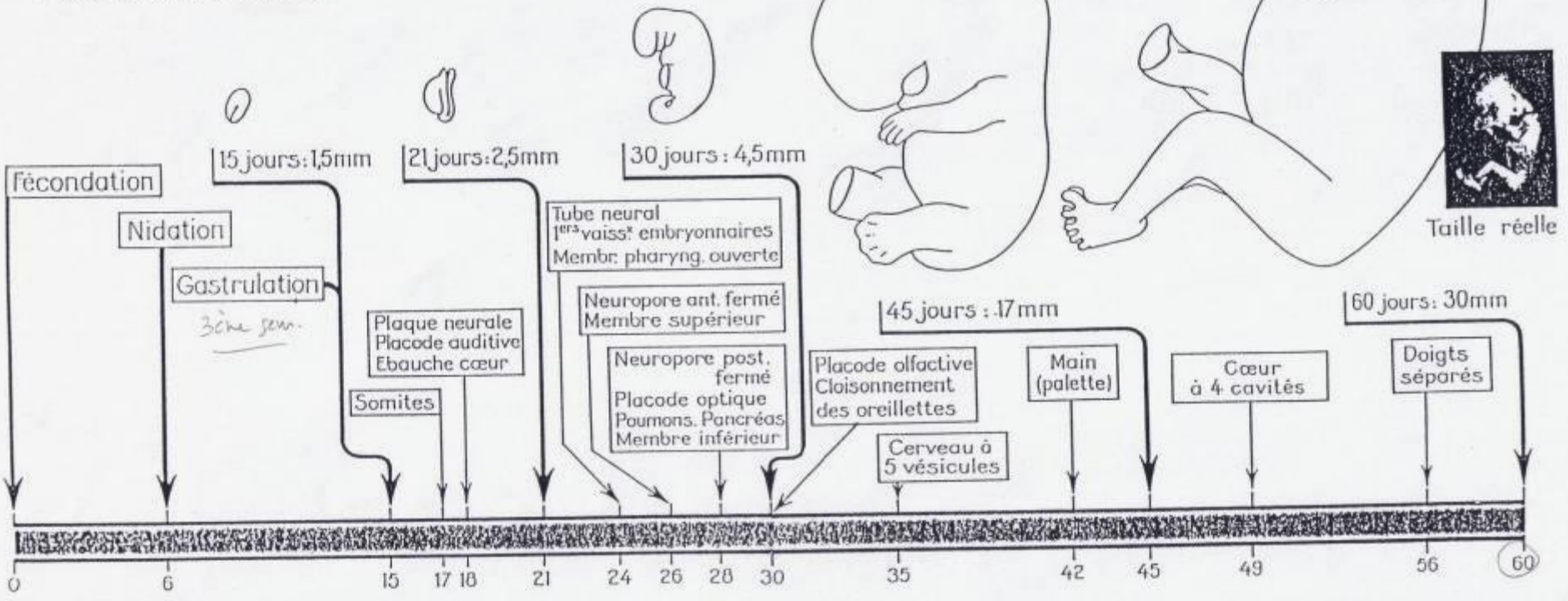
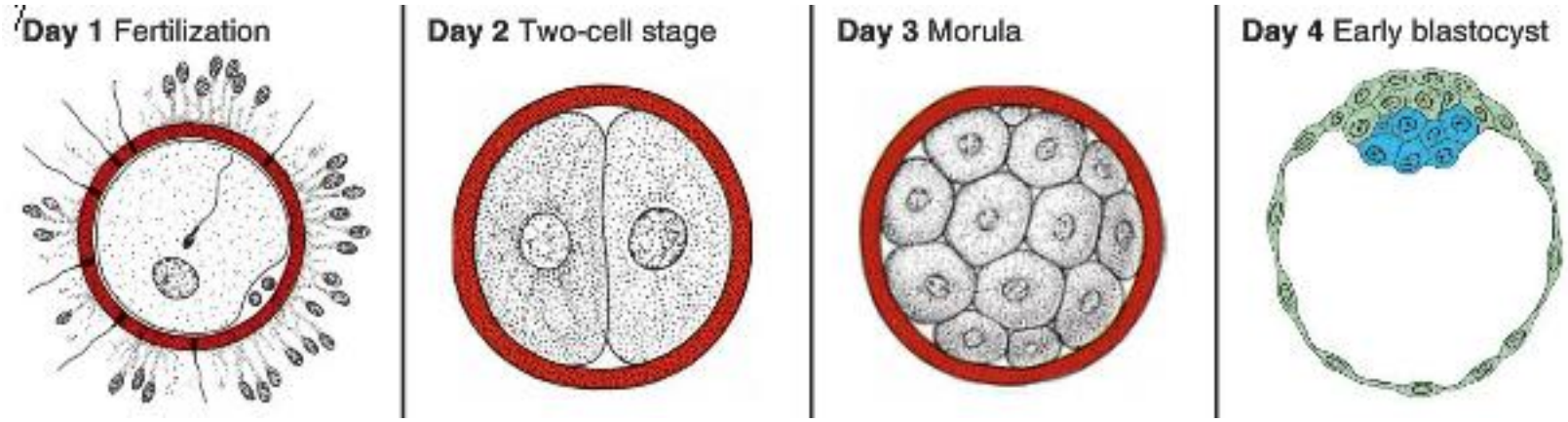
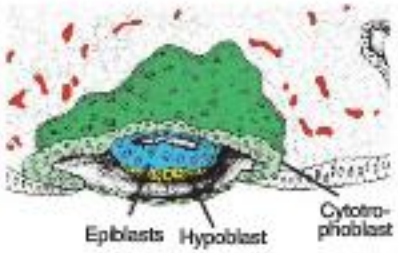


