Genetics and Birth Defects

Introduction to Foetopathology

Verdadero Retrato, y Relacion Anatomica de las dos Niñas unidas, que nacieron en Barcelona.

Permanent Education Course in Human Genetics

Dr Christian Dugauquier IPG Gosselies

IPG
• ANATOMOPATHOLOGIE
• GÉNÉTIQUE CLINIQUE
• BIOLOGIE MOLÉCULAIRE ET CELLULAIRE

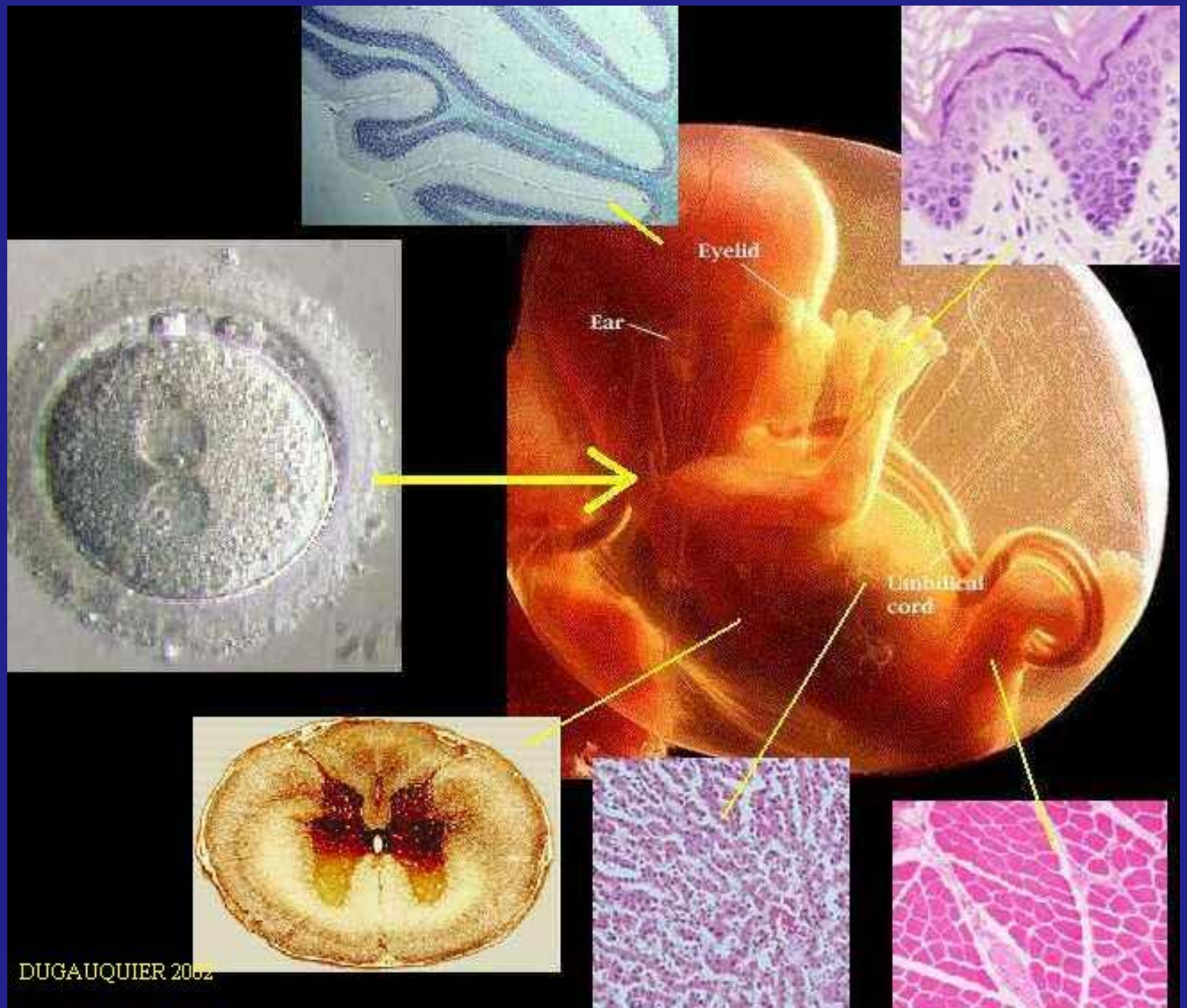
BeSHG

« Menu »

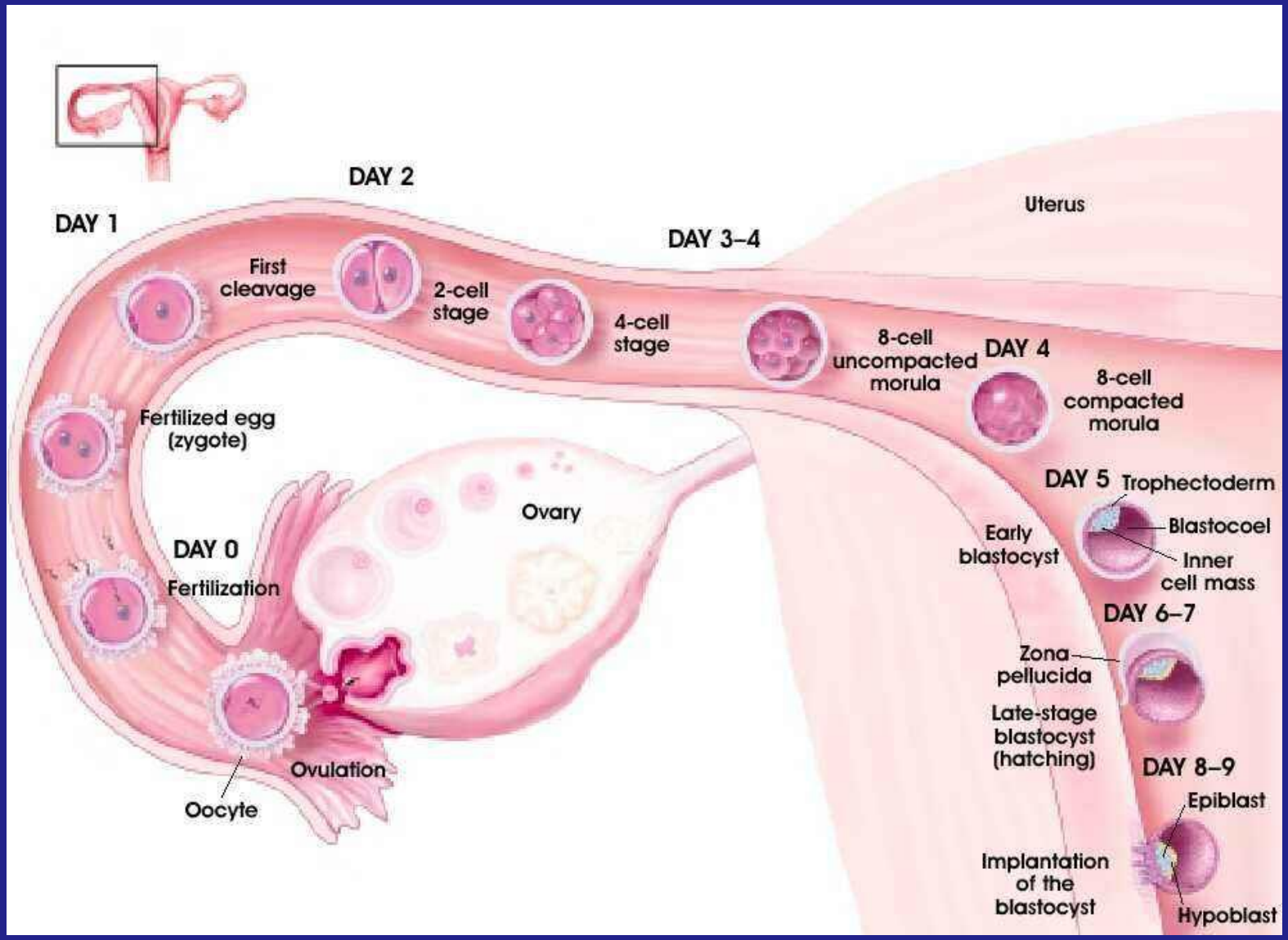
- 1.Overview of normal development
- 2.Definition and basic principles
- 3.Illustrations of common anomalies