(les figures sont à l'échelle 5/1)

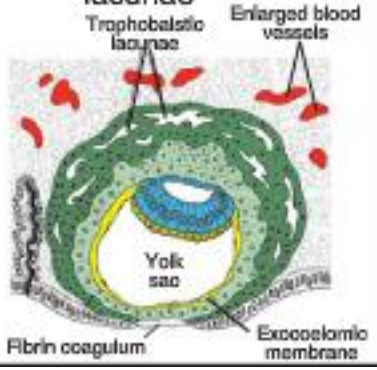
résumé de la période embryonnaire



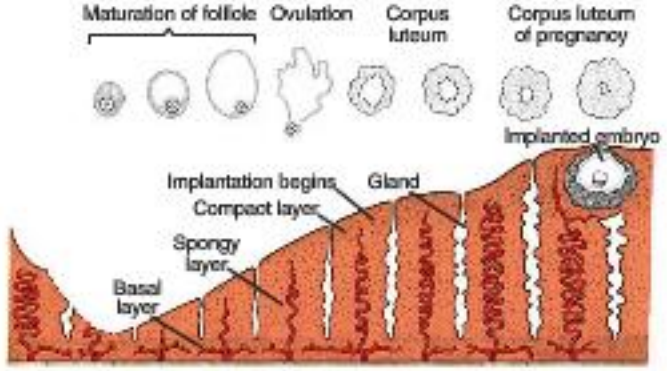
Day 8 Fertilization



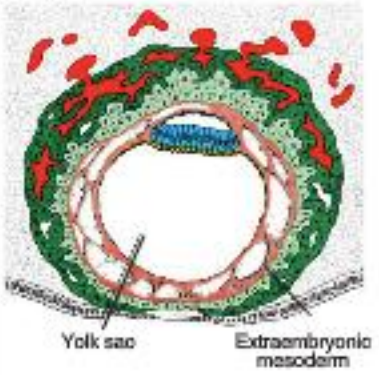
Day 9 Trophoblast with lacunae



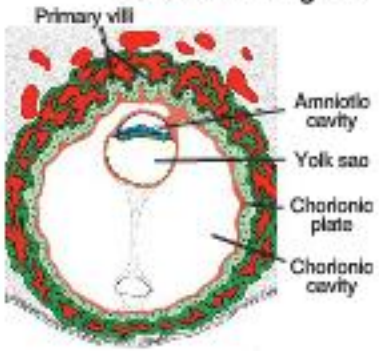
Day 10-11 Embryo in uterus 10-11 days after ovulation



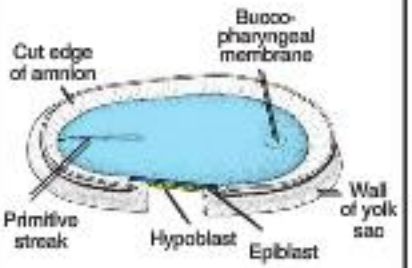
Day 12 Fertilization



Day 13 Uteroplacental circulation begins

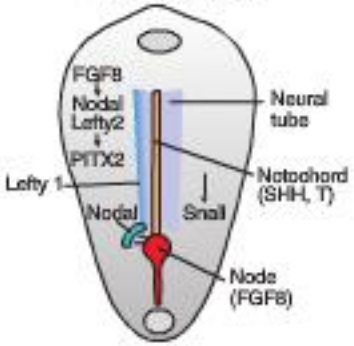


Day 14 Embryonic disc: dorsal view

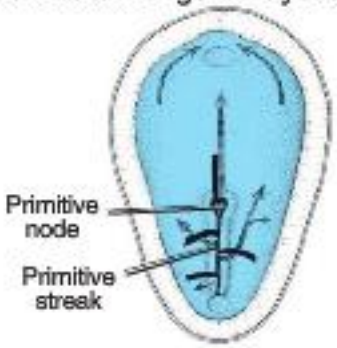


Development Week 2

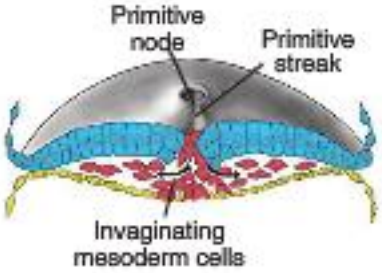
Day 15 Laterality established



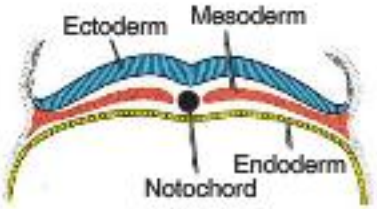
Day 16 Gastrulation: Formation of germ layers