Ref: Thompson & Thompson/ Chapter 14

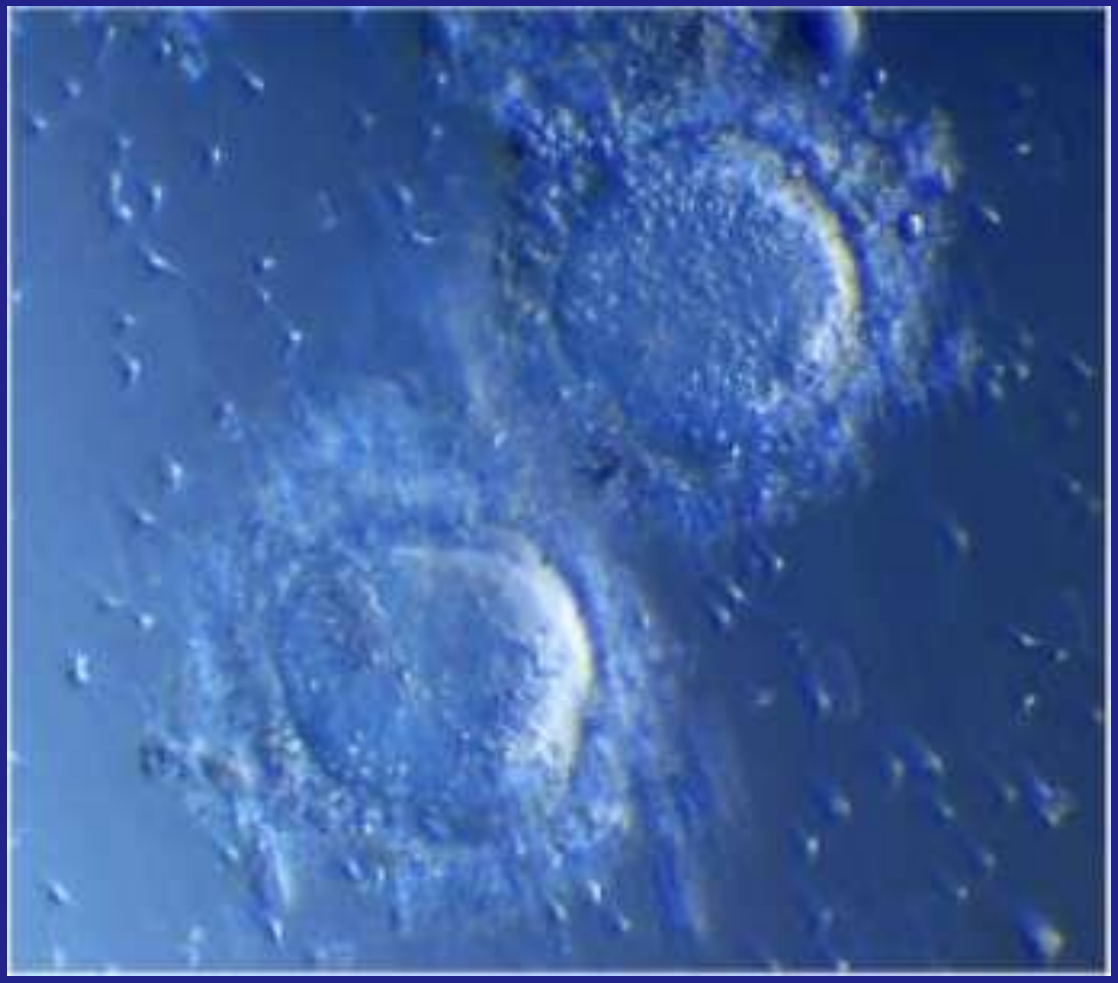
1. Normal Development



Fecondation > implantation

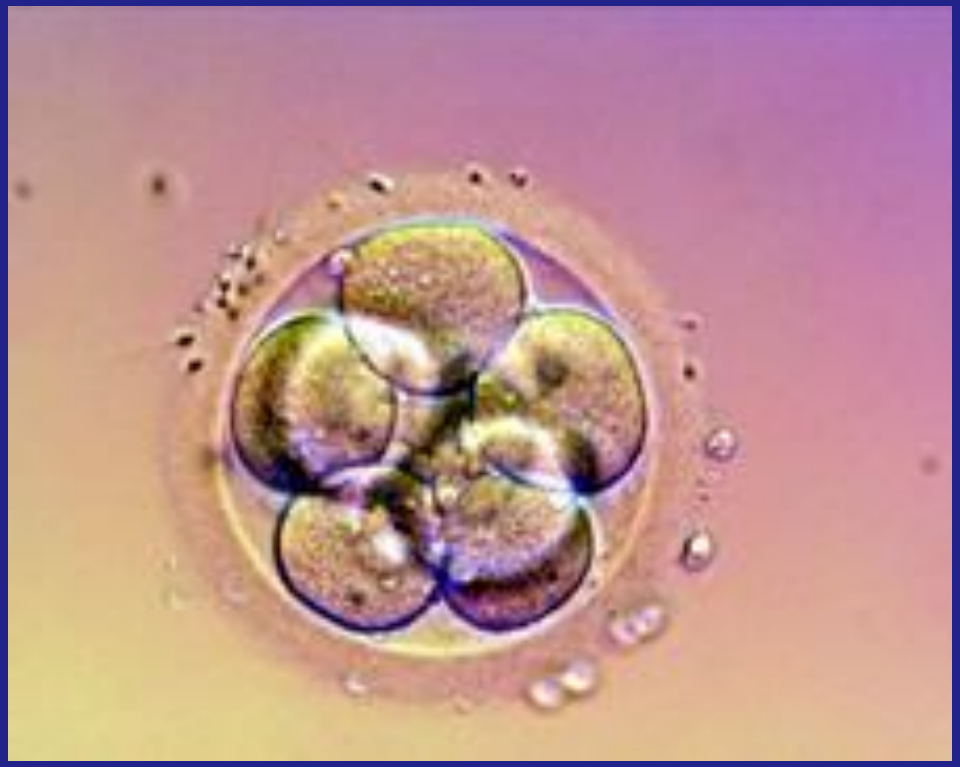


Fécondation

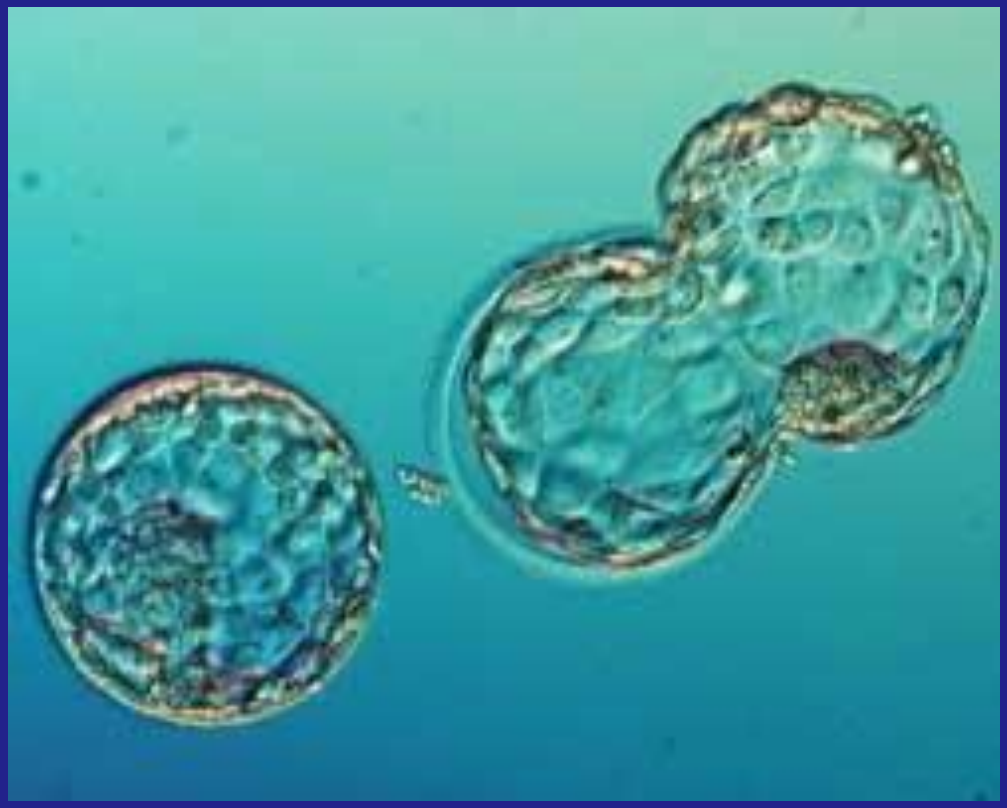


Expulsion of second polar body

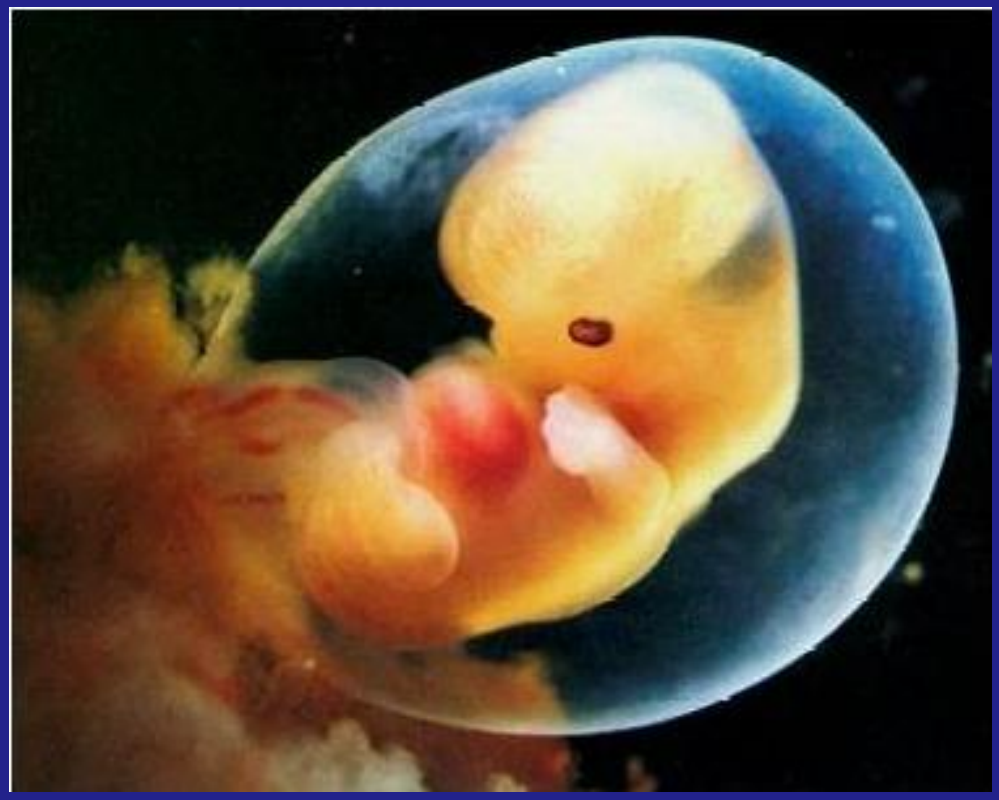
First divisions > morula



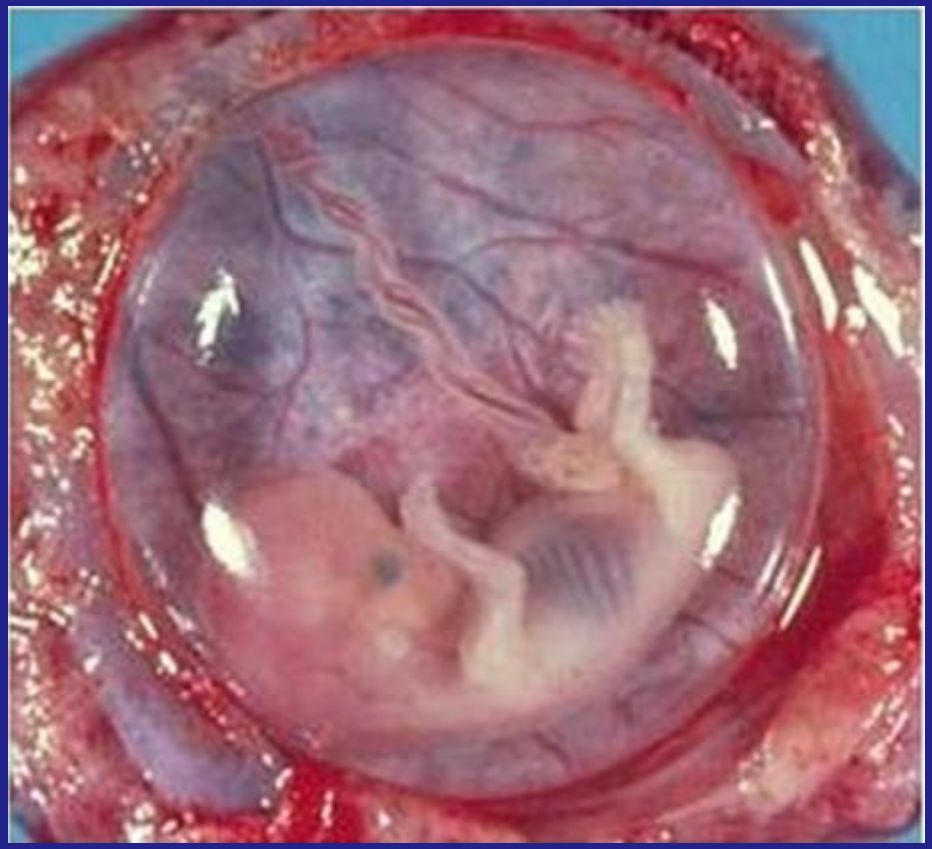
Blastocyst > hatching



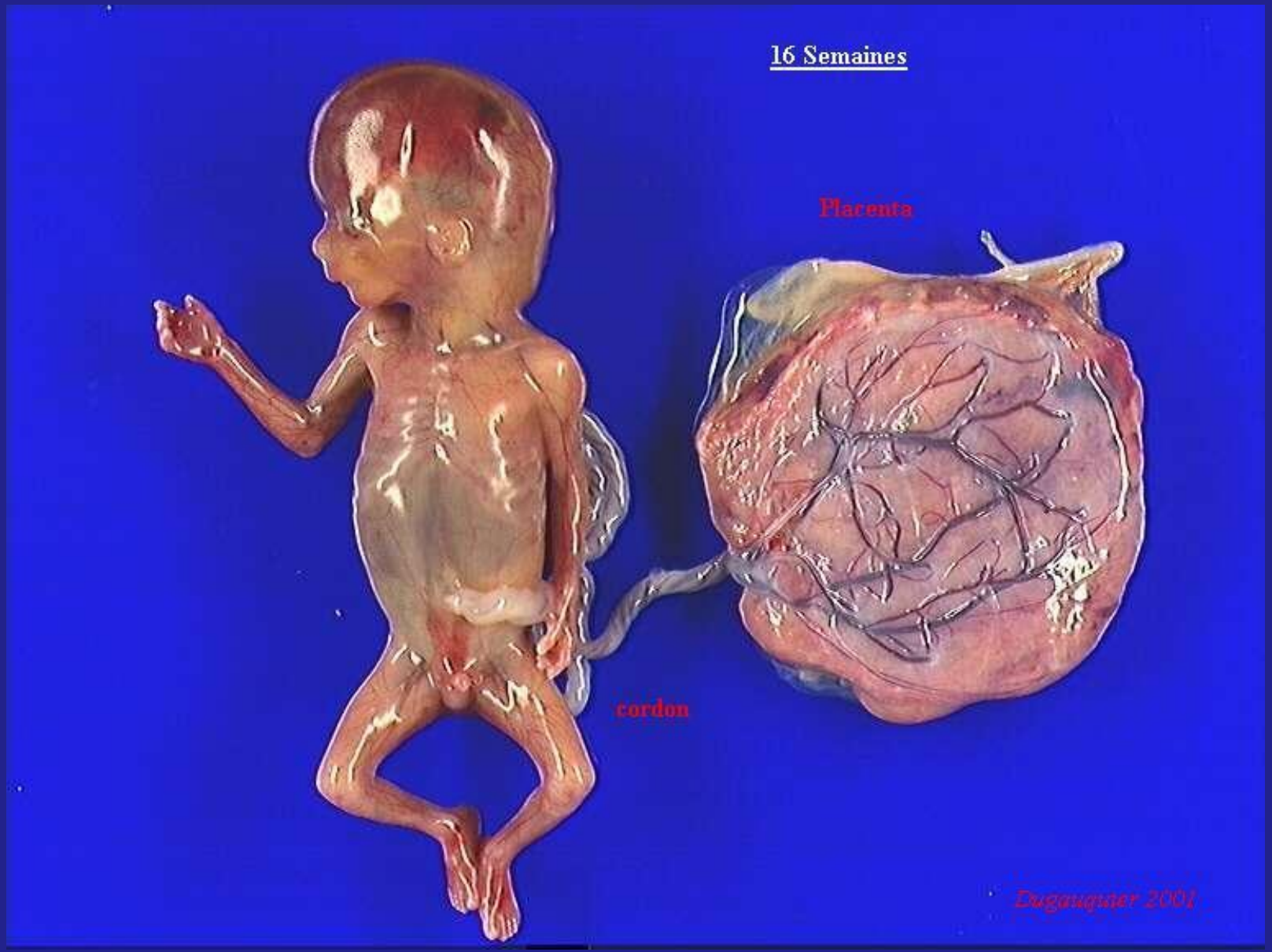
4 Week



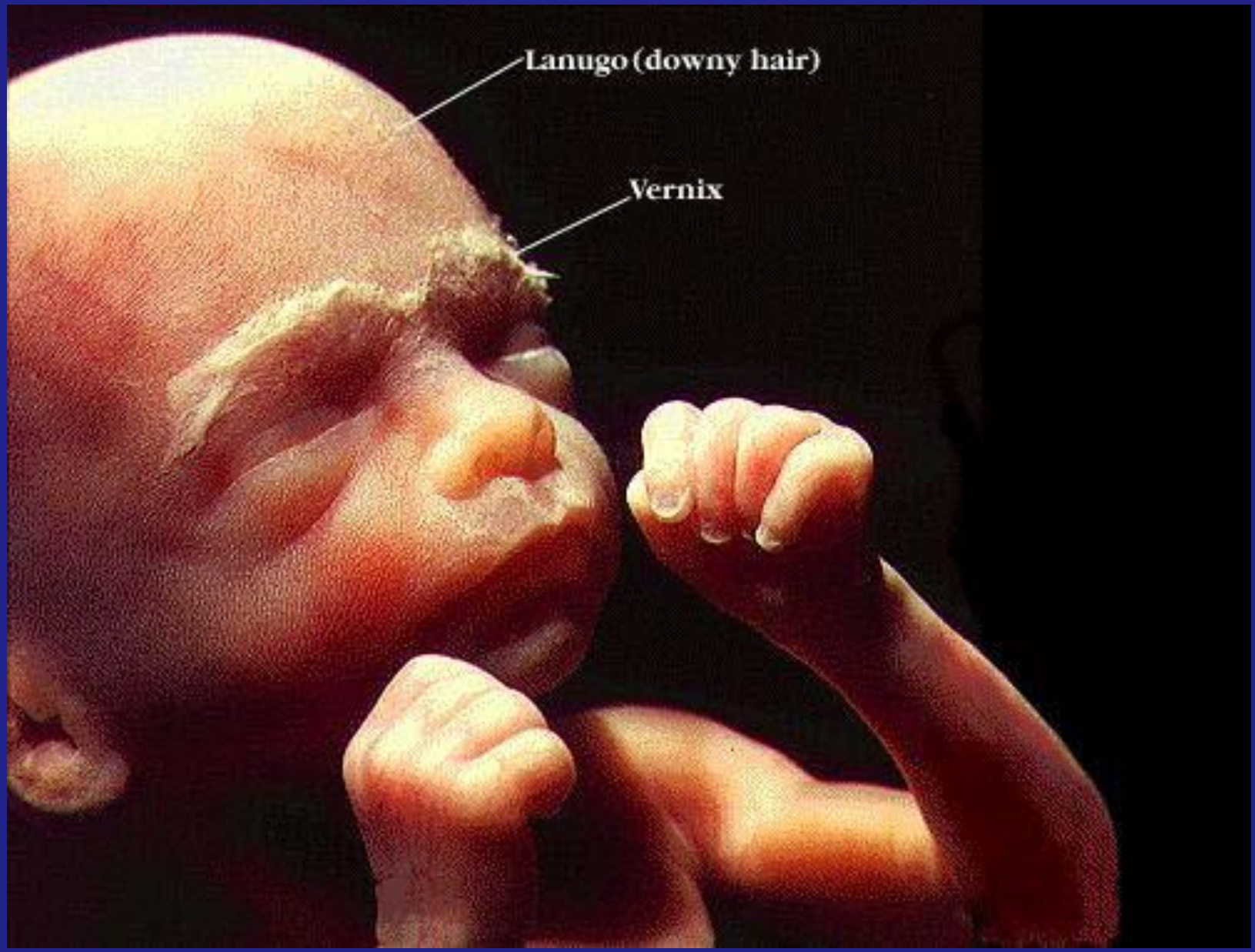
7 Week



9 Week



16 Week



22 Week

40 Week: Welcome to the world

2. Basic principles

- Causes of human malformation
- relative frequency
- Induction window

Causes of human malformation

- Single Gene mutation 20%
- Chromosomal imbalance 25%

- Environmental 5%
  - Radiation <1%
  - Infection 3%
  - Iatrogenic / Toxic 2%

- **Complex (unknown) 50 % !!!**

Relative frequency

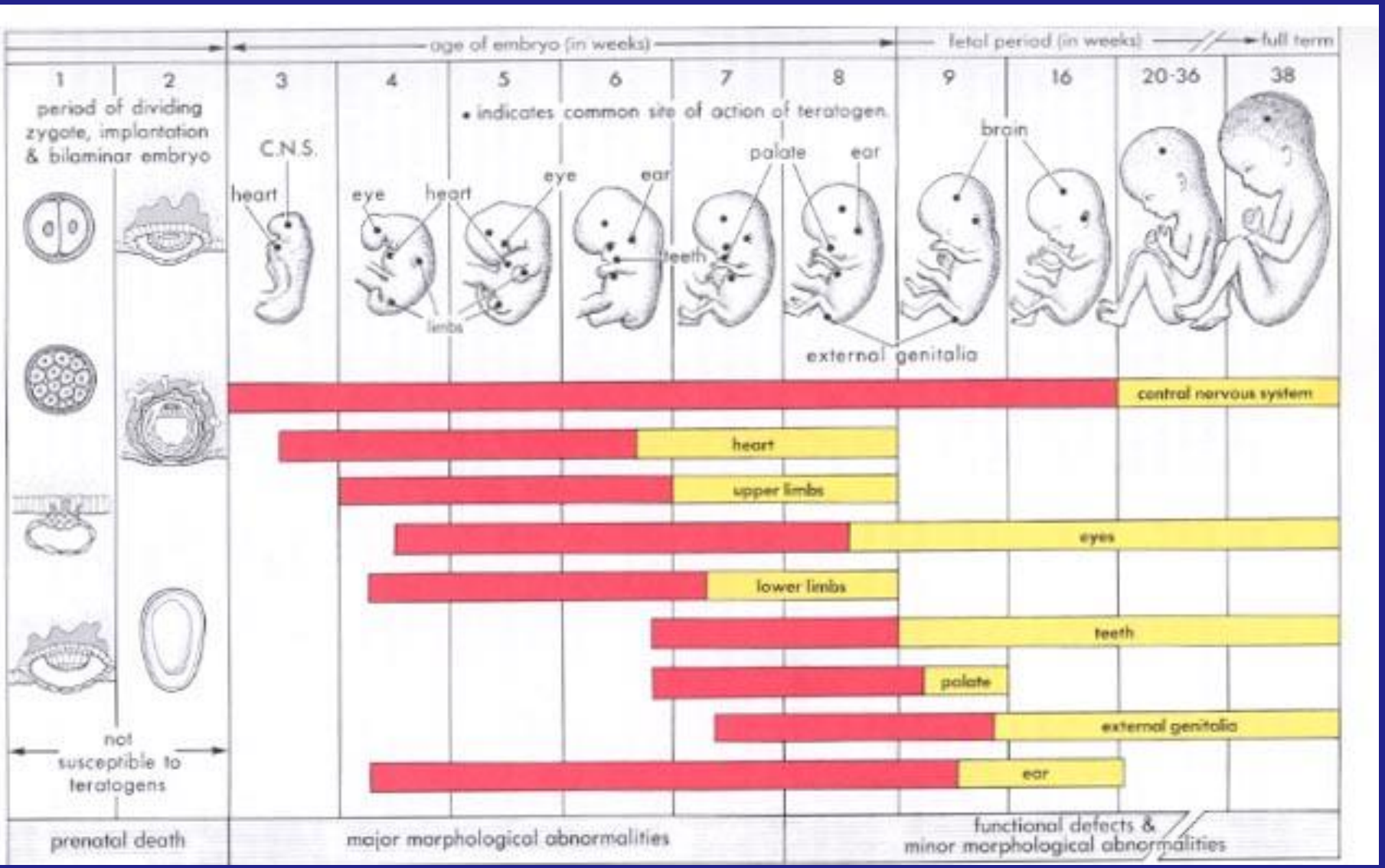
- For 1000 live birth (in percent):

– cardiac anomaly	4 à 5 %
– anencephaly	2
– hypospadias	1,8
– hydrocephaly	1,4
– spina bifida	1,4
– polydactyly	1,1
– cleft palate	0,6
– diaphragmatic hernia	0,5
– cleft lip	0,4
– omphalocele	0,4
– renal agenesis	0,4
– anal imperforation	0,4

Induction period

Malformation	*before:*
cyclopia, sirenomelia	*23 d*
anencephaly	*26 d*
esophageal atresia	*30 d*
transposition of great vessels	*34 d*
cleft lip	*36 d*
Diaphragmatic hernia	*6 week*
Cleft palate	*9 week*
omphalocele	*10 week*
hypospadias	*12 week*

Induction period > sensibility to teratogenic agents



Malformation & Disruption

Malformation

morphological defect of an organ, part of an organ or a larger region resulting from an intrinsically abnormal developmental process

Ex: polydactyly, holoprosencephaly.

Disruption

morphological defect of an organ, part of an organ or a larger region resulting from the extrinsic breakdown of, or interference with,

an originally normal developmental process

Ex: amniotic band

Sequence & Syndrome

Sequence

Initial isolated defect or malformation cause a cascade of secondary effects.

Ex: Potter's Sequence

Syndrome

Primary defect cause multiples abnormalities in parallel.

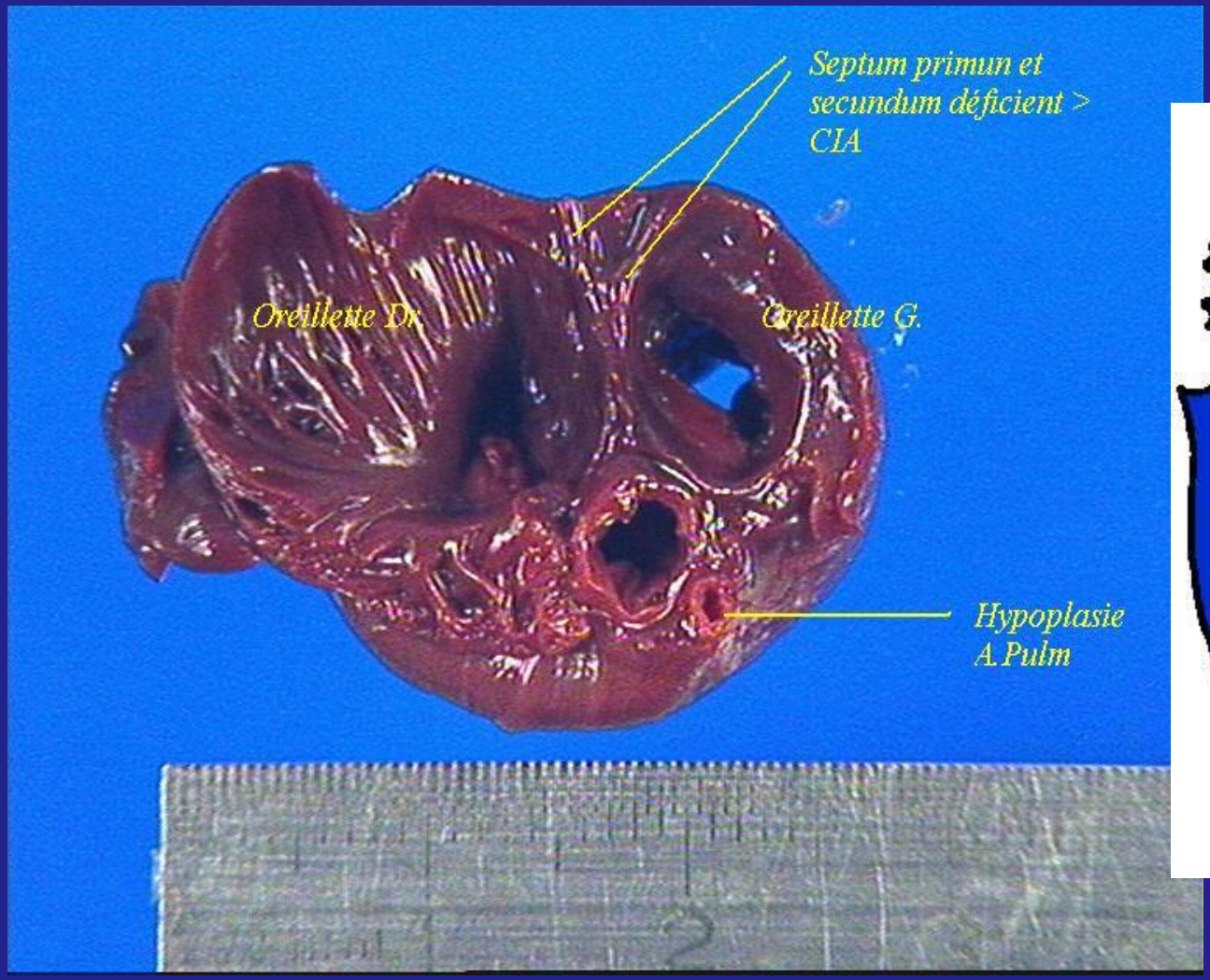
Ex: Trisomy 21

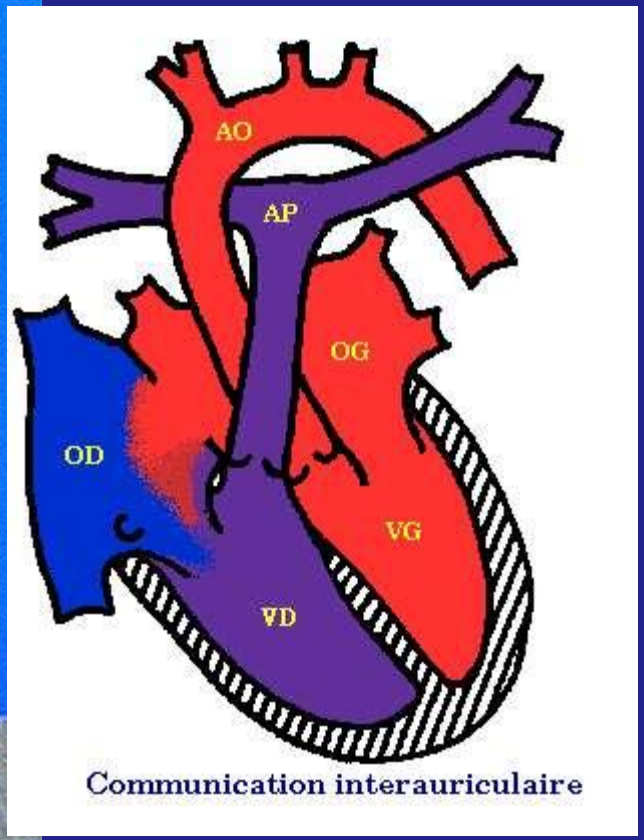
3. **Illustrations**

- By System:
  - Heart
  - Central nervous system
  - Urogenital
  - Lungs
  - Digestive system
  - Musculoskeletal
- Particular syndromes
- Chromosomal aberration

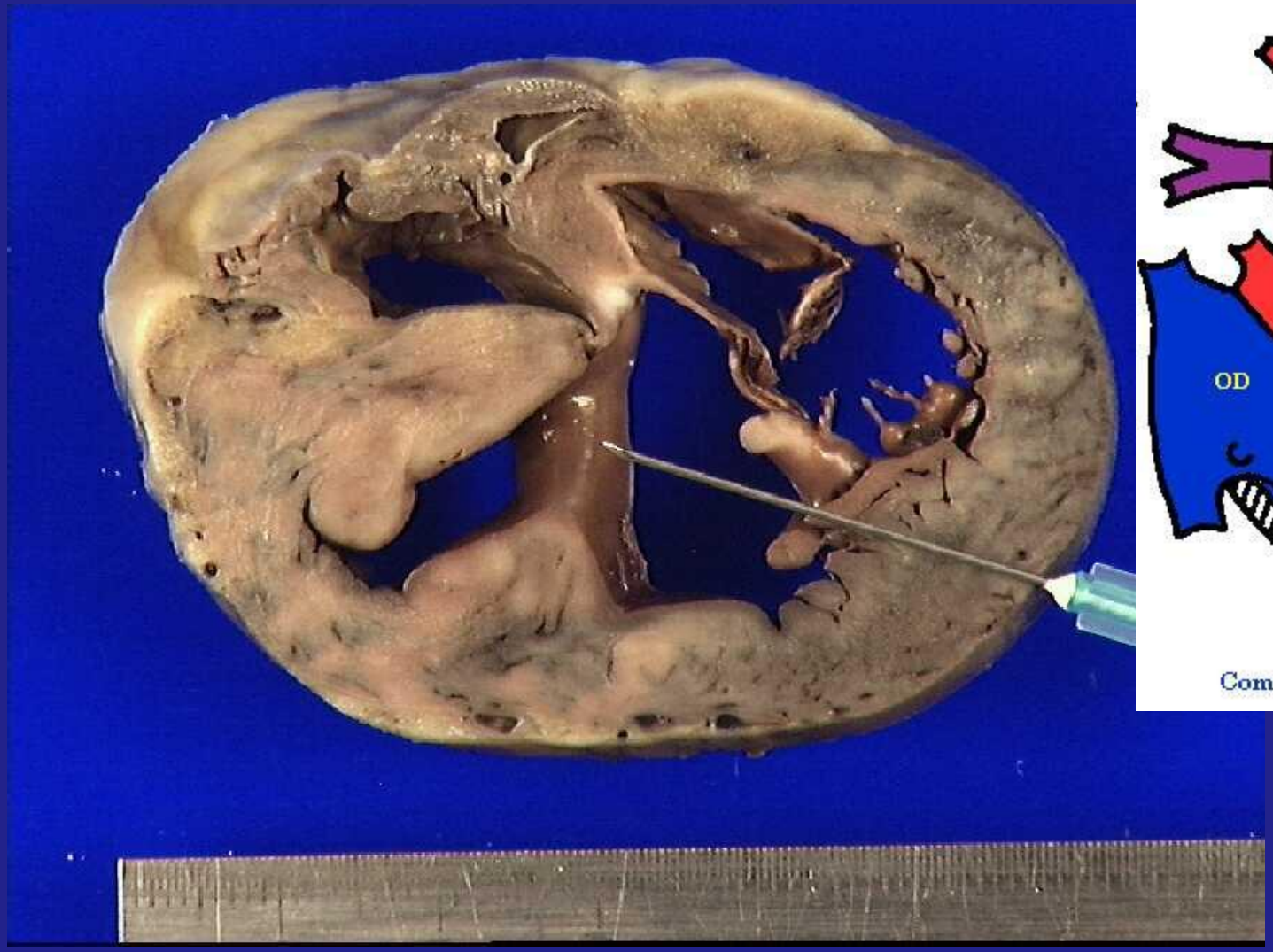
Heart

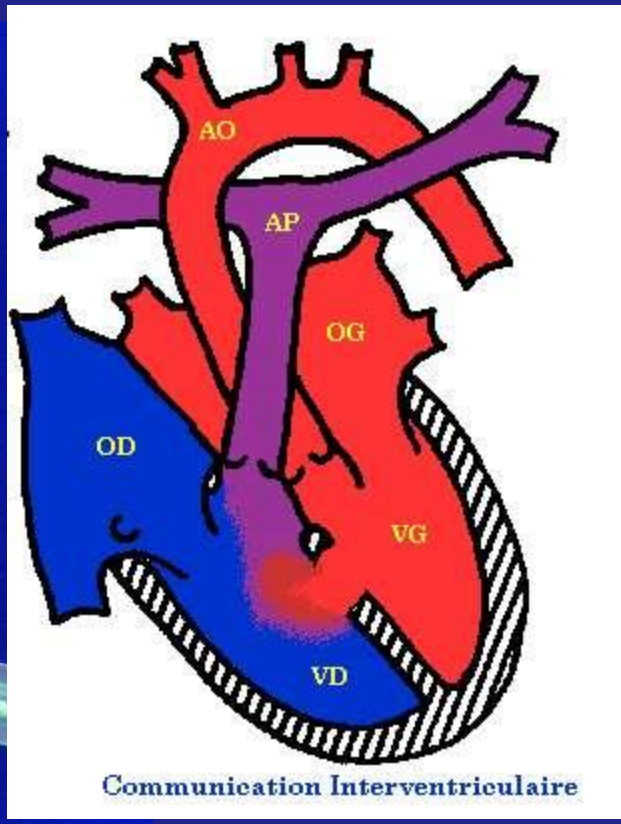
- CIA = 10%


Septum primun et
secundum déficient >
CIA
Oreillette Dr.
Oreillette G.
Hypoplasie
A.Pulm

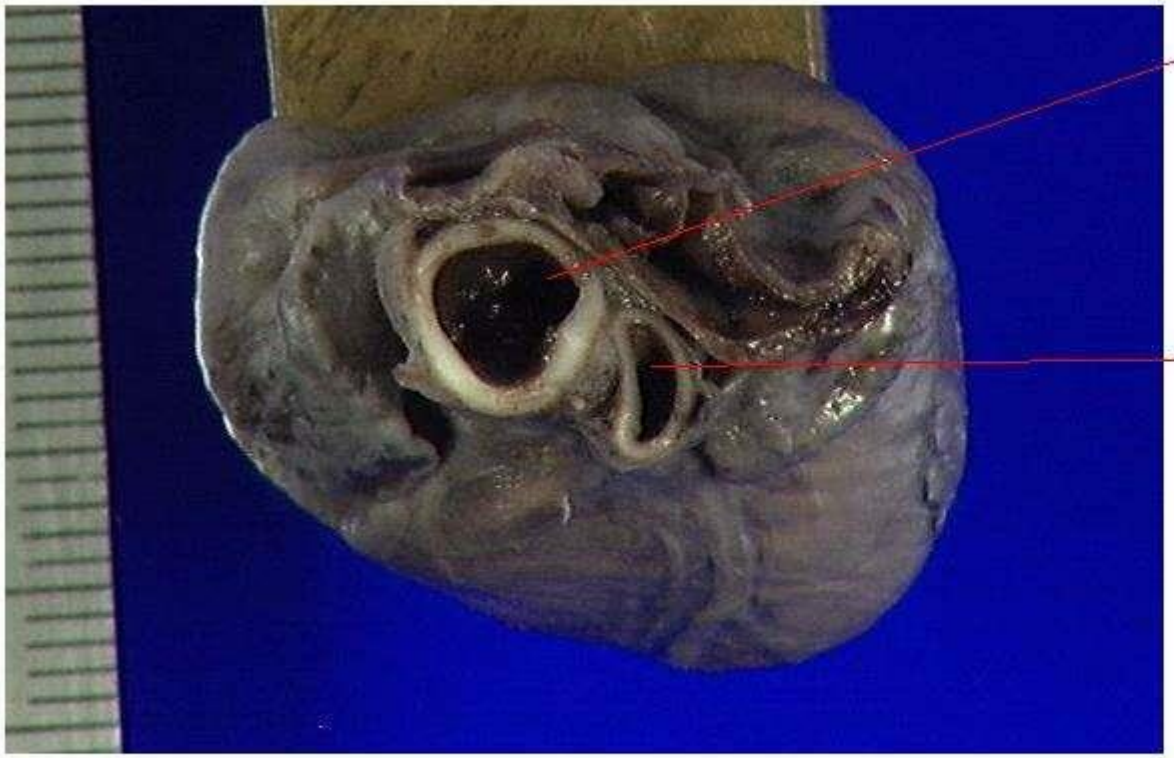

AO
AP
OG
OD
VG
VD
Communication interauriculaire

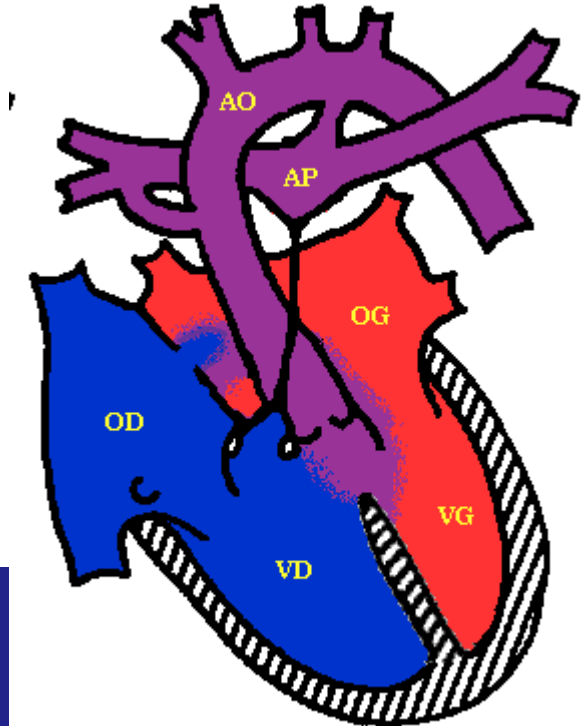
CIV +/- 20 %





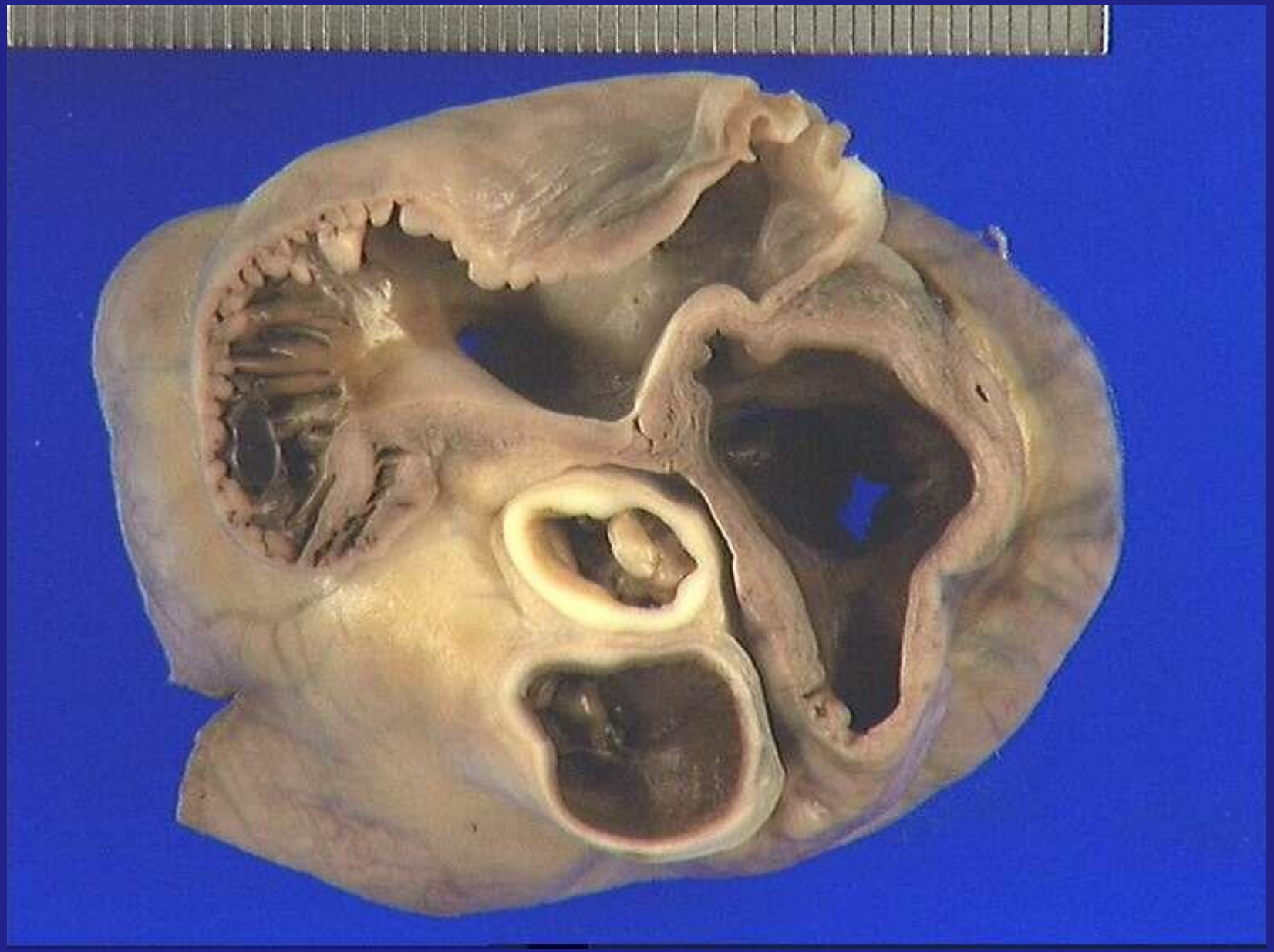
Pulmonary stenosis



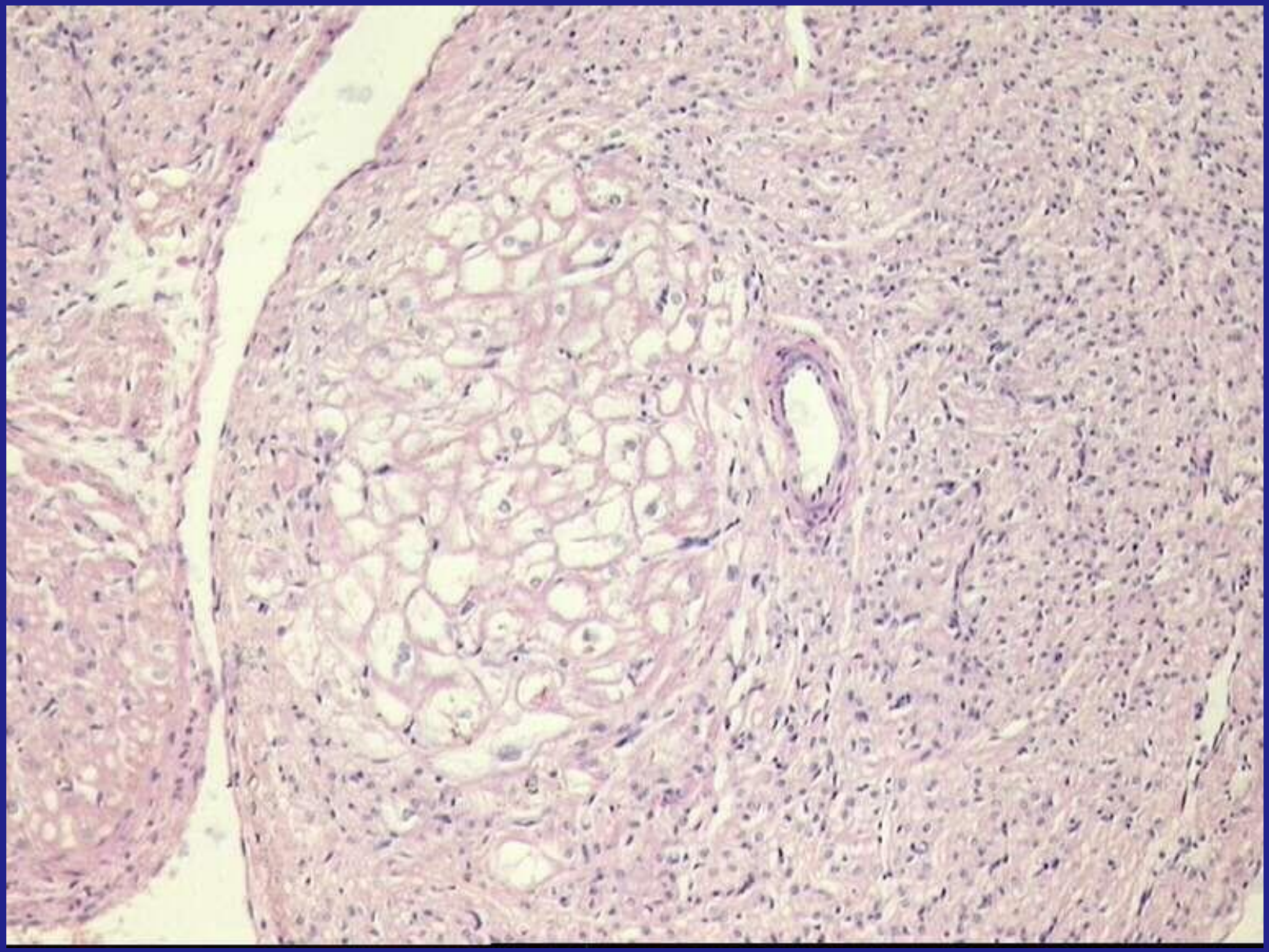


ATRESIE PULMONAIRE AVEC CIV

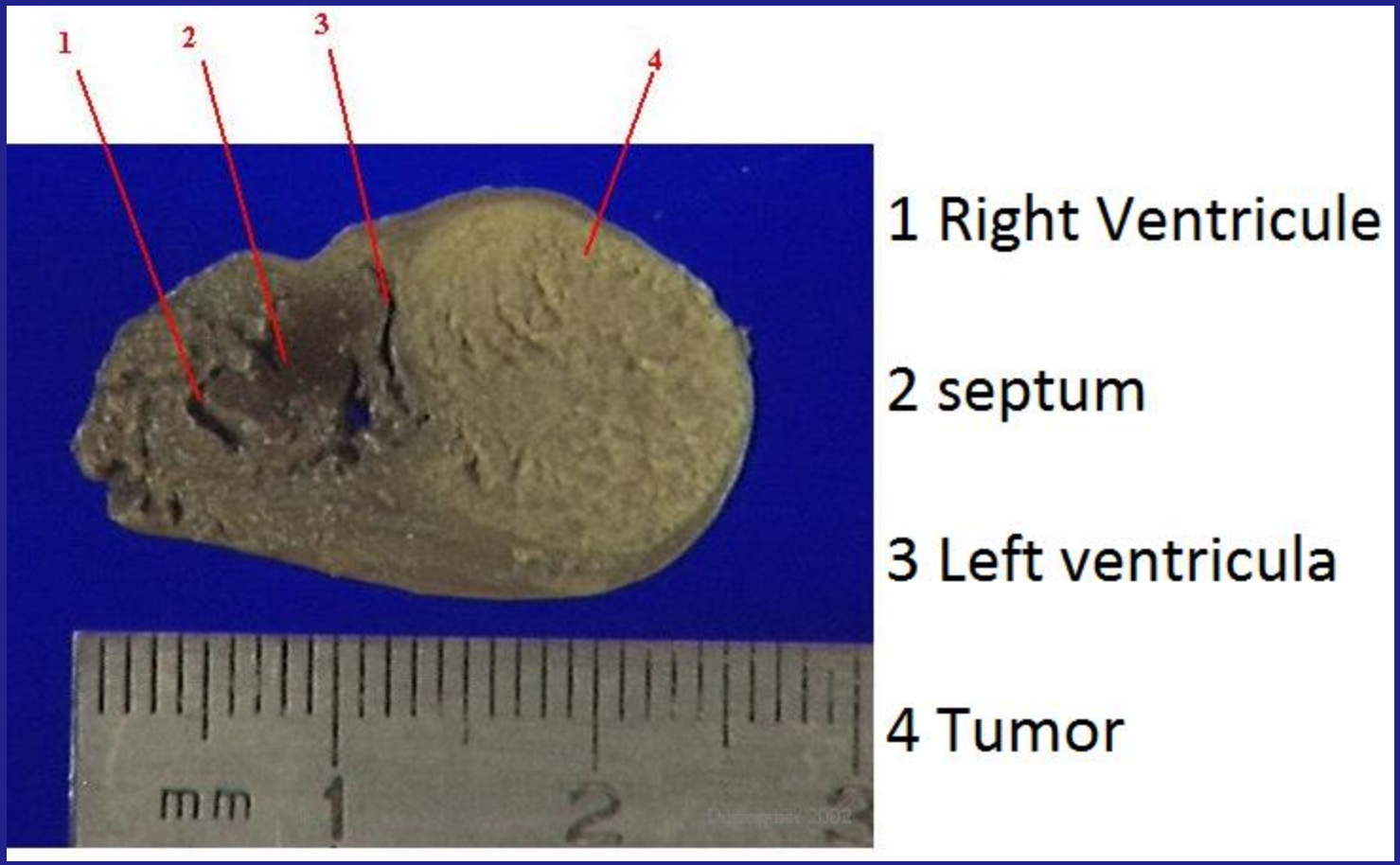
Aortic stenosis



Tumors: rhabdomyoma, teratoma, lipoma

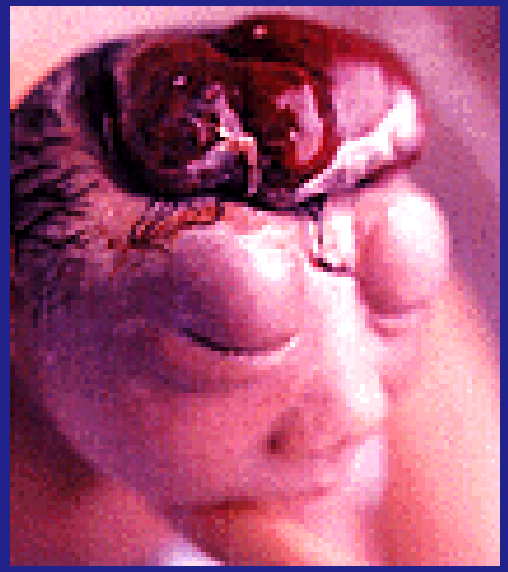


Cardiac teratoma > cardiac failure> IU Death

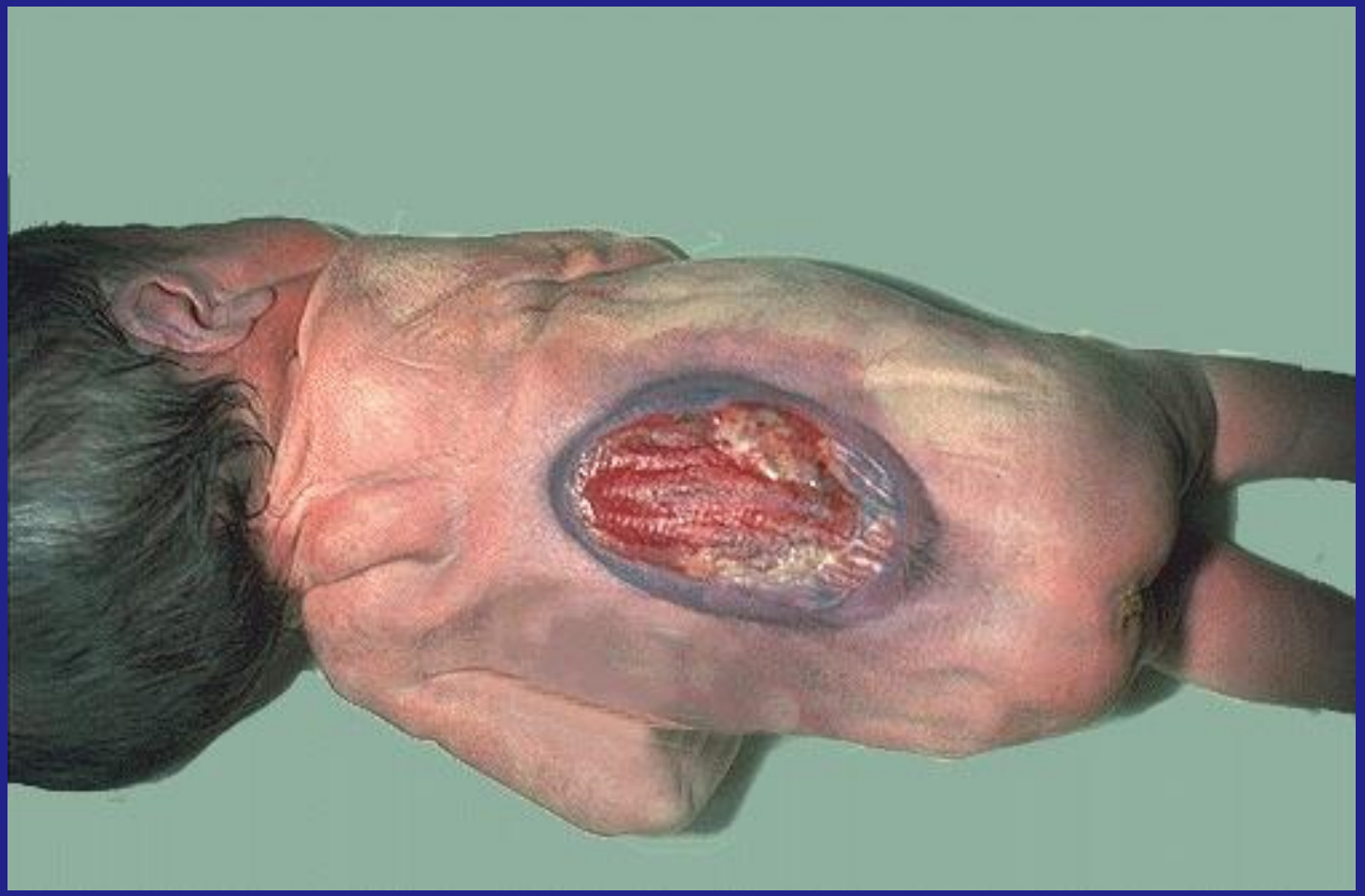


Central nervous system

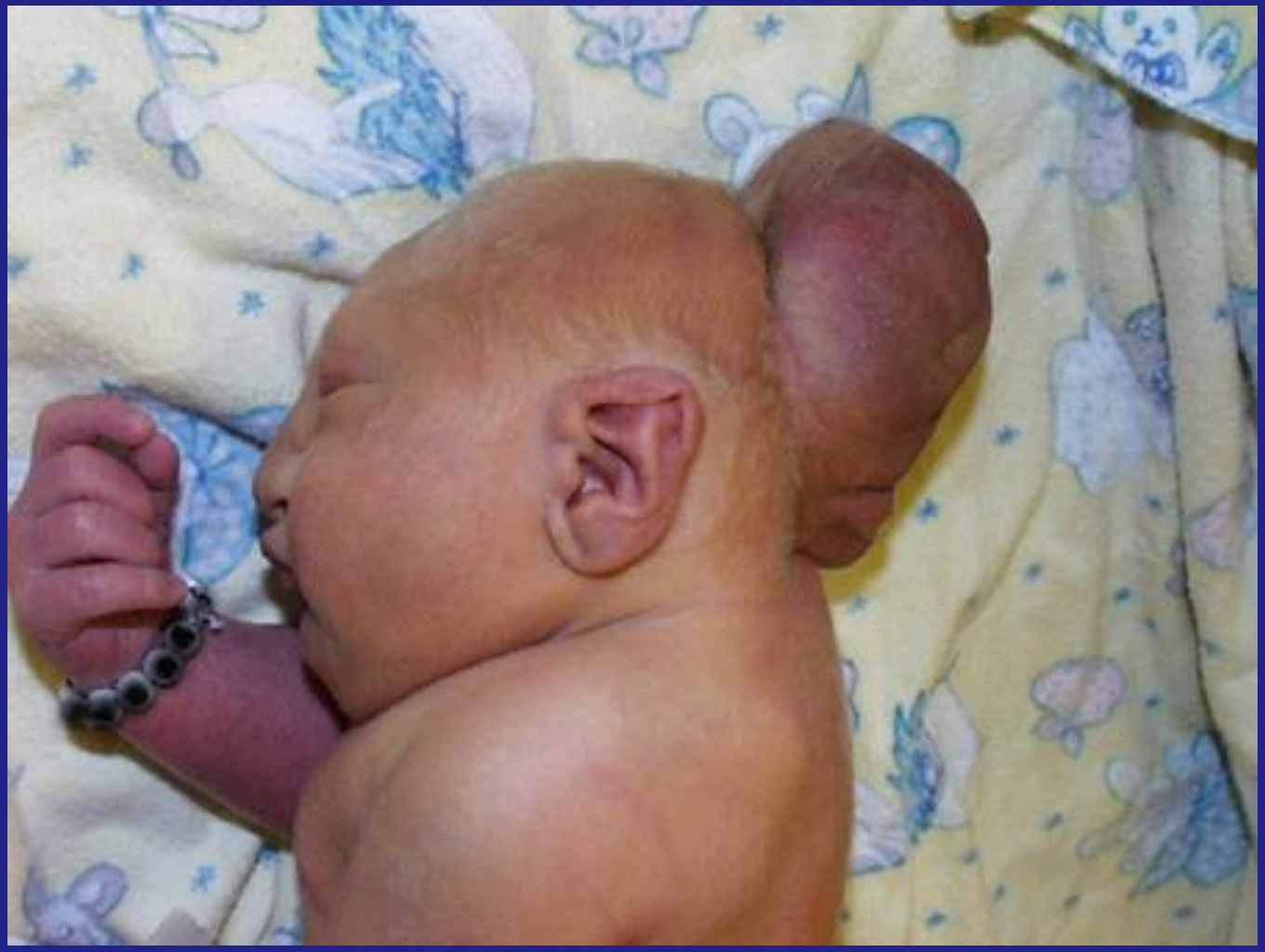
- Anencephaly



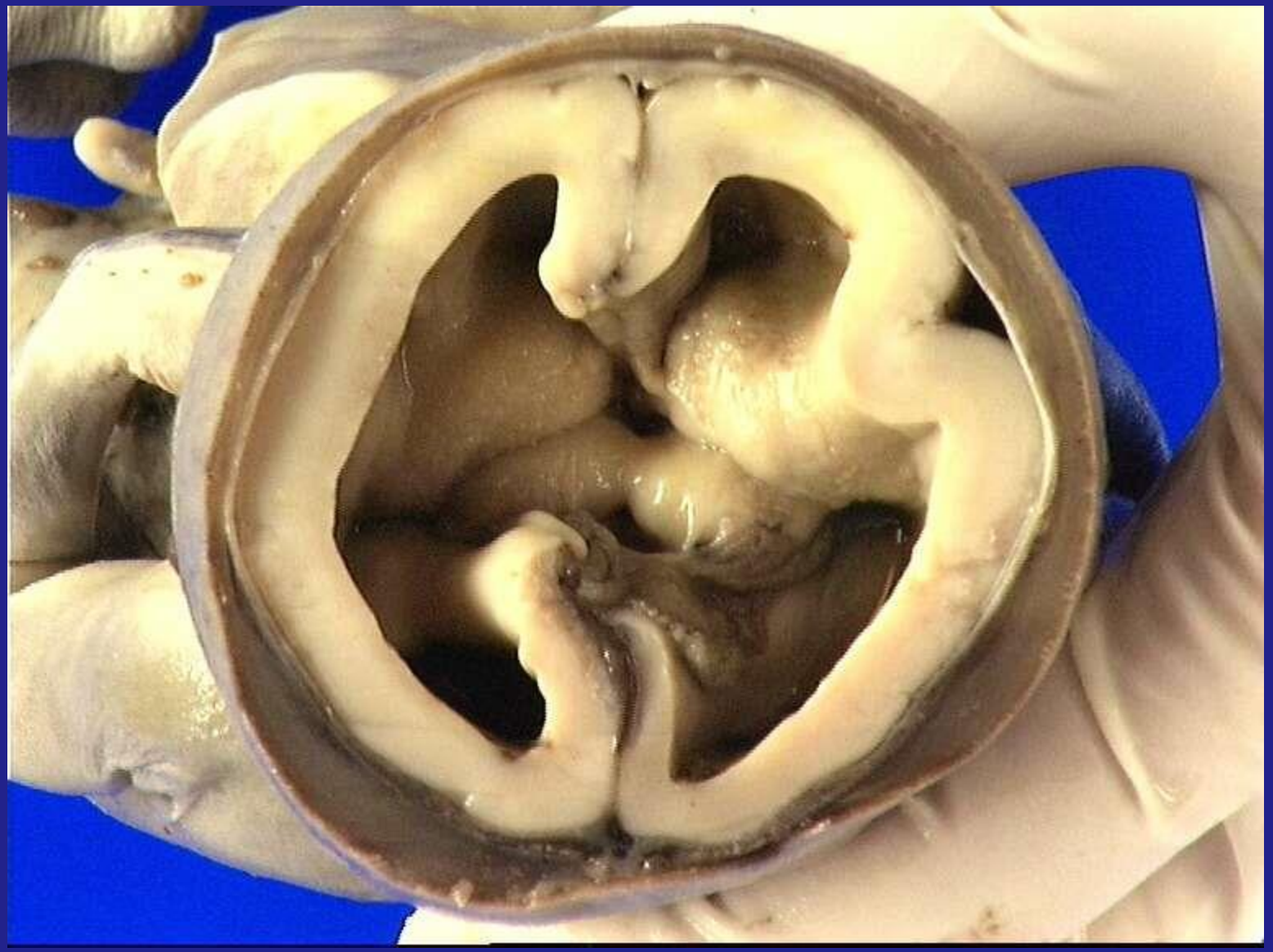