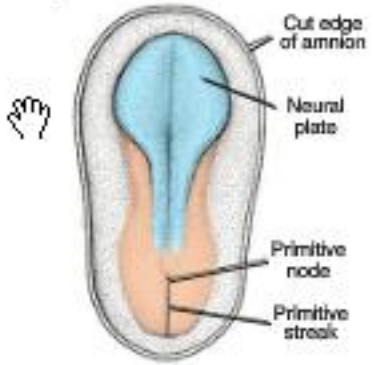
Day 17 Epiblast forms germ layers



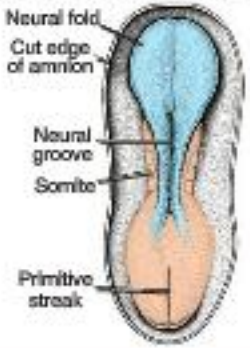
Day 18 Trilaminar embryonic disc



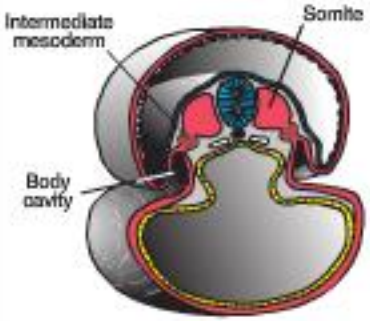
Day 19 CNS induction



Day 20 Neurulation: Neural folds elevate



Day 21 Transverse section through somite region

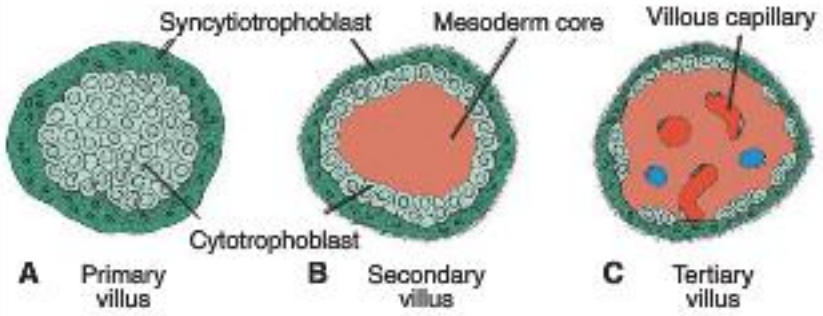


Development Week 3

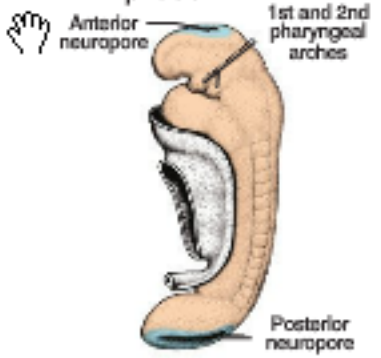
Day 22 Neural tube closure begins

Day 23 Neural tube zippers

Day 24-25 Villus formation continues in the placenta



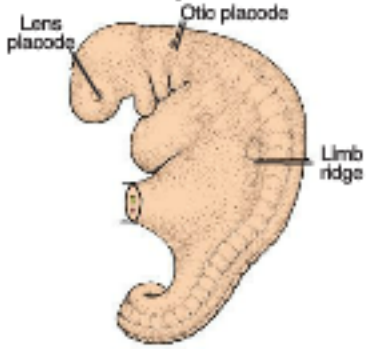
Day 26 Pharyngeal arches present



Day 27

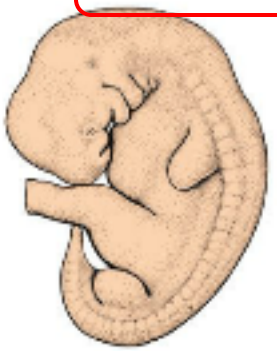
Approx. Age (Days)	No. of Somites
20	1-4
21	4-7
22	7-10
23	10-13
24	13-17
25	17-20
26	20-23
27	23-26
28	26-29
30	34-35