Spina bifida



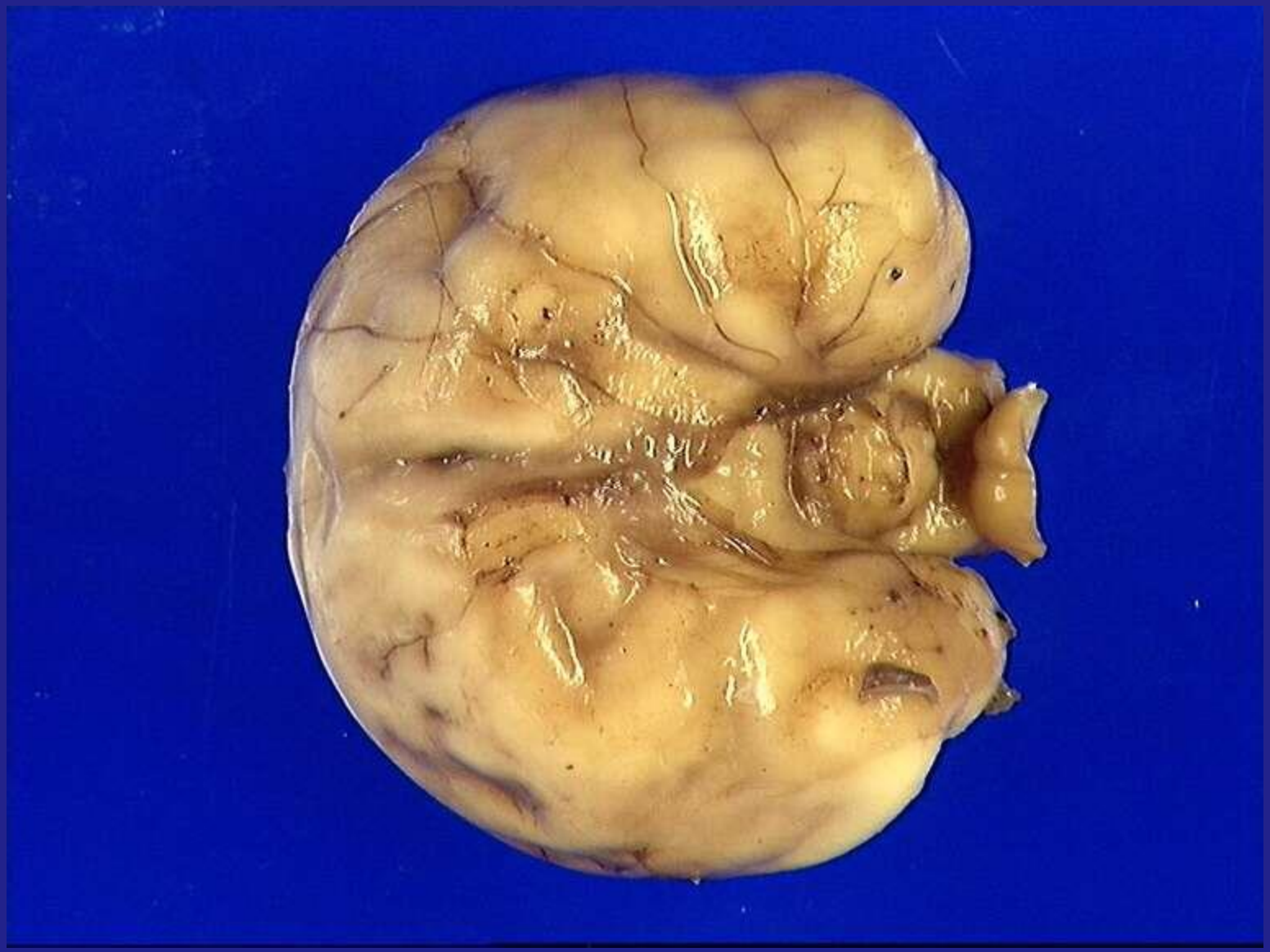
Encephalocele



Hydrocephaly

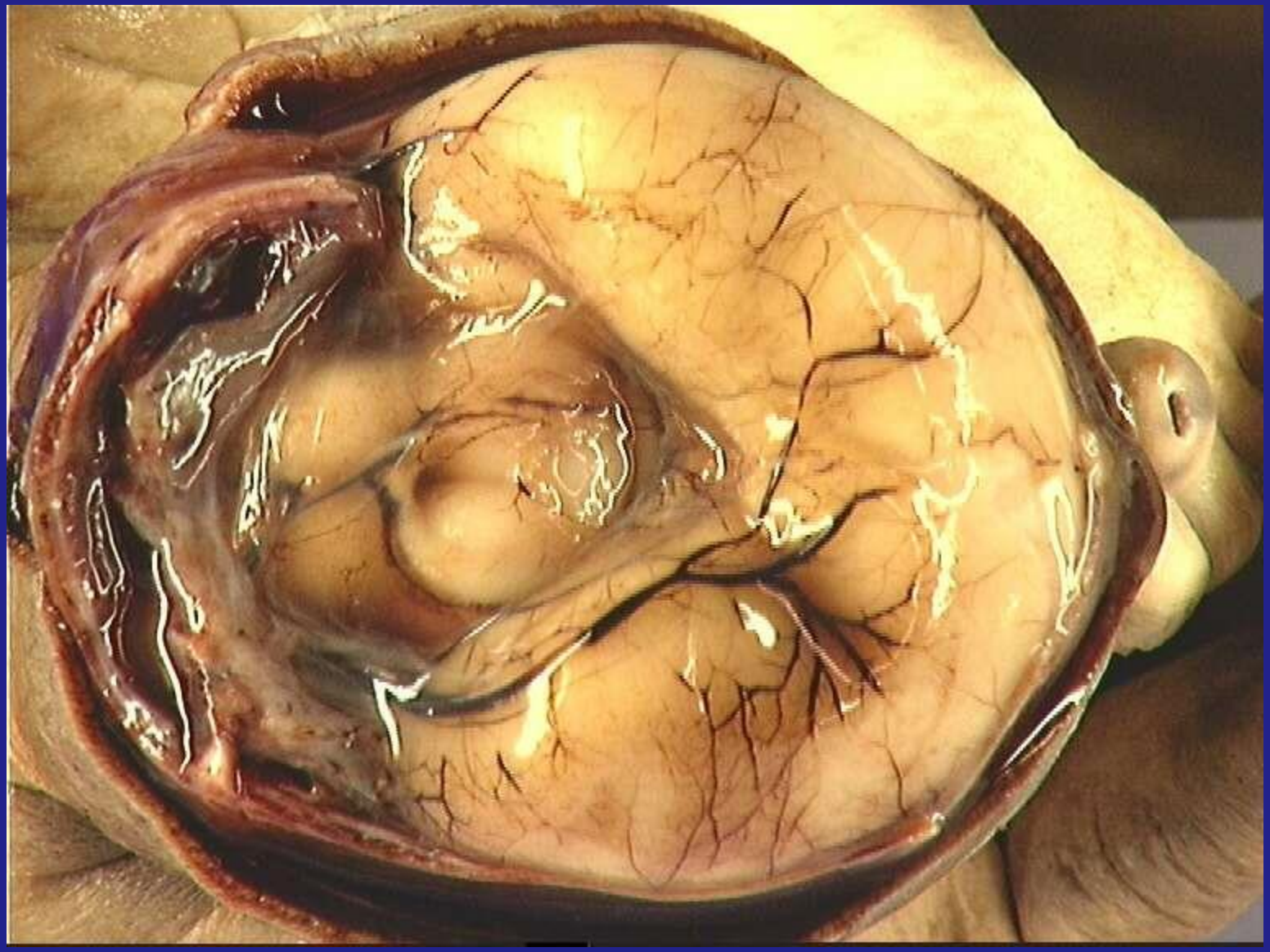


holoprosencephaly

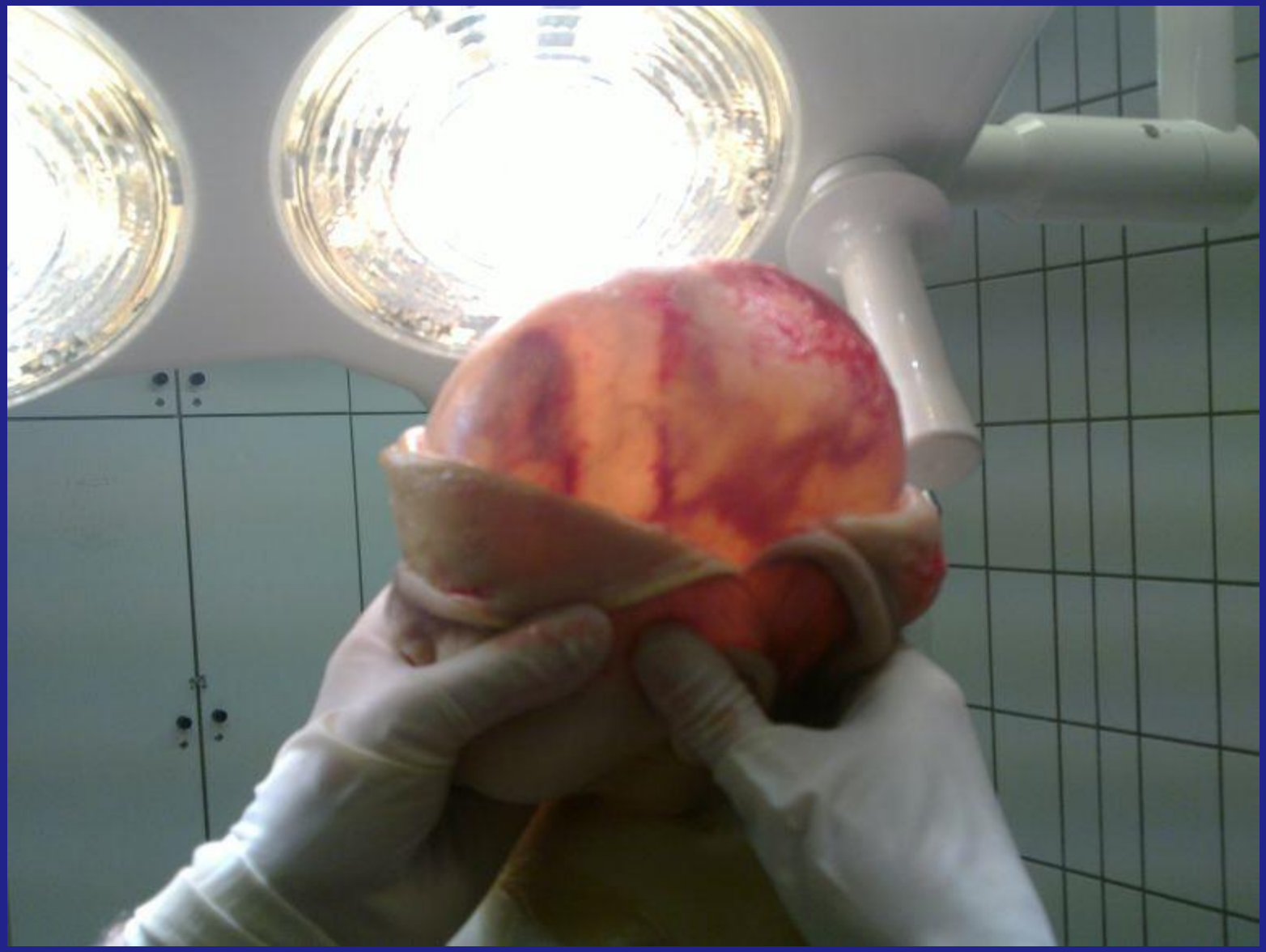


Holoprosencephaly - cyclopia

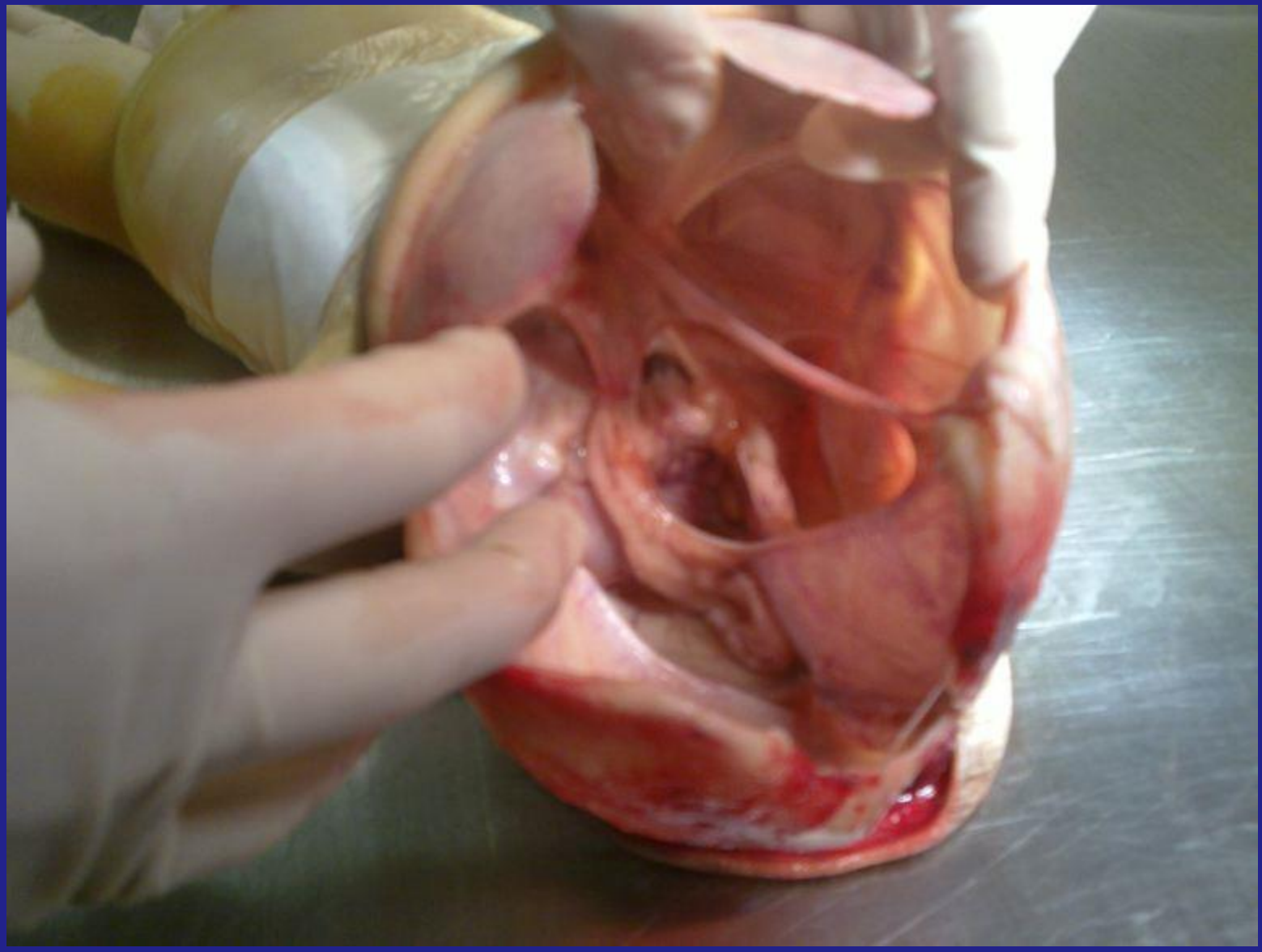
Holoprosencephaly - cyclopia



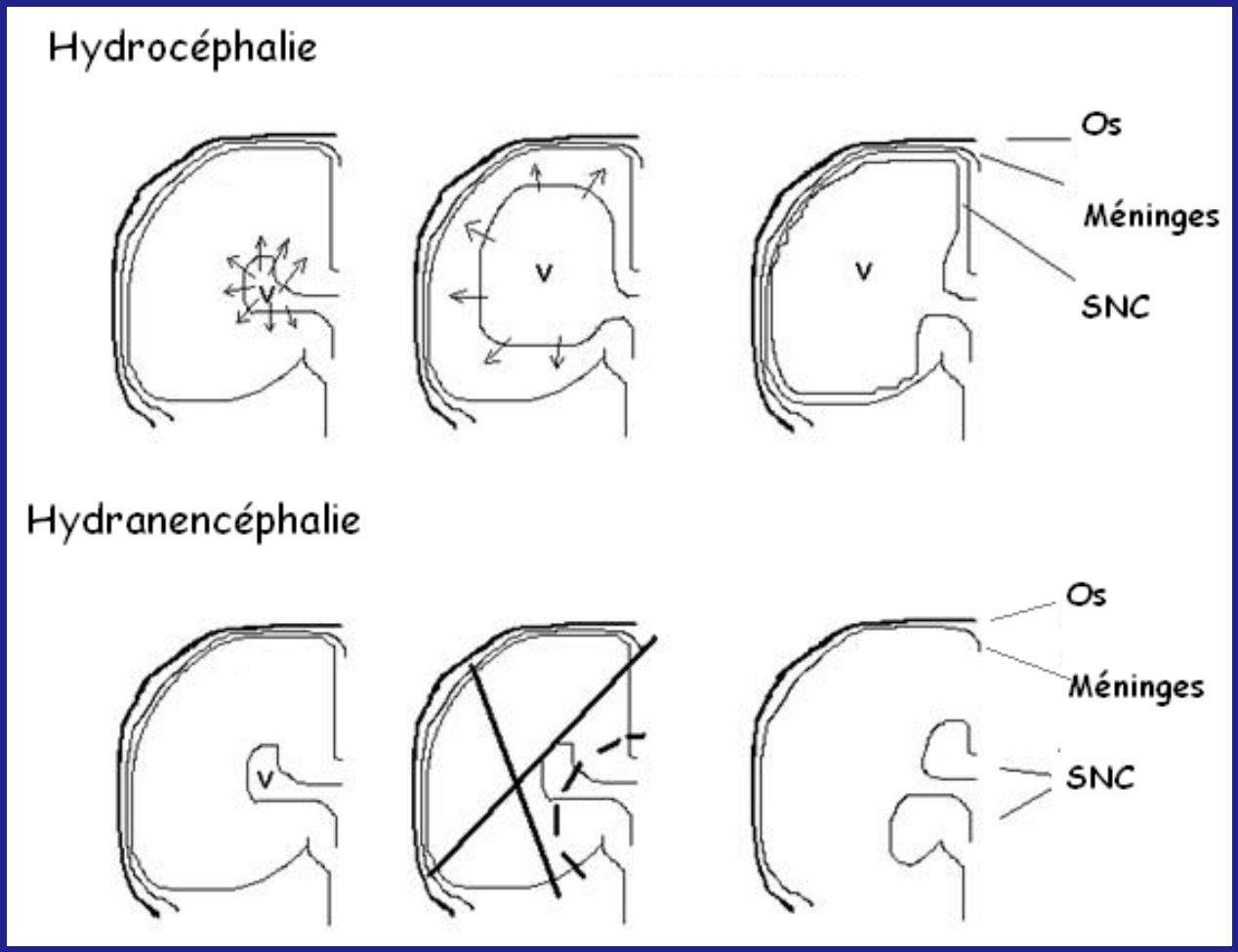
Hydranencephaly



Hydranencéphaly

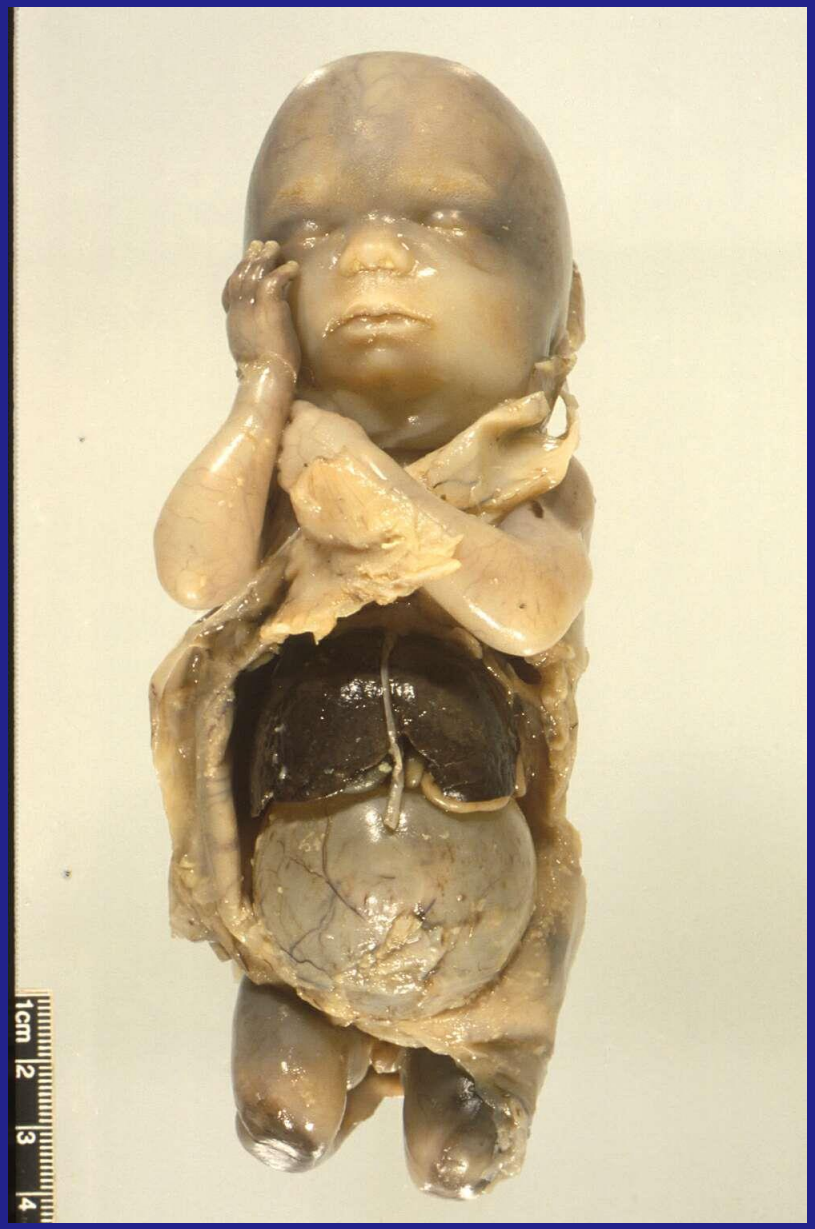


Hydranencéphalie > <hydrocéphalie

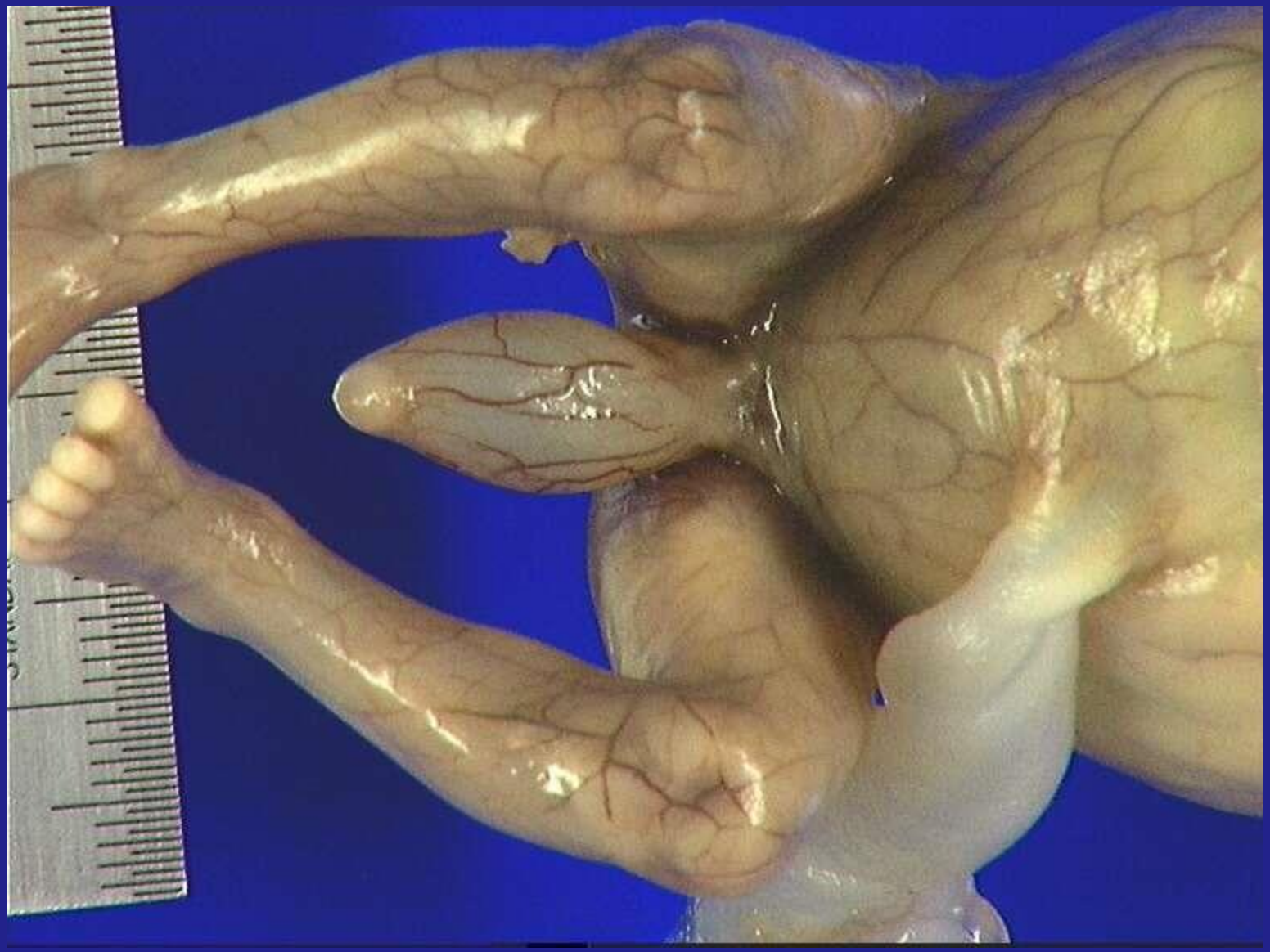


Urogenital anomaly

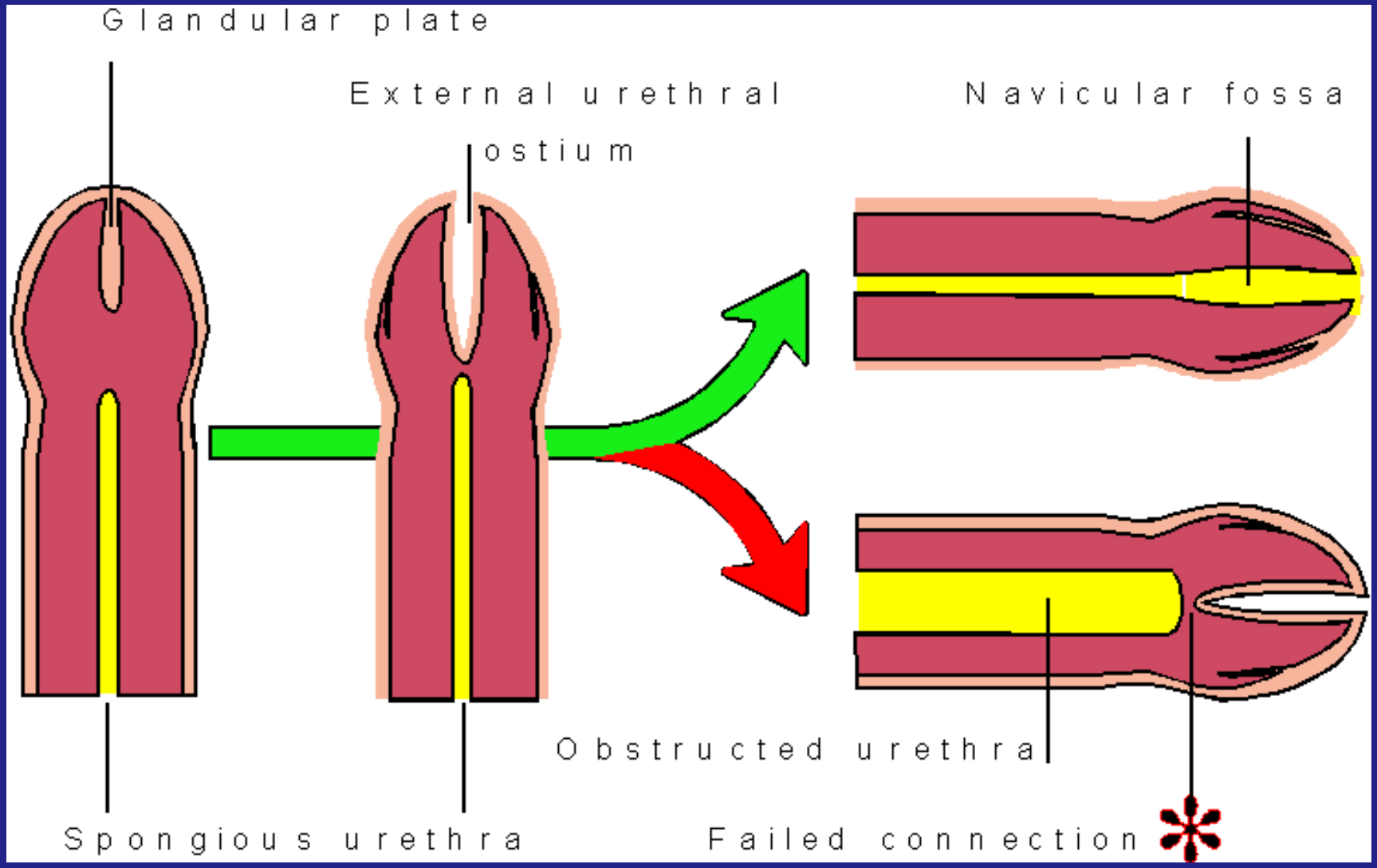
- « Prune Belly »:
  - Urethral stenosis
  - or posterior valves
  - Mostly in male fetuses



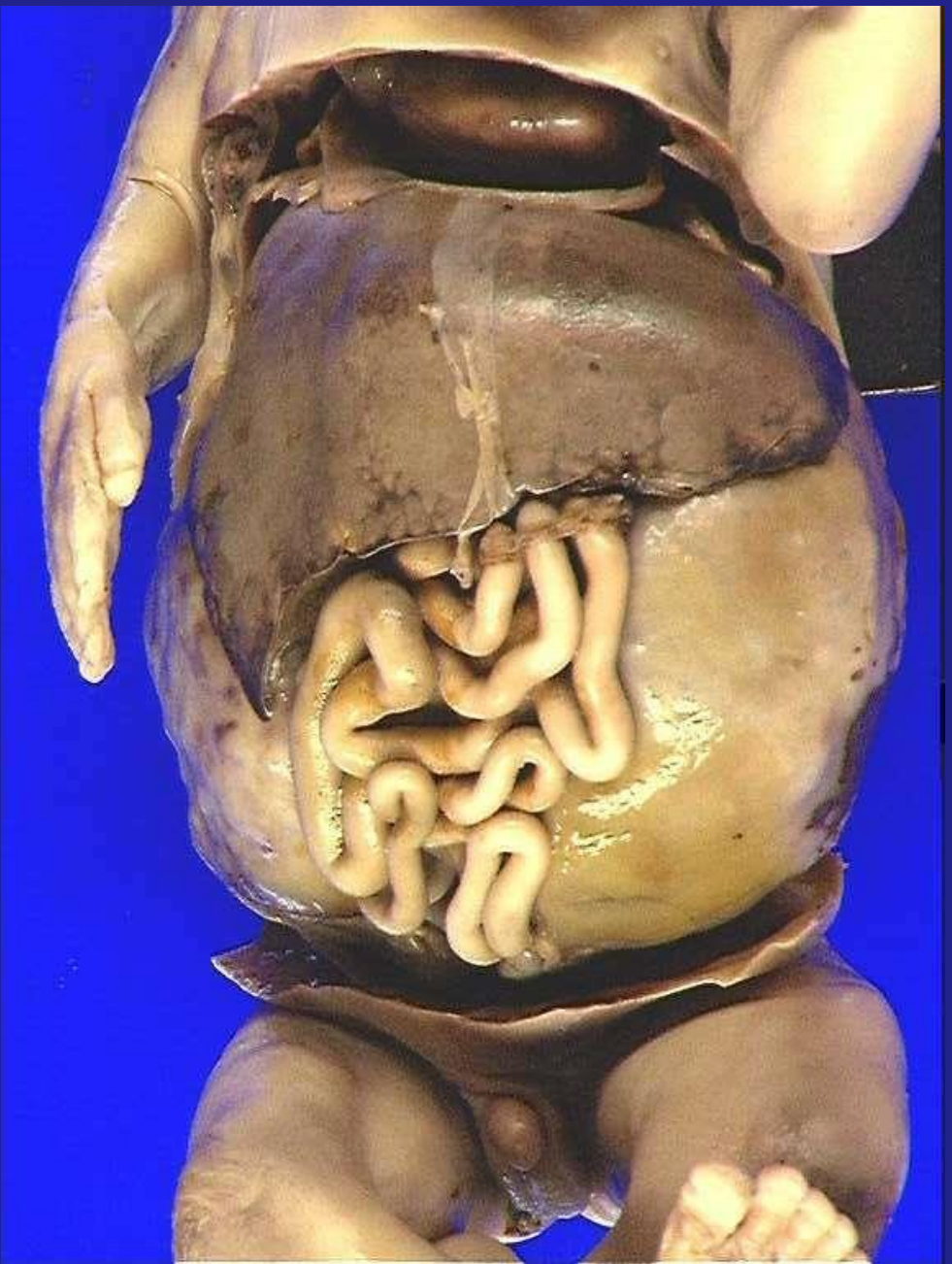
Distal urethral stenosis

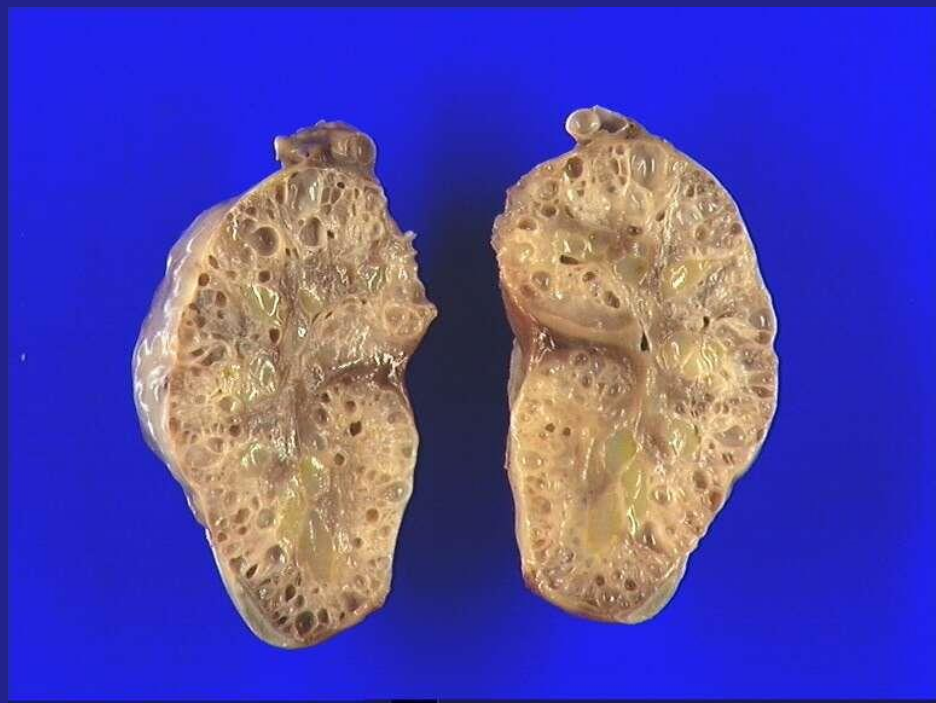


Distal urethral stenosis

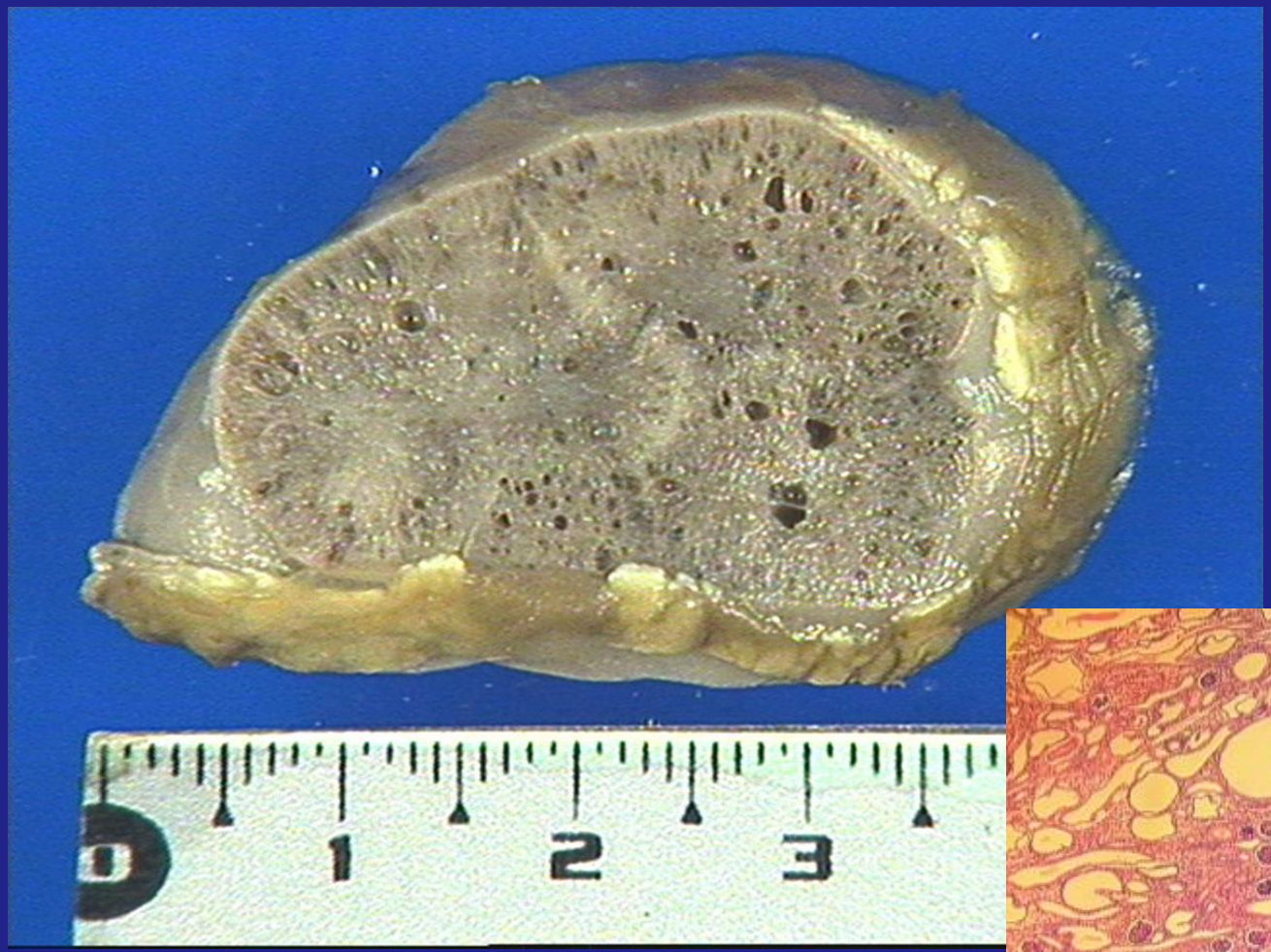


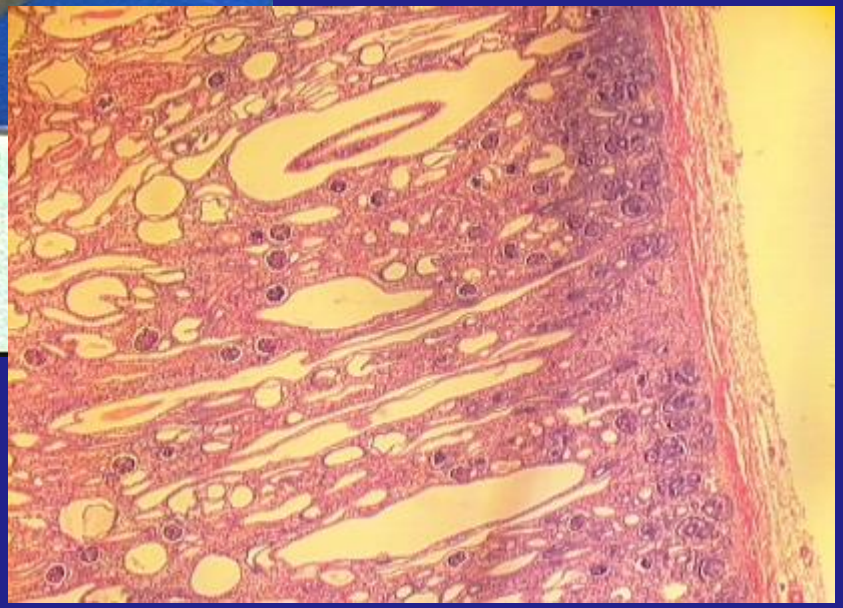
Polycystic kidneys



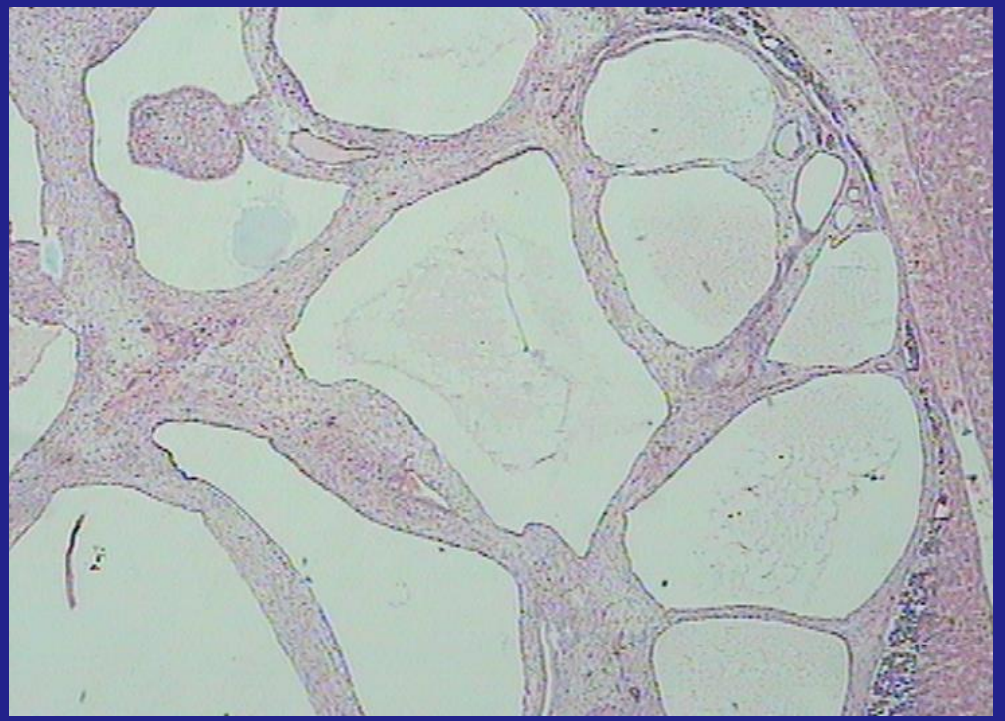


Autosomal recessive polycystic kidney disease (ARPKD)