Day 28 Neurulation complete

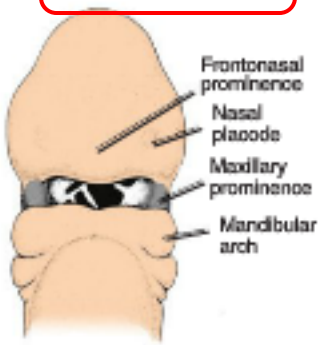


Development Week 4

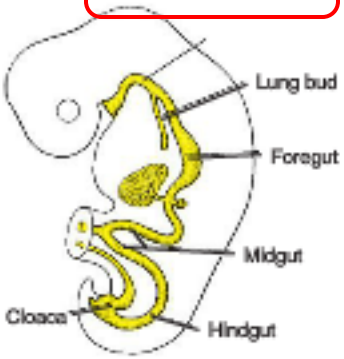
Day 29 Arm and leg buds



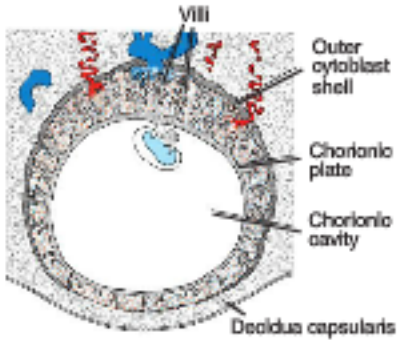
Day 30 Developing face



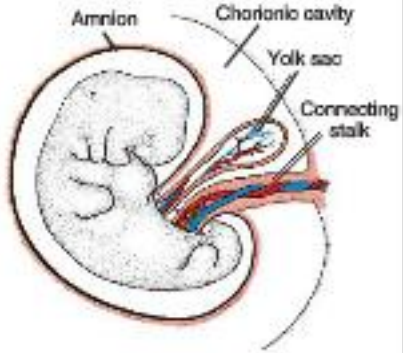
Day 31 Gut development



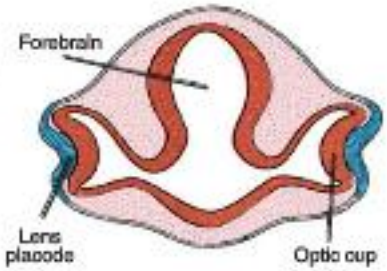
Day 32 Embryo in chorionic cavity



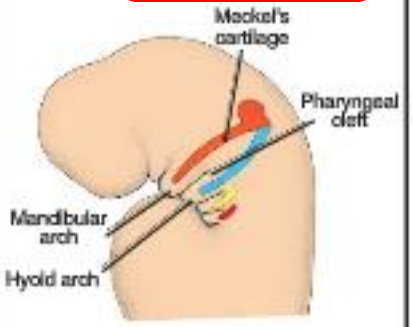
Day 33 Umbilical ring



Day 34 Optic cup and lens placode



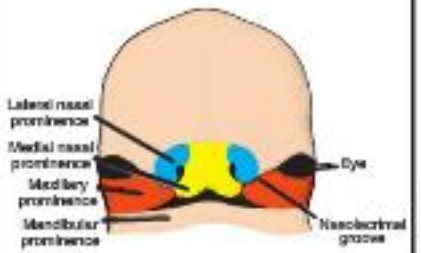
Day 35 Branchial arches and clefts



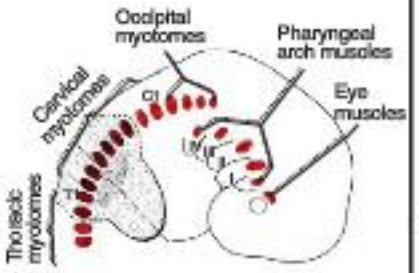
Development Week 5

Day 36 Physiological umbilical hernia

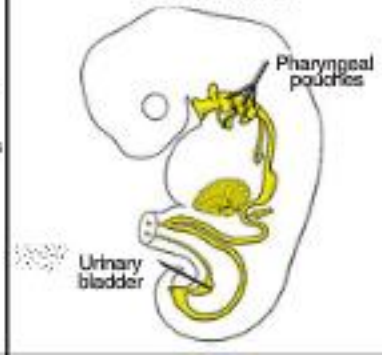
Day 37 Developing face



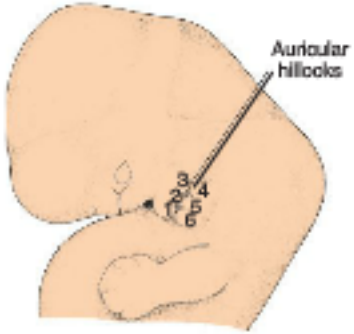
Day 38 Muscle development



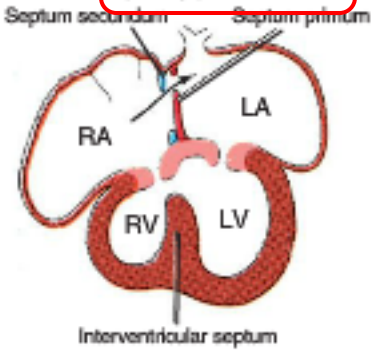
Day 39 Endodermal derivatives



Day 40 Auricular hillocks



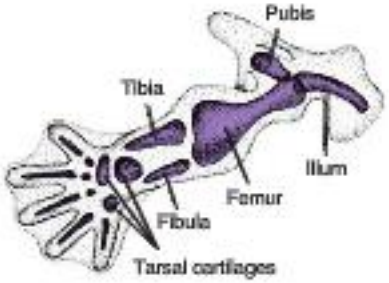
Day 41 Atrial septum formed



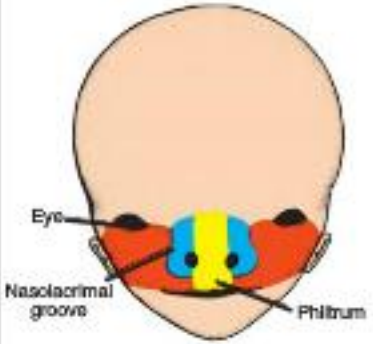
Day 42 Digit formation

Development Week 6

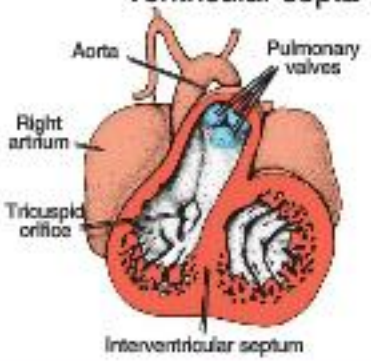
Day 43 Limb cartilages and digital rays



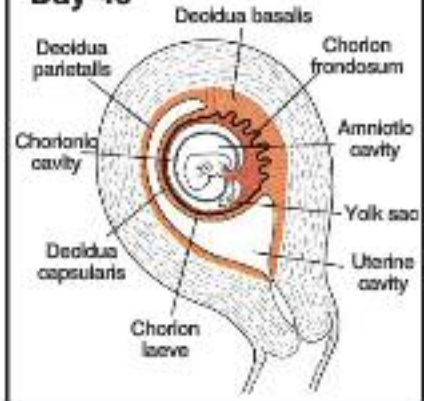
Day 44 Developing face



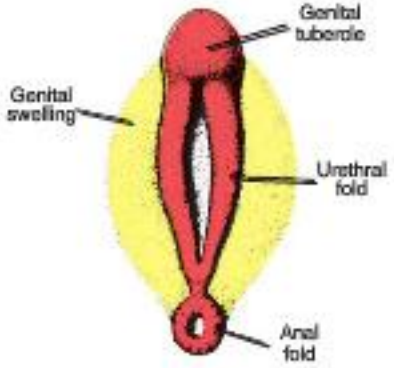
Day 45 Conotruncal and ventricular septa



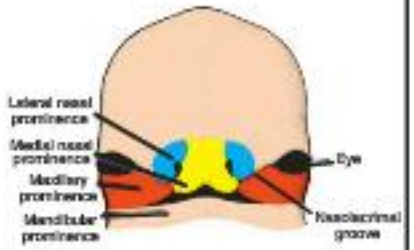
Day 46



Day 47 External genitalia



Day 48 Facial prominences fused



Day 49 Digits present, eyelids forming

Development Week 7

TABLE 5.4 Summary of Key Events During the Embryonic Period

Days	Somites	Length (mm)	Figure	Characteristic Features