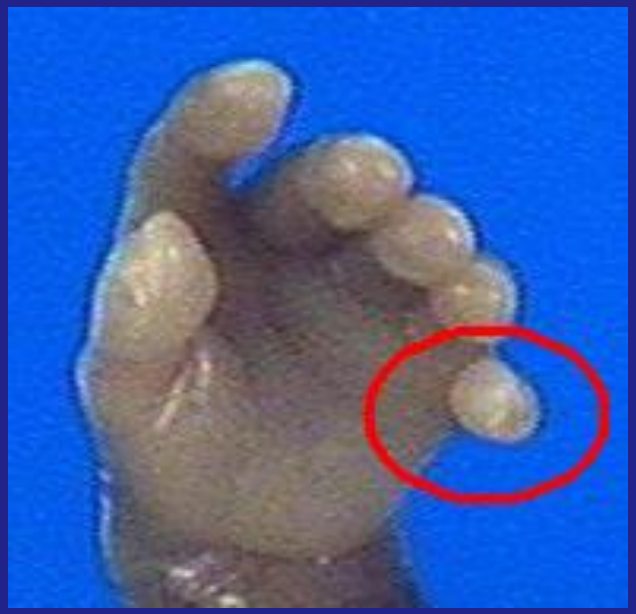


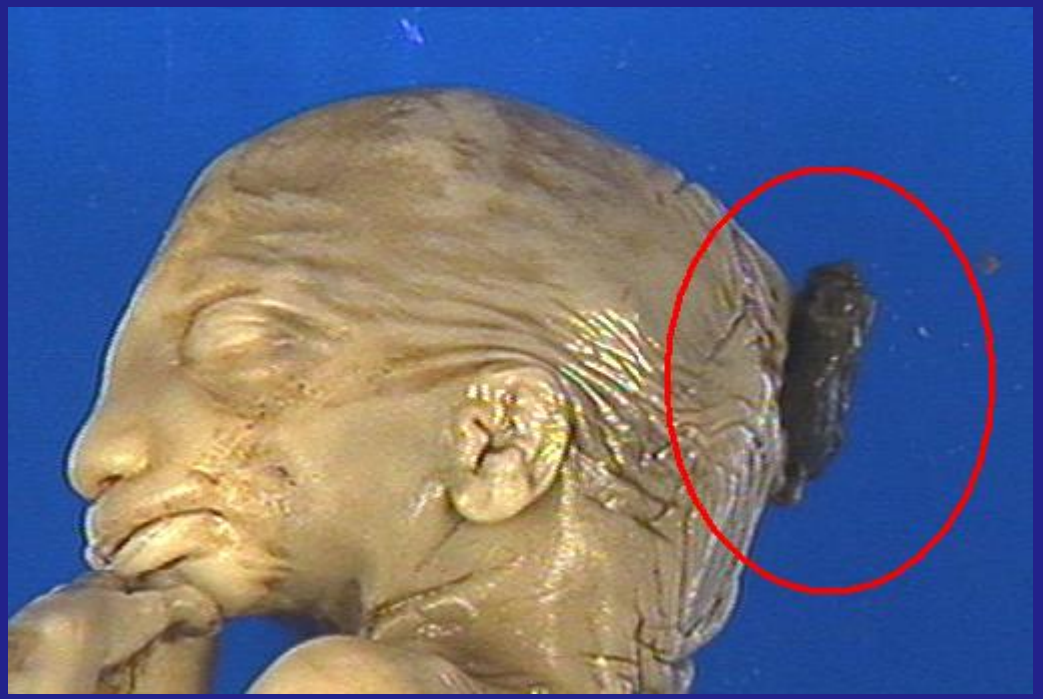


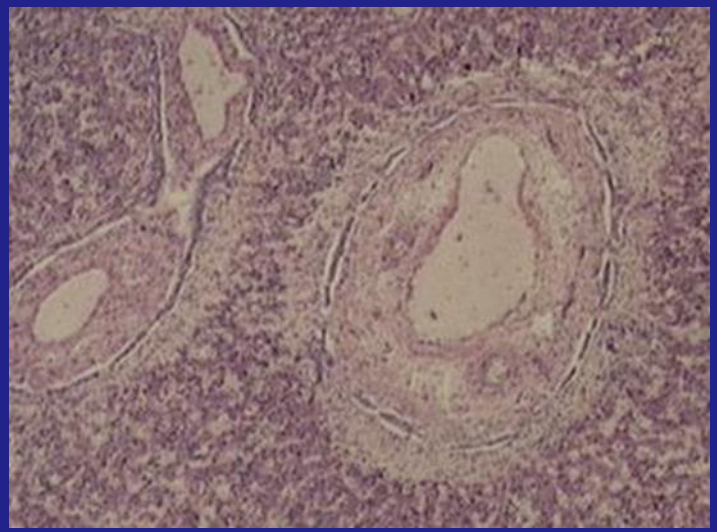
Meckel Gruber



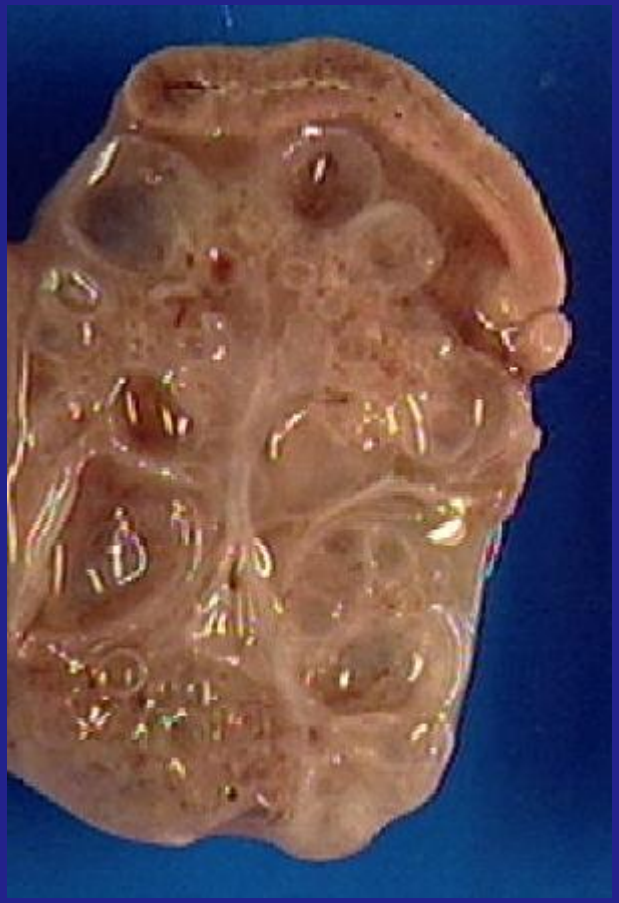
Meckel Gruber

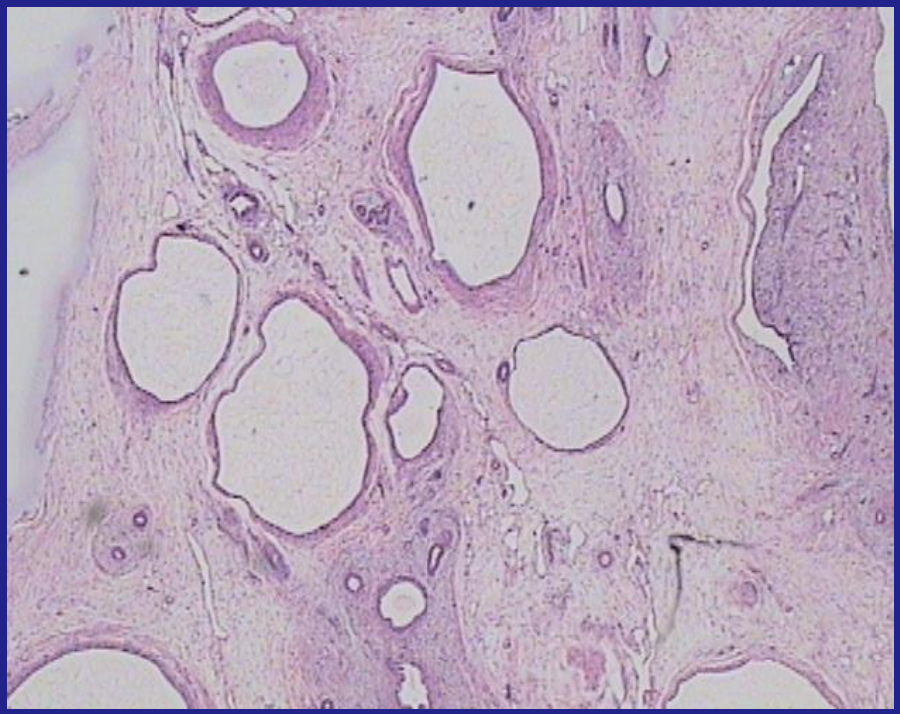




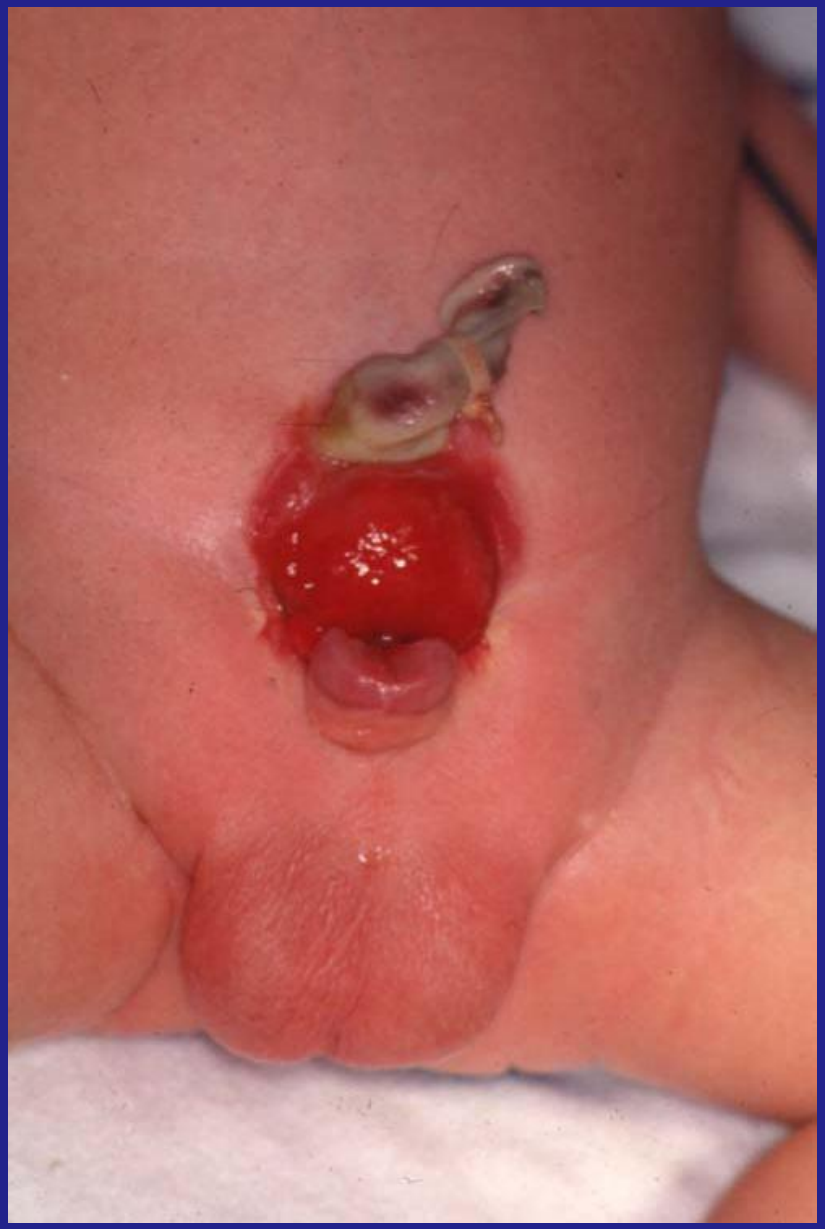


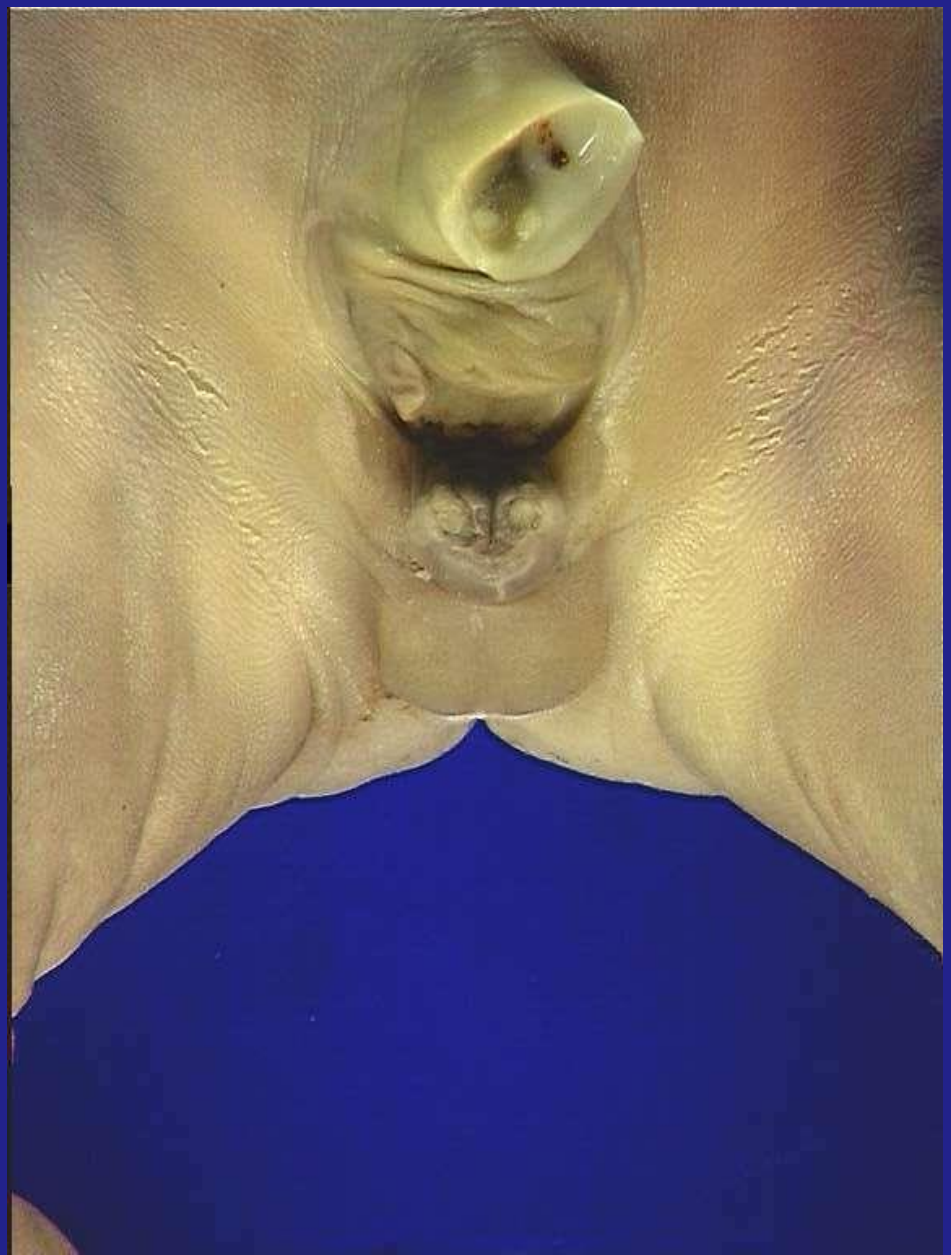
TCF2 / HNF1 mutation





Vesical Extrophy

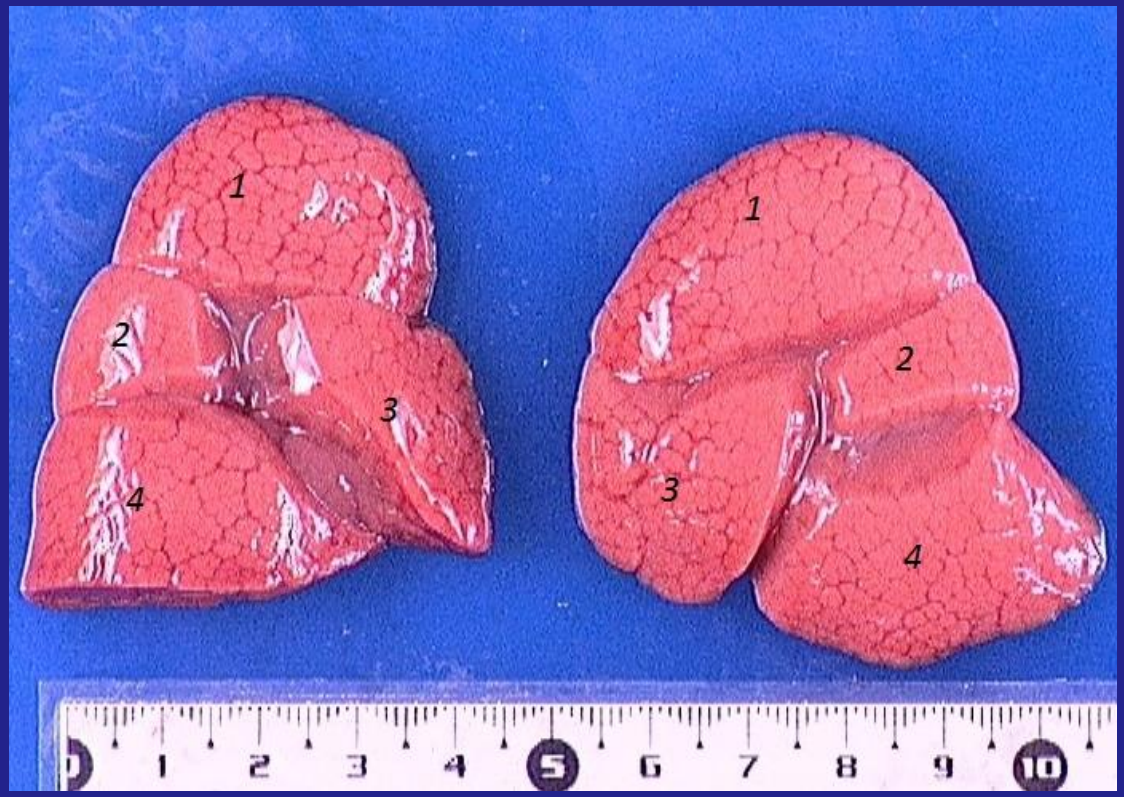




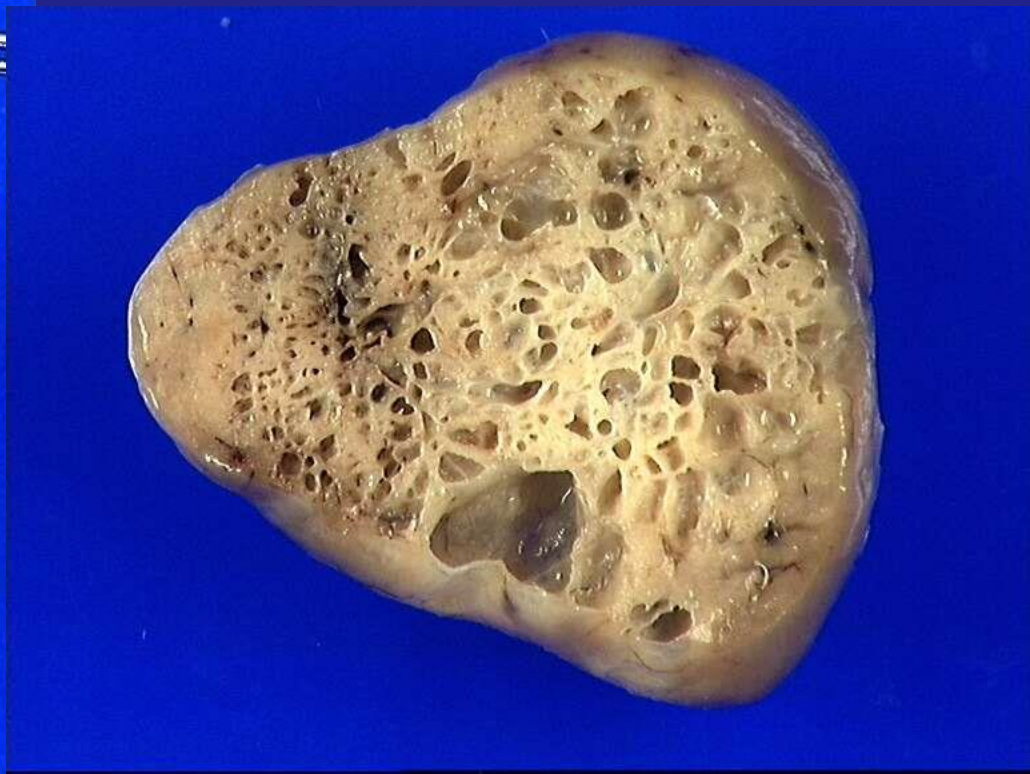
Lung malformations

- Lobation anomalies:

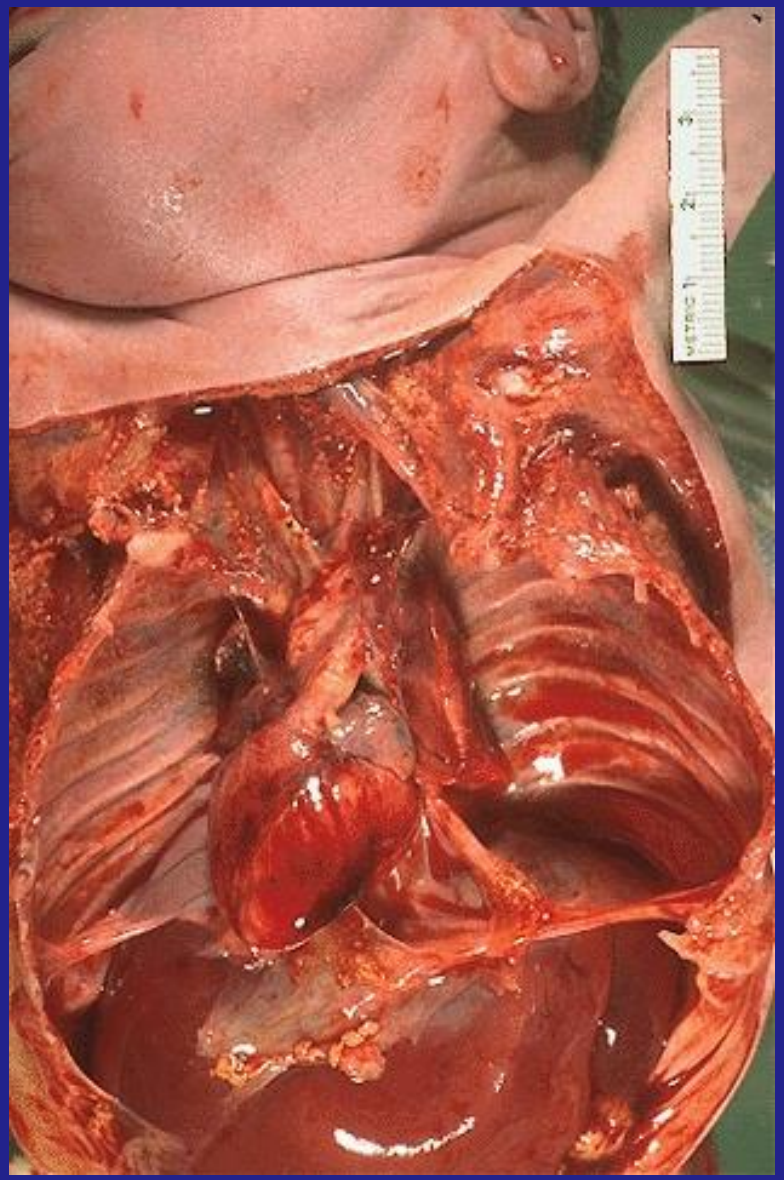
anatomical variant, lateralization syndrome, Ivemark



Congenital cystic adenomatoid malformation (CCAM)



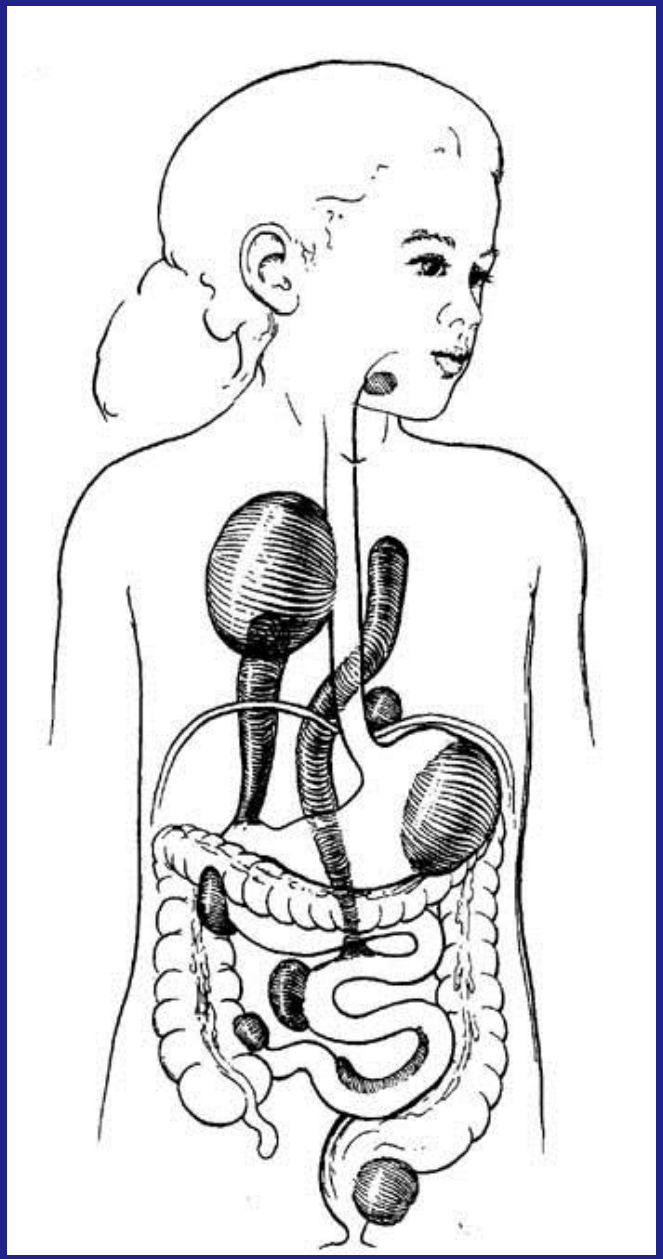
Lung Hypoplasia

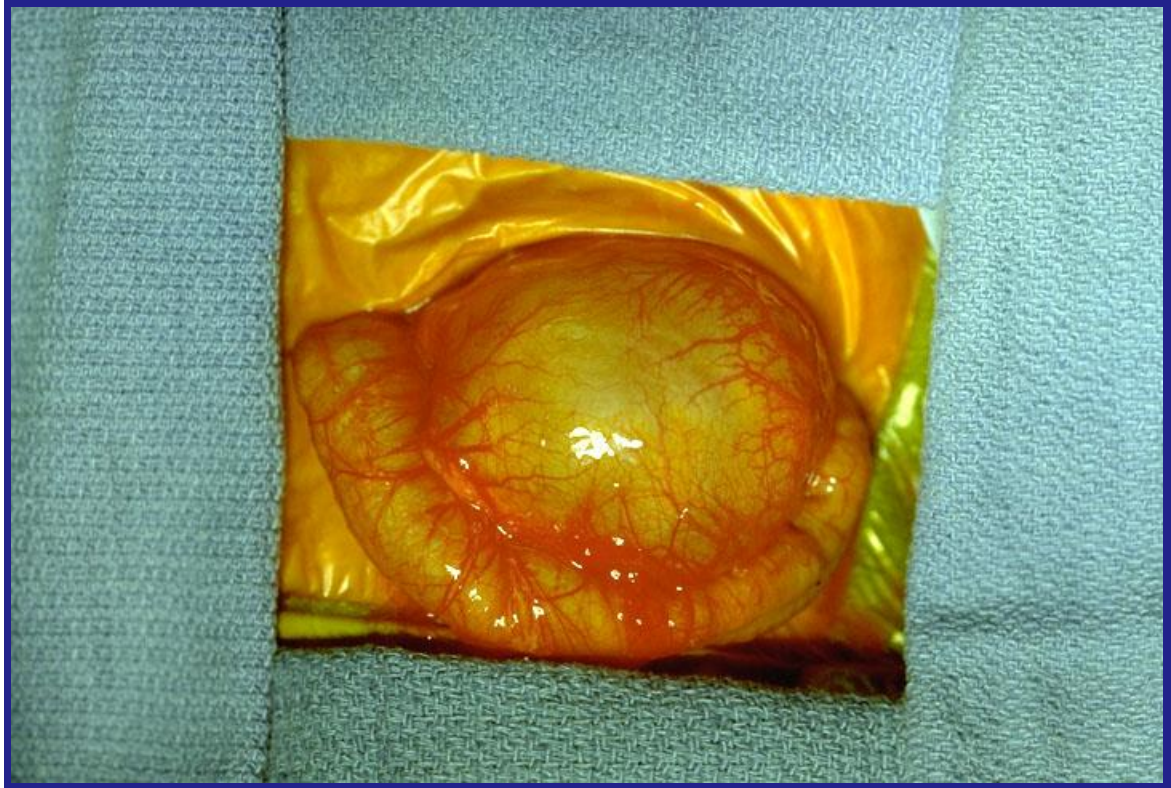


Digestive system

- Atresia and fistulae
- Cysts and duplications
- Rotation defect
- Abdominal wall defects
  - gastro/ laparoschisis
  - omphalocele
- Hernia

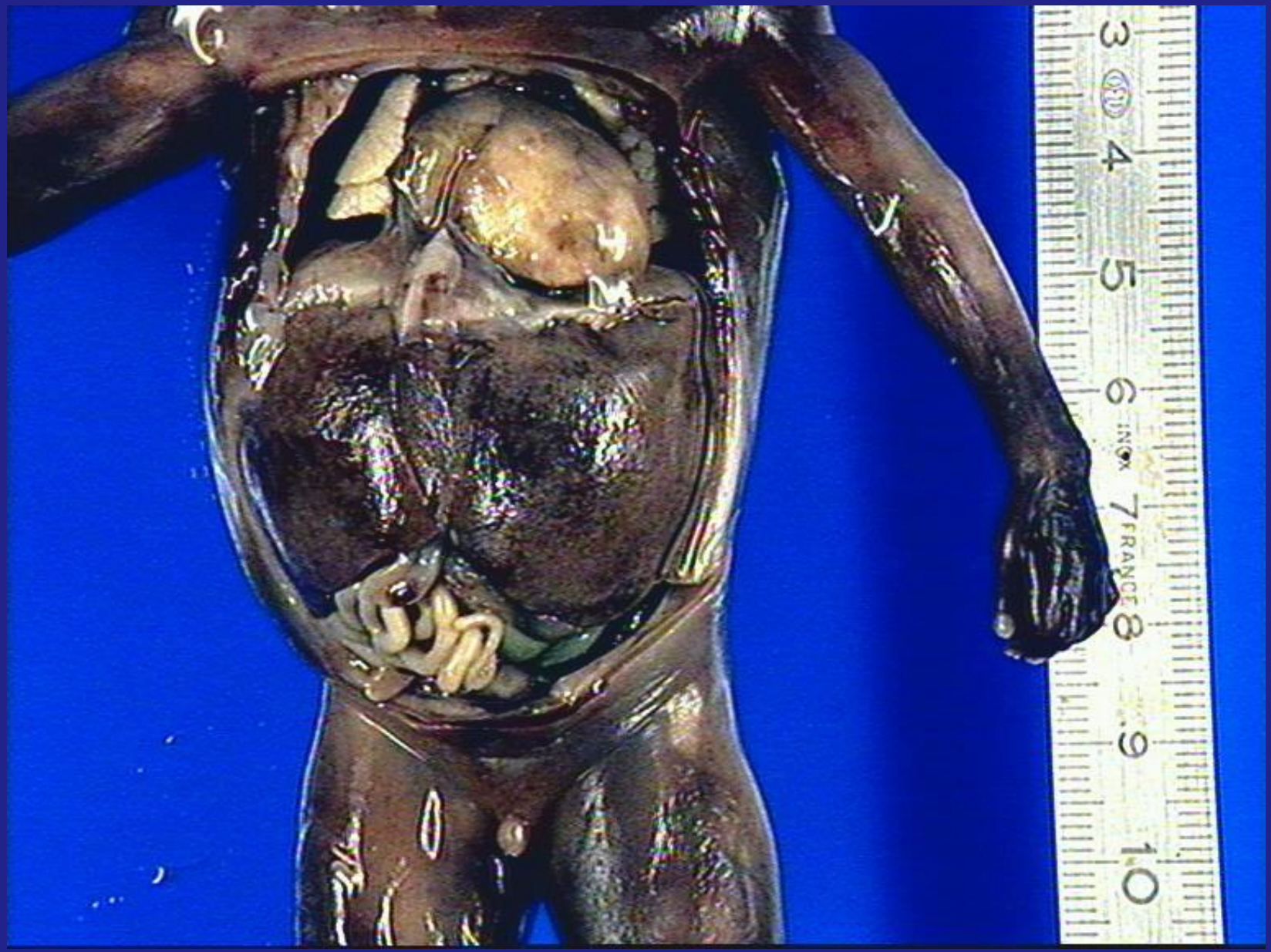
Digestives cysts



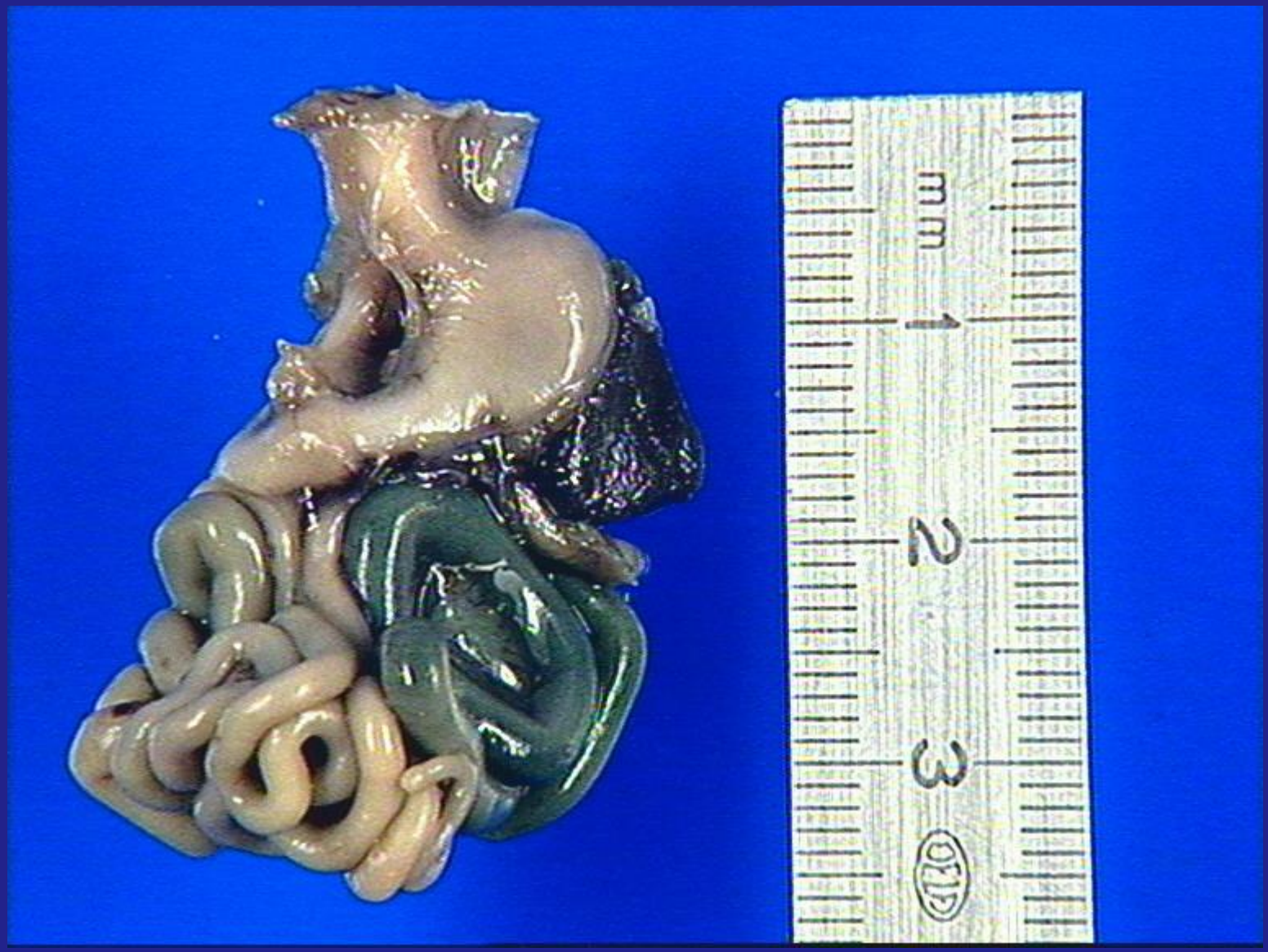


Intestinal cyst

Malrotation (1)



Malrotation (2)

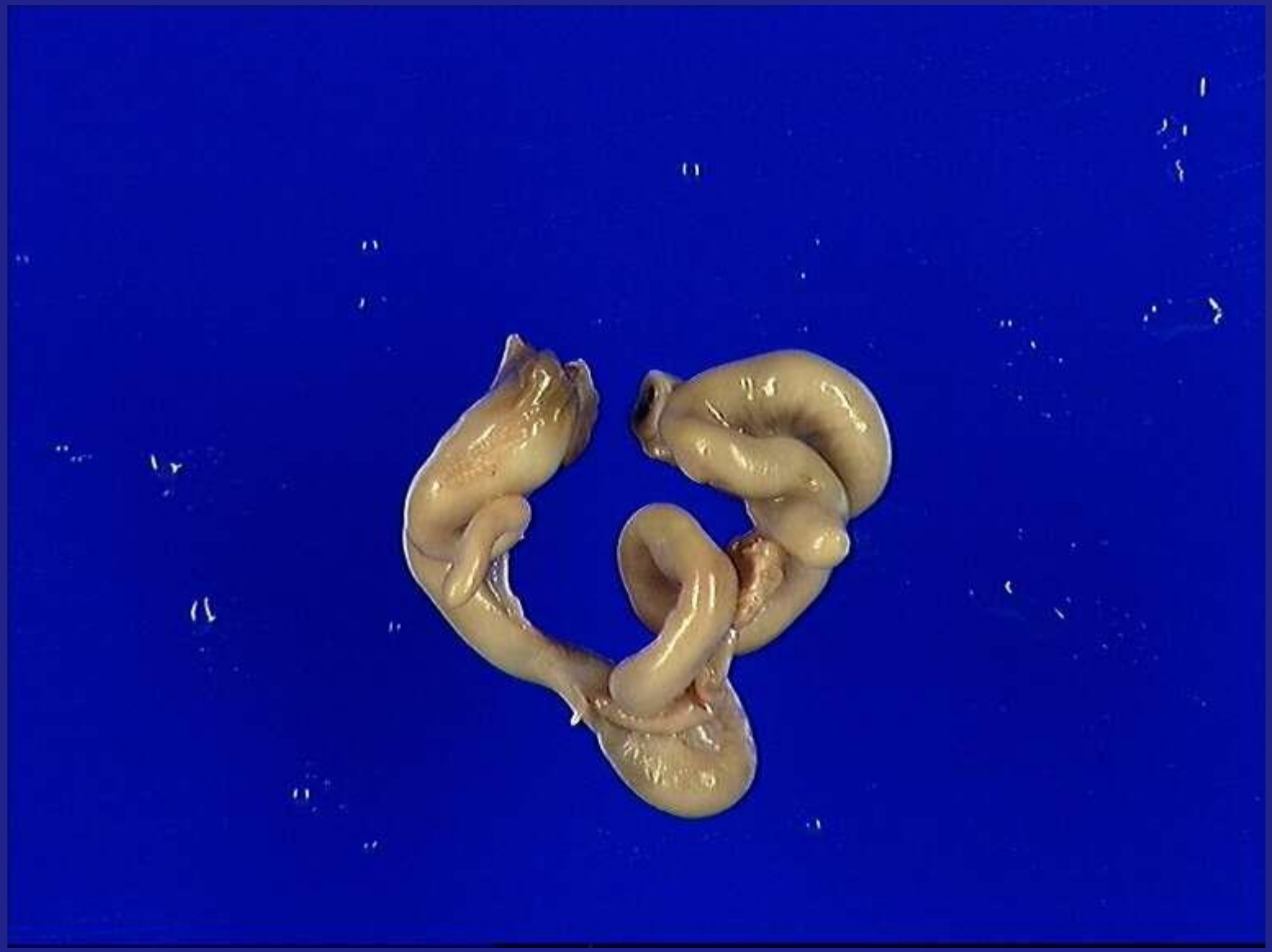


Gastroschisis

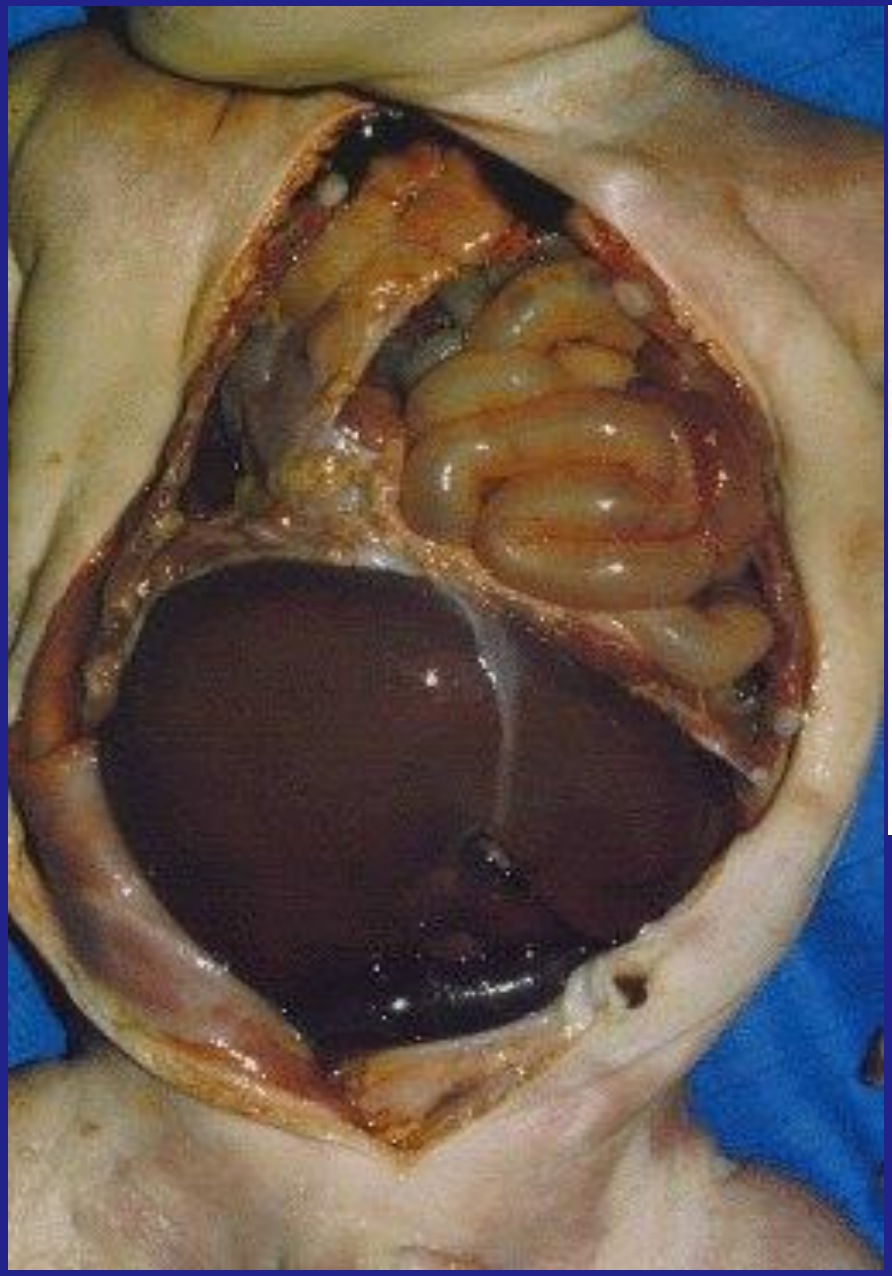
Omphalocele

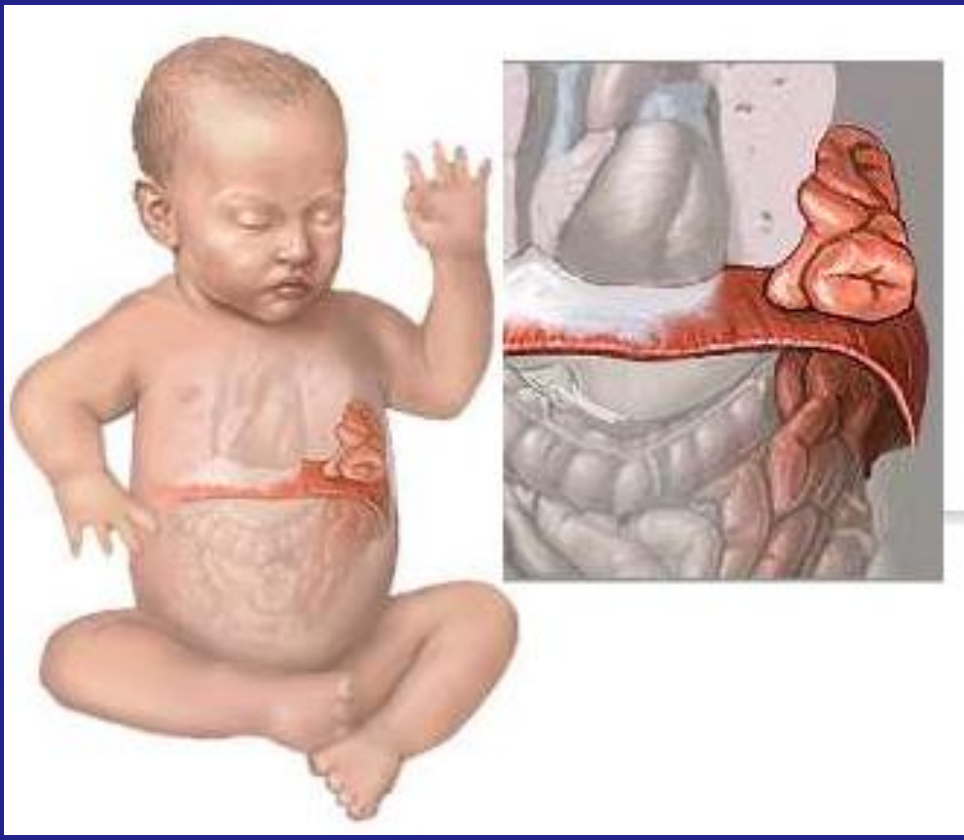
Omphalocele (2)

Meckel Diverticulum



Diaphragmatic hernia





Musculo-squelettal system

- Ossification disorders: osteogenesis imperfecta, achondrogenesis, chondrodysplasia…

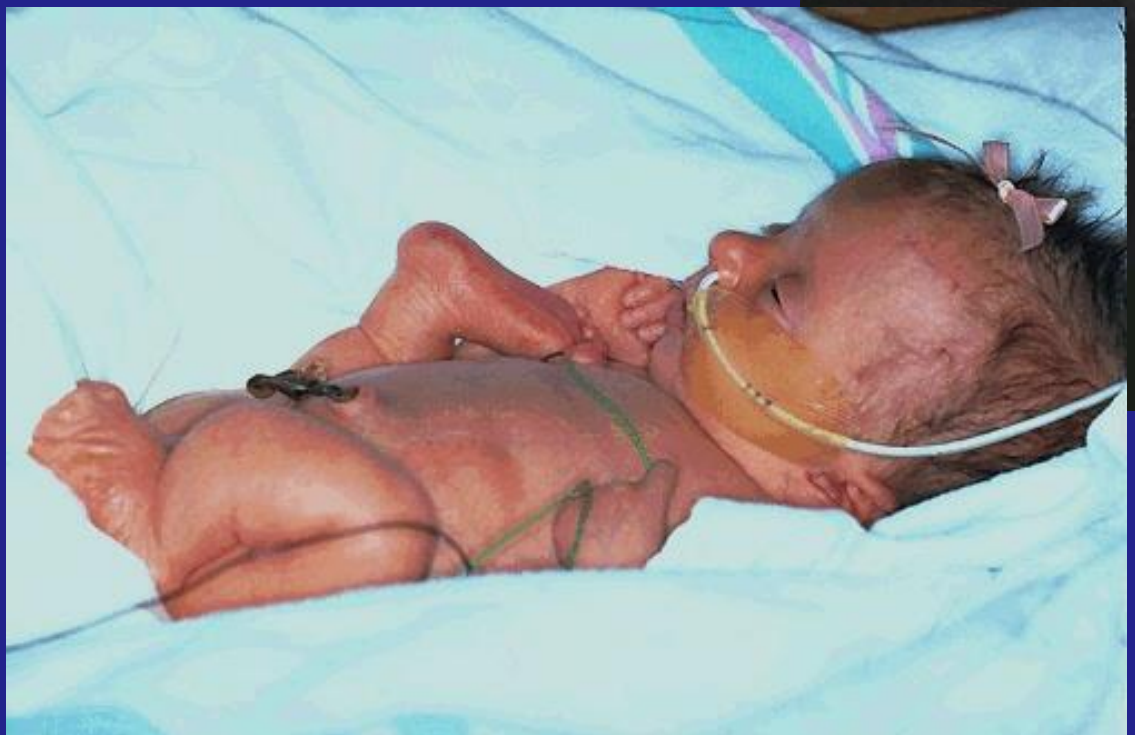
> Sometime complex to identify!

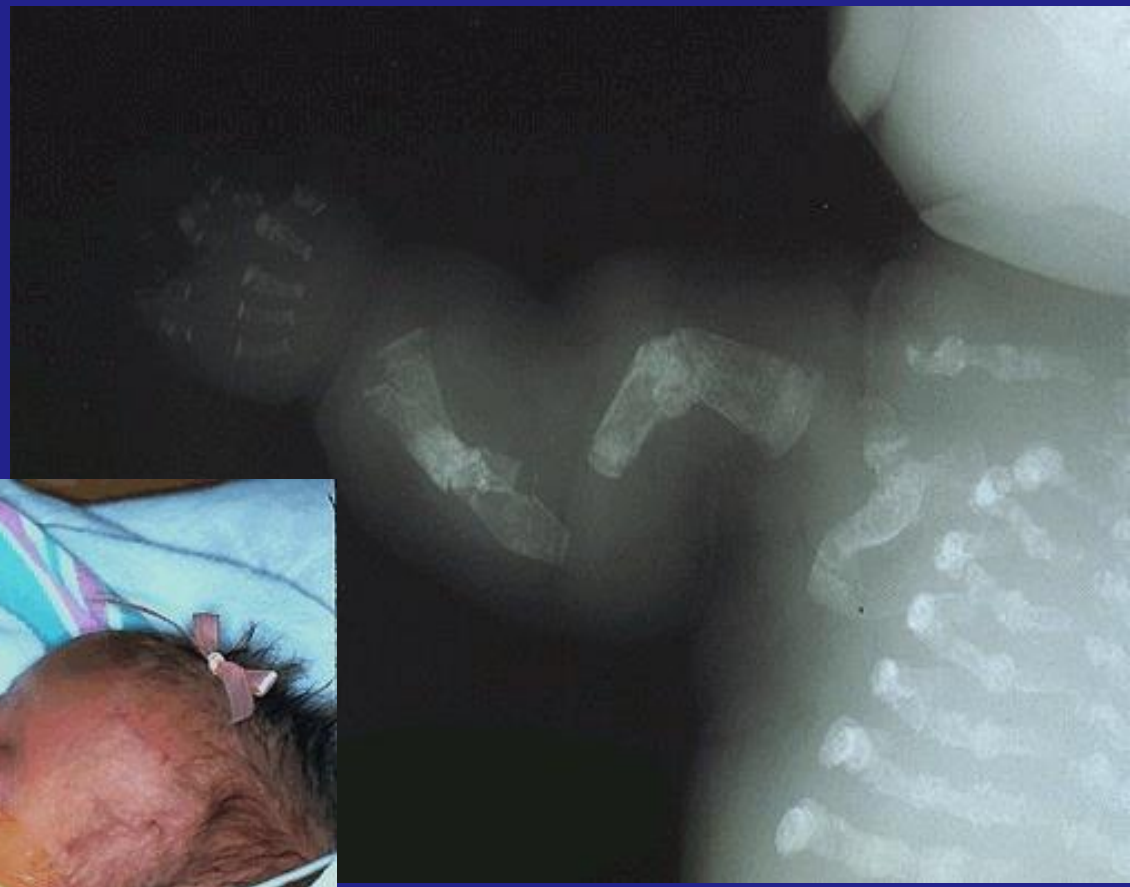
- Minor anomalies: polydactyly/syndactyly

- Member agenesis or atrophy

Osteogenesis imperfecta
(Lobstein disease, Osteopsathyrosis)

- Type II = most severe
- Numerous fractures IU
- « dwarfism »
- < 1/10.000 naissances



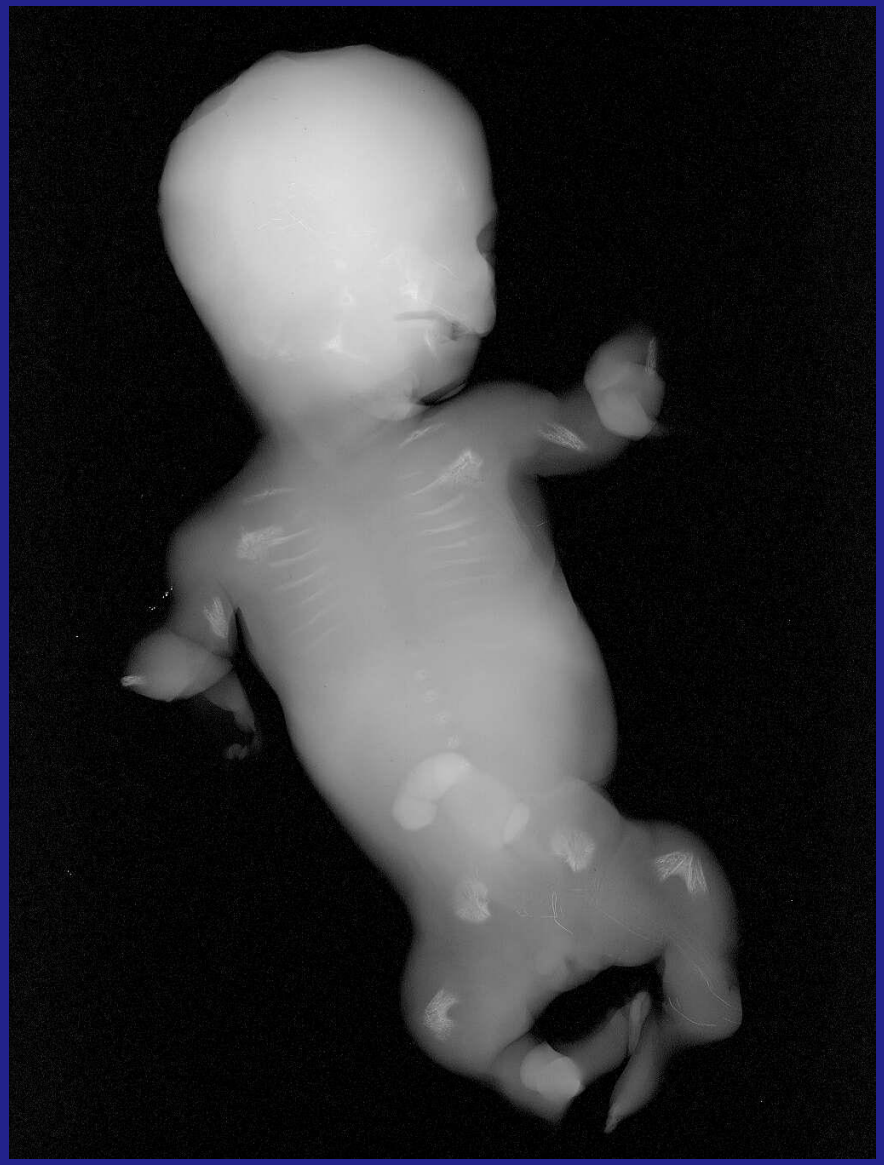


abnormal collagen
Mutation Col1A1 / A2

Achondrogenesis

- group of severe disorders that affect cartilage
- small body, short limbs, various skeletal abnormalities

ACHONDROGENESIS



At last 3 types:

1A (Trip11)

1B (SLC26A2)

2 (COL2A1)

Common feature

-short limbs

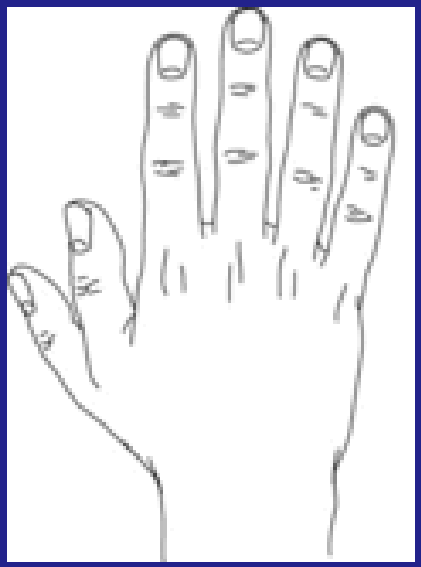
-narrow chest

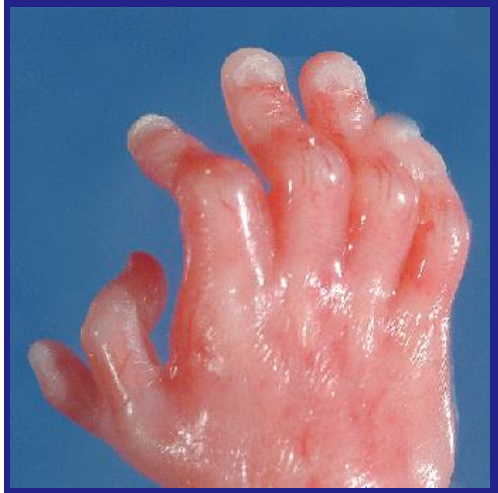
-Spine and pelvis ossification defect

Polydactyly

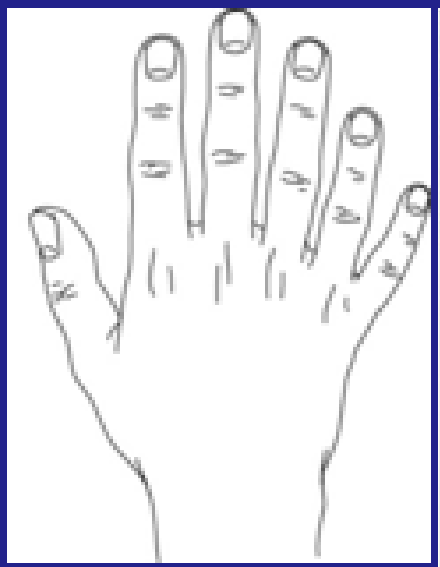
- Isolated (familial marquor) or part of a syndrome