14–15	0	0.2	5.1*A*	Appearance of primitive streak
16–18	0	0.4	5.1*B*	Notochordal process appears; hemopoietic cells in yolk sac
19–20	0	1.0–2.0	5.2*A*	Intraembryonic mesoderm spread under cranial ectoderm; primitive streak continues; umbilical vessels and cranial neural folds beginning to form
20–21	1–4	2.0–3.0	5.2*B, C*	Cranial neural folds elevated, and deep neural groove established; embryo beginning to bend
22–23	5–12	3.0–3.5	5.5*A, B*; 5.6; 5.7	Fusion of neural folds begins in cervical region; cranial and caudal neuropores open widely; visceral arches 1 and 2 present; heart tube beginning to fold
24–25	13–20	3.0–4.5	5.8*A*	Cephalocaudal folding under way; cranial neuropore closing or closed; optic vesicles formed; otic placodes appear
26–27	21–29	3.5–5.0	5.8*B*; 5.20*A, B*	Caudal neuropore closing or closed; upper limb buds appear; 3 pairs of visceral arches
28–30	30–35	4.0–6.0	5.8*B*	Fourth visceral arch formed; hindlimb buds appear; otic vesicle and lens placode
31–35		7.0–10.0	5.19	Forelimbs paddle-shaped; nasal pits formed; embryo tightly C-shaped
36–42		9.0–14.0	5.21	Digital rays in hand and footplates; brain vesicles prominent; external auricle forming from auricular hillocks; umbilical herniation initiated
43–49		13.0–22.0	5.23	Pigmentation of retina visible; digital rays separating; nipples and eyelids formed; maxillary swellings fuse with medial nasal swellings as upper lip forms; prominent umbilical herniation
50–56		21.0–31.0	5.24	Limbs long, bent at elbows, knees; fingers, toes free; face more human-like; tail disappears; umbilical herniation persists to end of third month

Table 5–1 Criteria for Estimating Developmental Stages in Human Embryos

AGE (DAYS)	FIGURE REFERENCE	CARNEGIE STAGE	NO. OF SOMITES	LENGTH (MM)*	MAIN EXTERNAL CHARACTERISTICS†
20–21	5–1*A*$_1$	9	1–3	1.5–3.0	Flat embryonic disc. Deep neural groove and prominent neural folds. One to three pairs of somites present. Head fold evident.
22–23	5–8*A* 5–9*A,B*	10	4–12	1.0–3.5	Embryo straight or slightly curved. Neural tube forming or formed opposite somites, but widely open at rostral and caudal neuropores. First and second pairs of pharyngeal arches visible.
24–25	5–8*C* 5–10	11	13–20	2.5–4.5	Embryo curved owing to head and tail folds. Rostral neuropore closing. Otic placodes present. Optic vesicles formed.
26–27	5–8*D* 5–11	12	21–29	3.0–5.0	Upper limb buds appear. Rostral neuropore closed. Caudal neuropore closing. Three pairs of pharyngeal arches visible. Heart prominence distinct. Otic pits present.
28–30	5–8*E* 5–12	13	30–35	4.0–6.0	Embryo has C-shaped curve. Caudal neuropore closed. Upper limb buds are flipper-like. Four pairs of pharyngeal arches visible. Lower limb buds appear. Otic vesicles present. Lens placodes distinct. Tail-like caudal eminence present.
31–32	5–15 5–16	14	‡	5.0–7.0	Upper limbs are paddle shaped. Lens pits and nasal pits visible. Optic cups present.
33–36		15		7.0–9.0	Hand plates formed; digital rays visible. Lens vesicles present. Nasal pits prominent. Lower limbs are paddle shaped. Cervical sinuses visible.
37–40		16		8.0–11.0	Footplates formed. Pigment visible in retina. Auricular hillocks developing.
41–43	5–17	17		11.0–14.0	Digital rays clearly visible in hand plates. Auricular hillocks outline future auricle of external ear. Trunk beginning to straighten. Cerebral vesicles prominent.
44–46		18		13.0–17.0	Digital rays clearly visible in footplates. Elbow region visible. Eyelids forming. Notches between the digital rays in the hands. Nipples visible.
47–48	5–18	19		16.0–18.0	Limbs extend ventrally. Trunk elongating and straightening. Midgut herniation prominent.
49–51	5–19*C*	20		18.0–22.0	Upper limbs longer and bent at elbows. Fingers distinct but webbed. Notches between the digital rays in the feet. Scalp vascular plexus appears.
52–53	5–19	21		22.0–24.0	Hands and feet approach each other. Fingers are free and longer. Toes distinct but webbed.
54–55		22		23.0–28.0	Toes free and longer. Eyelids and auricles of external ears more developed.
56	5–20 5–21	23		27.0–31.0	Head more rounded and shows human characteristics. External genitalia still have indistinct appearance. Distinct bulge still present in umbilical cord, caused by herniation of intestines. Caudal eminence ("tail") has disappeared.

*The embryonic lengths indicate the usual range. In stages 9 and 10, the measurement is greatest length; in subsequent stages, crown–rump measurements are given (see Fig. 5-20).
†Based on Nishimura et al (1974), O'Rahilly and Müller (1987), Shiota (1991), and Gasser (2004).
‡At this and subsequent stages, the number of somites is difficult to determine and so is not a useful criterion.