- Radial or preaxial



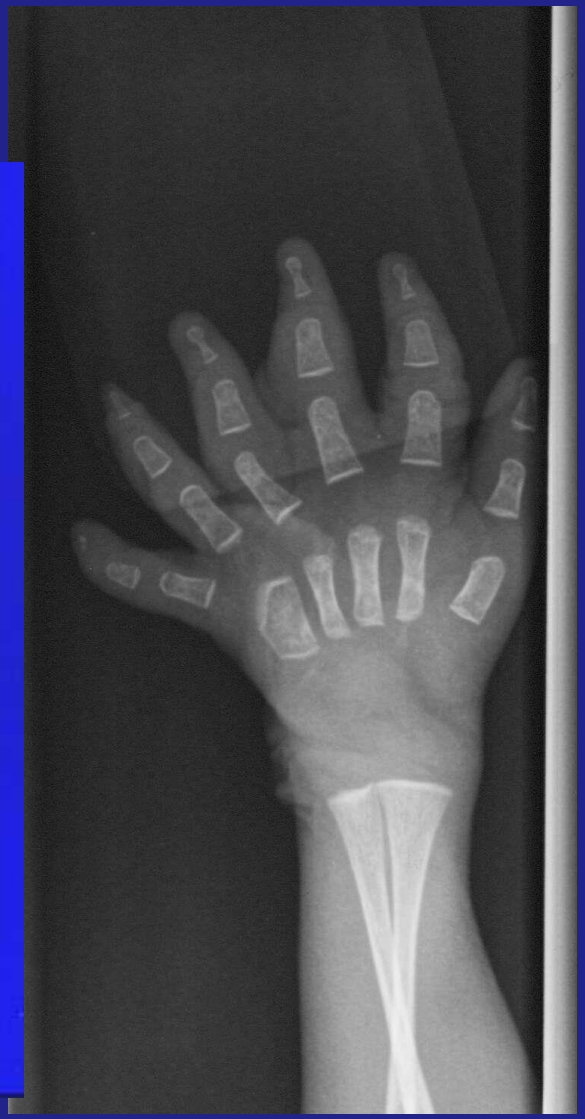


Ulnar or postaxial



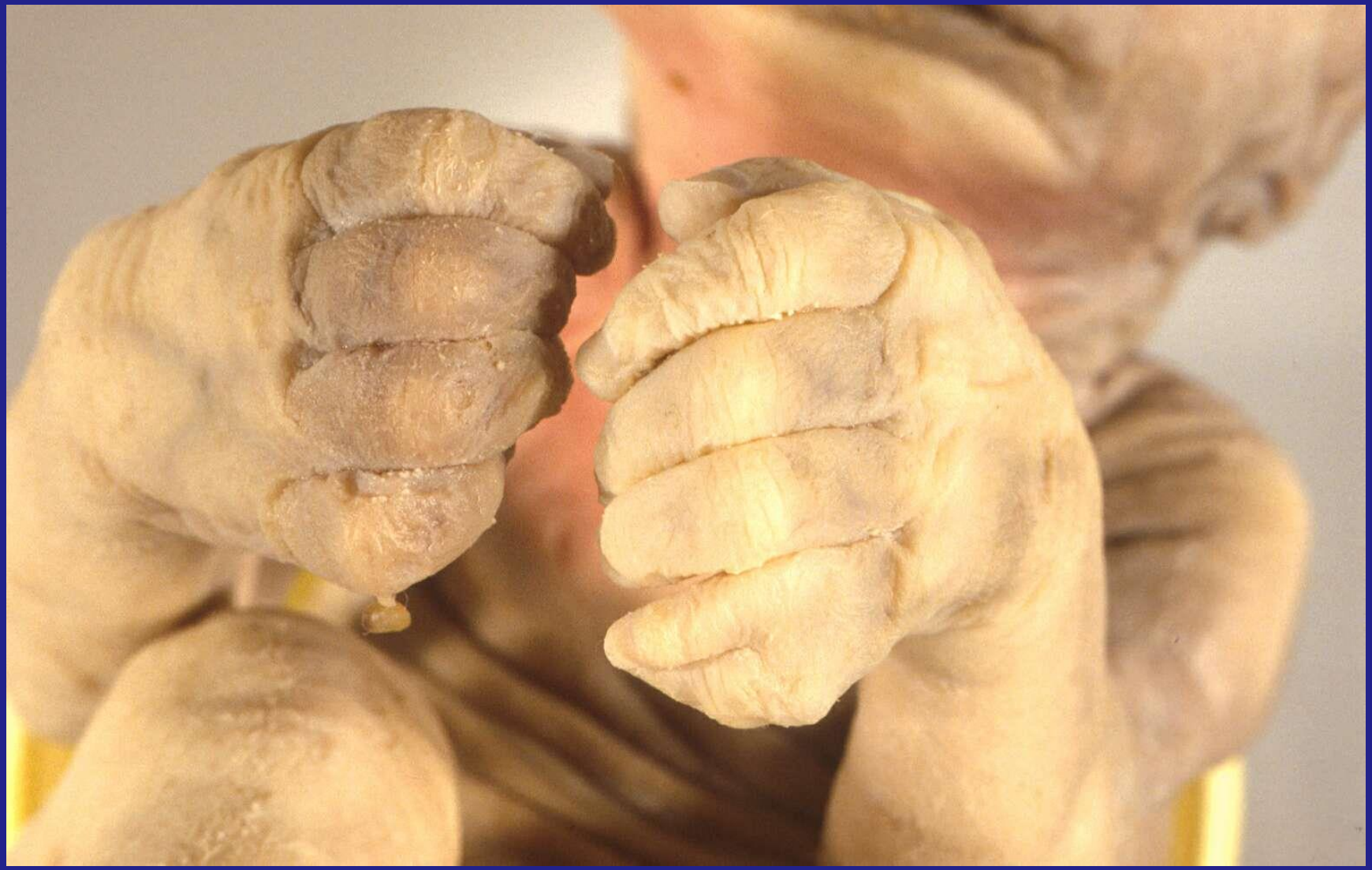
Polydactyly

- Meckel Gruber

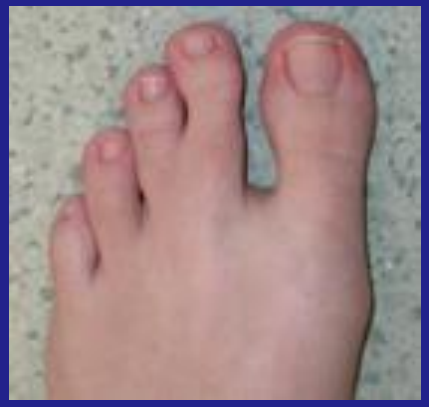


POLYDACTYLY

Trisomy 13



Syndactyly

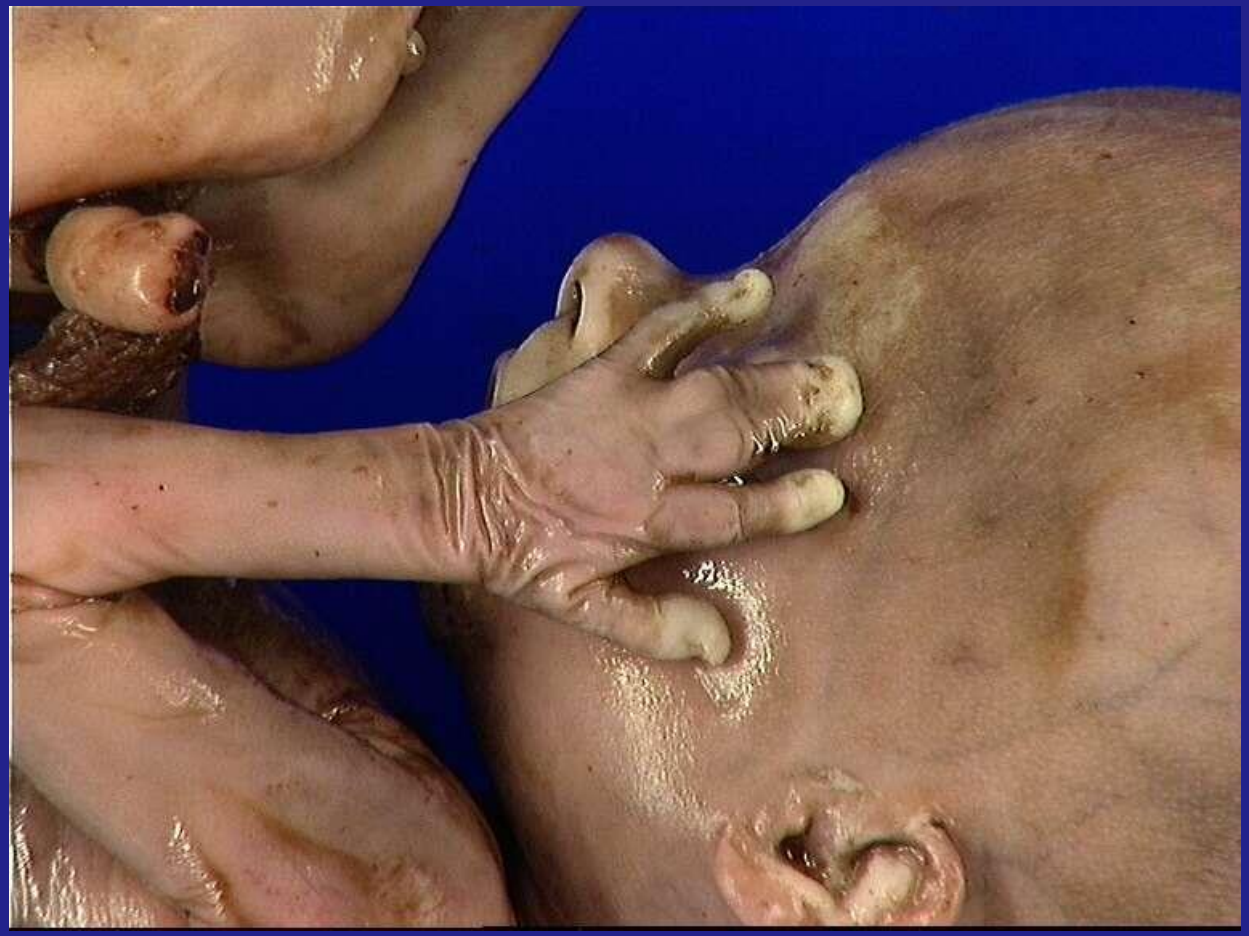


Isolated or Syndromic (Apert, Poland, …)

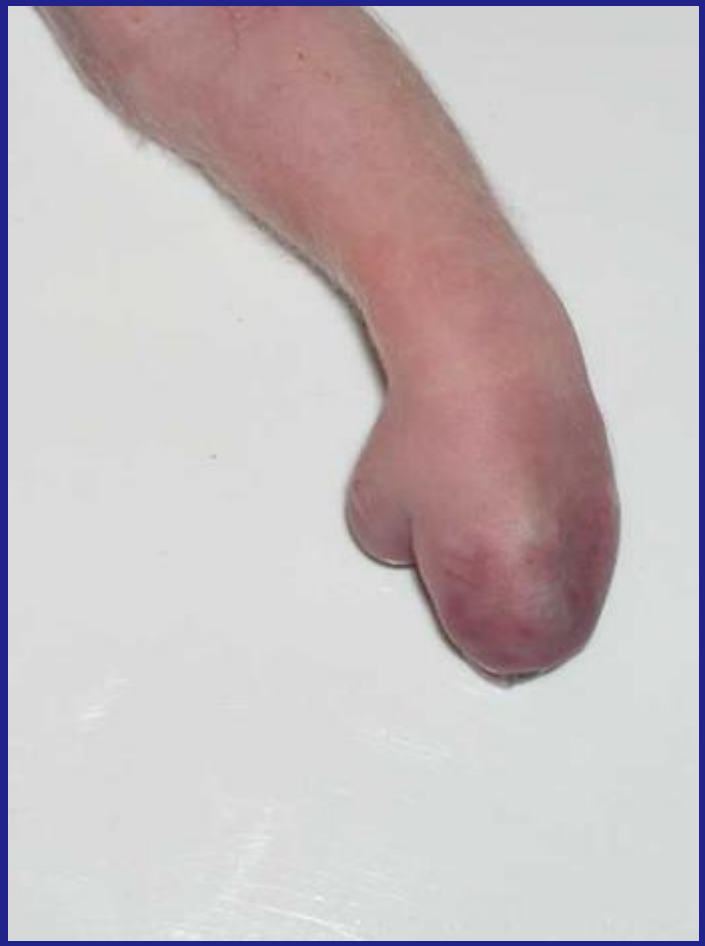
Complete or partial

Syndactyly

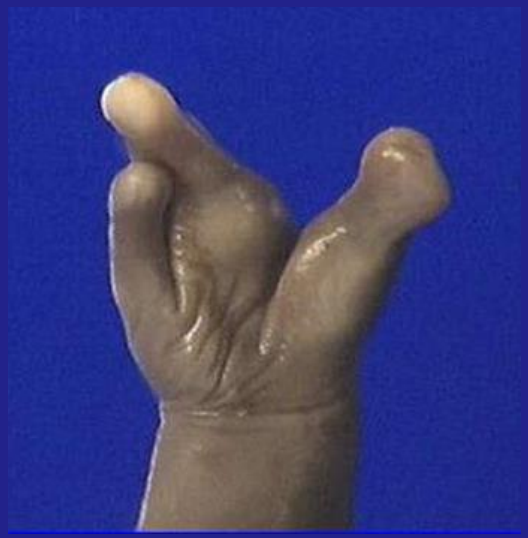
Bilateral syndactyly III-IV > Triploïdy



"mitten" hand / Pseudosyndactyly.



Ectrodactyly (cleft hand)



- Could be seen in a lot of genetic disorders:

-split hand/split foot malformation (SHFM1 > 4)

-Trisomy 6

-Ectrodactyly-Cleft Palate (ECP) syndrome

-Ectrodactyly-Polydactyly

-Ectrodactyly-Ectodermal Dysplasia-Clefting (EEC) syndrome

In total more than 50 syndromes!

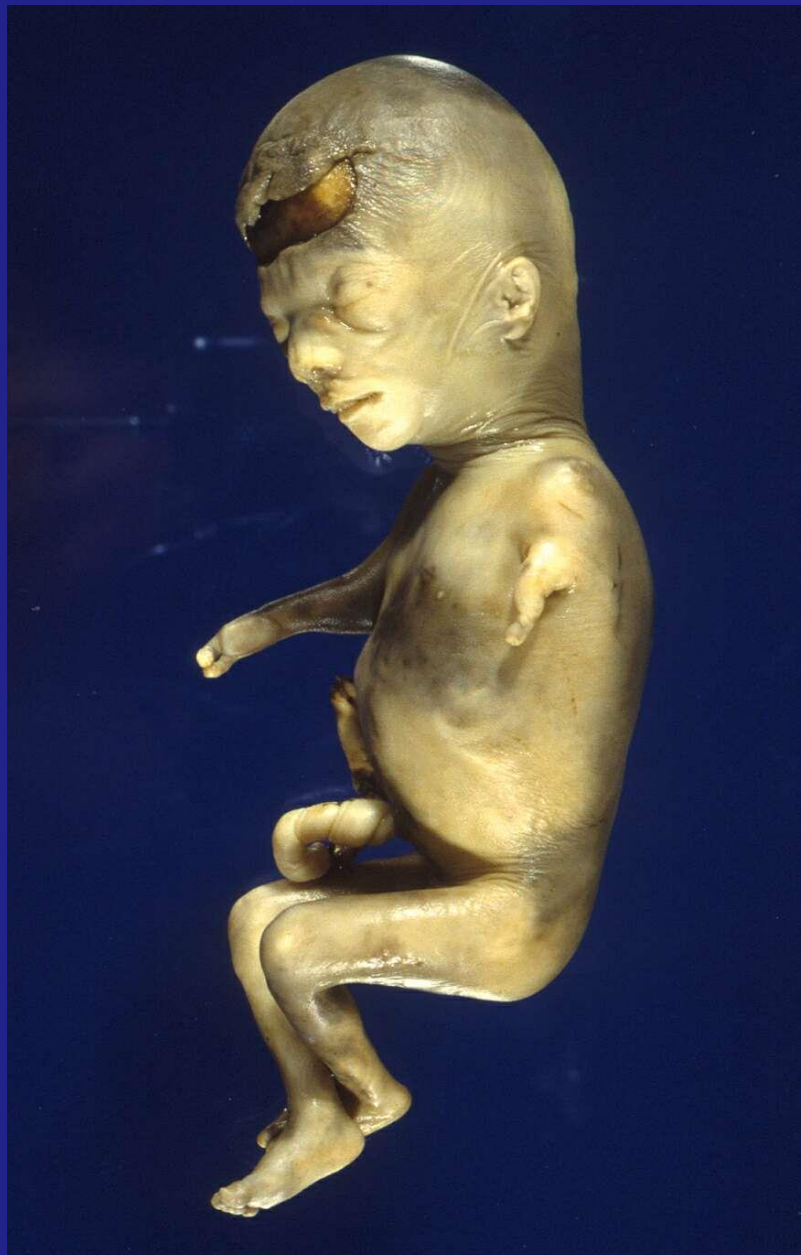
Phocomelia / Thalidomide like

- Multiples types
- Heterogenous group
- Multifactorial

- Thalidomide was withdraw in 1962

Other agents:

Retinoic acid, Mebendazole, Radiations.

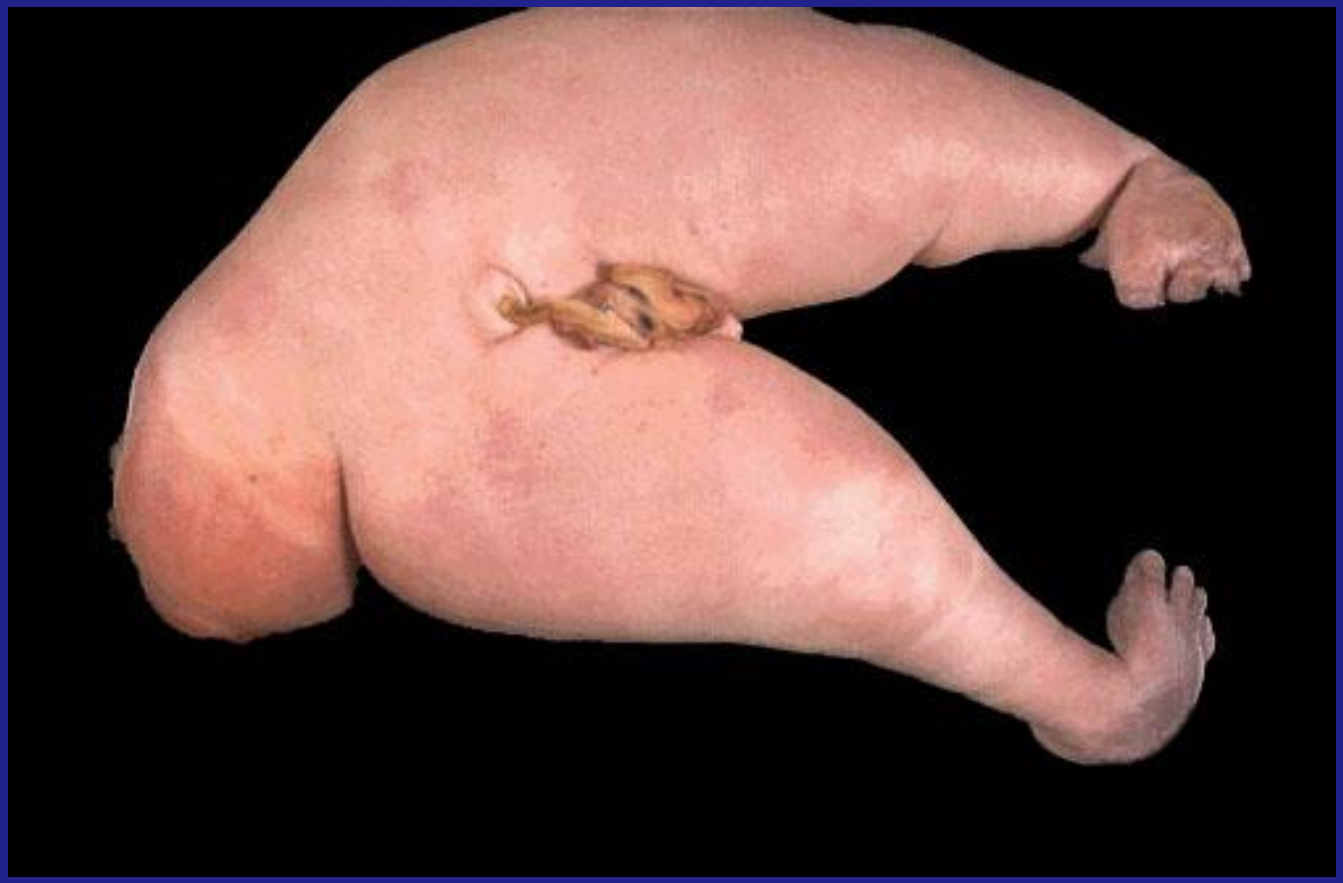


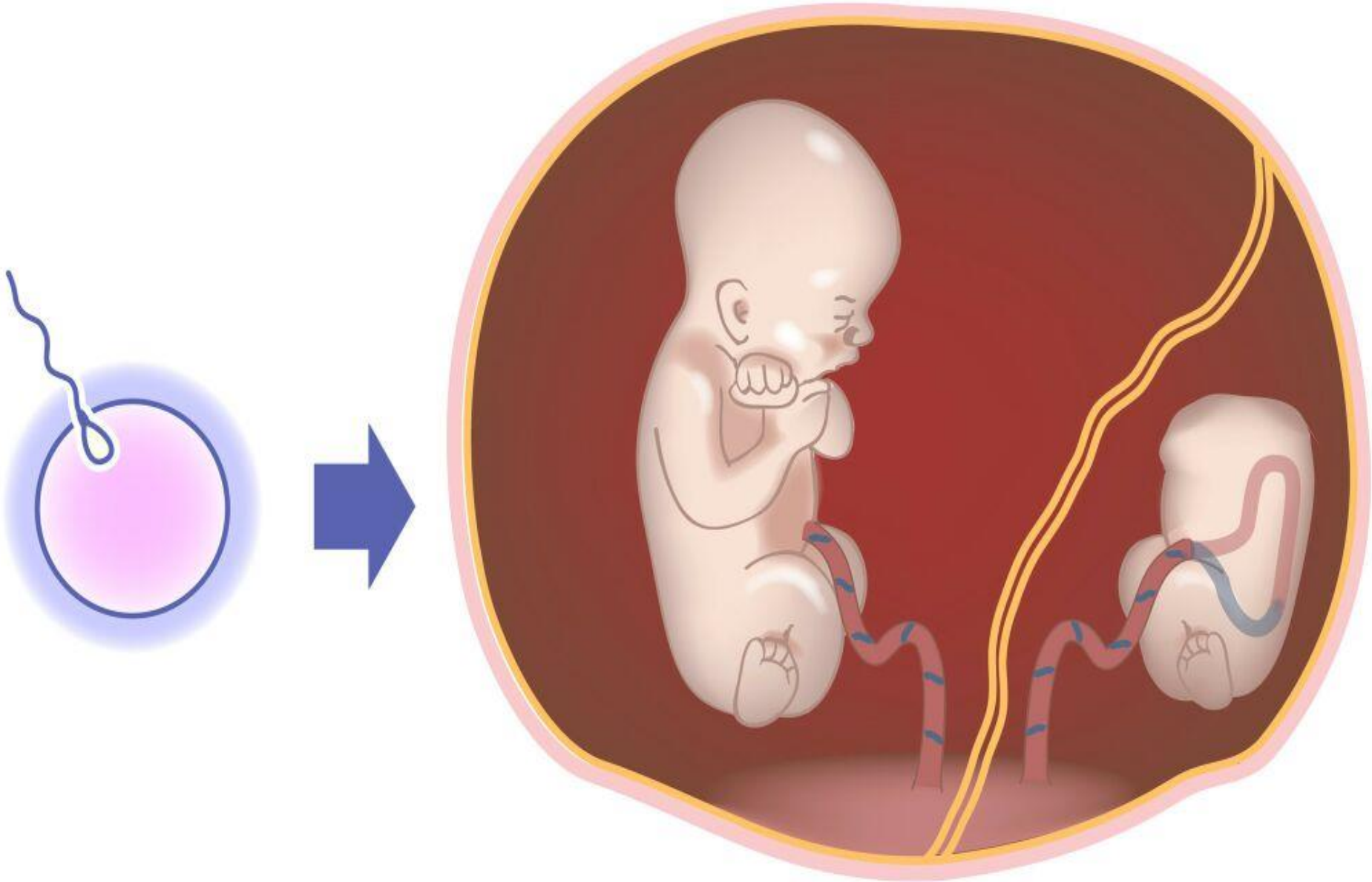
Particular syndromes

- Acardiac « monsters »
- body stalk anomaly
- iniencephaly
- Caudal regression syndrome
- sirenomely
- Amniotic band syndrome
- Twin-twin transfusion syndrome
- Siamese twins

Acardiac « Monster »

- TRAP Sequence:
- Twin Reversed Arterial Perfusion

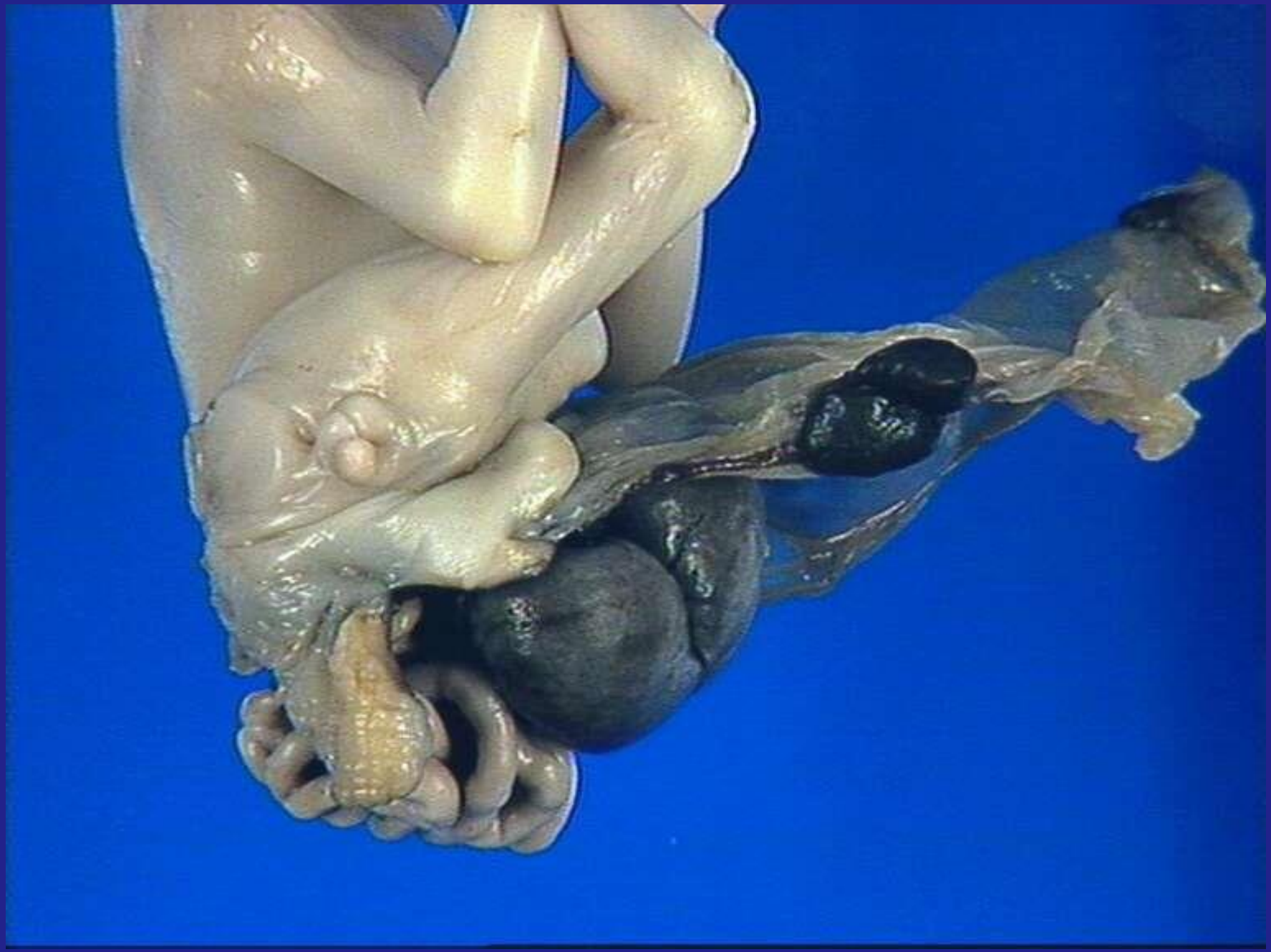




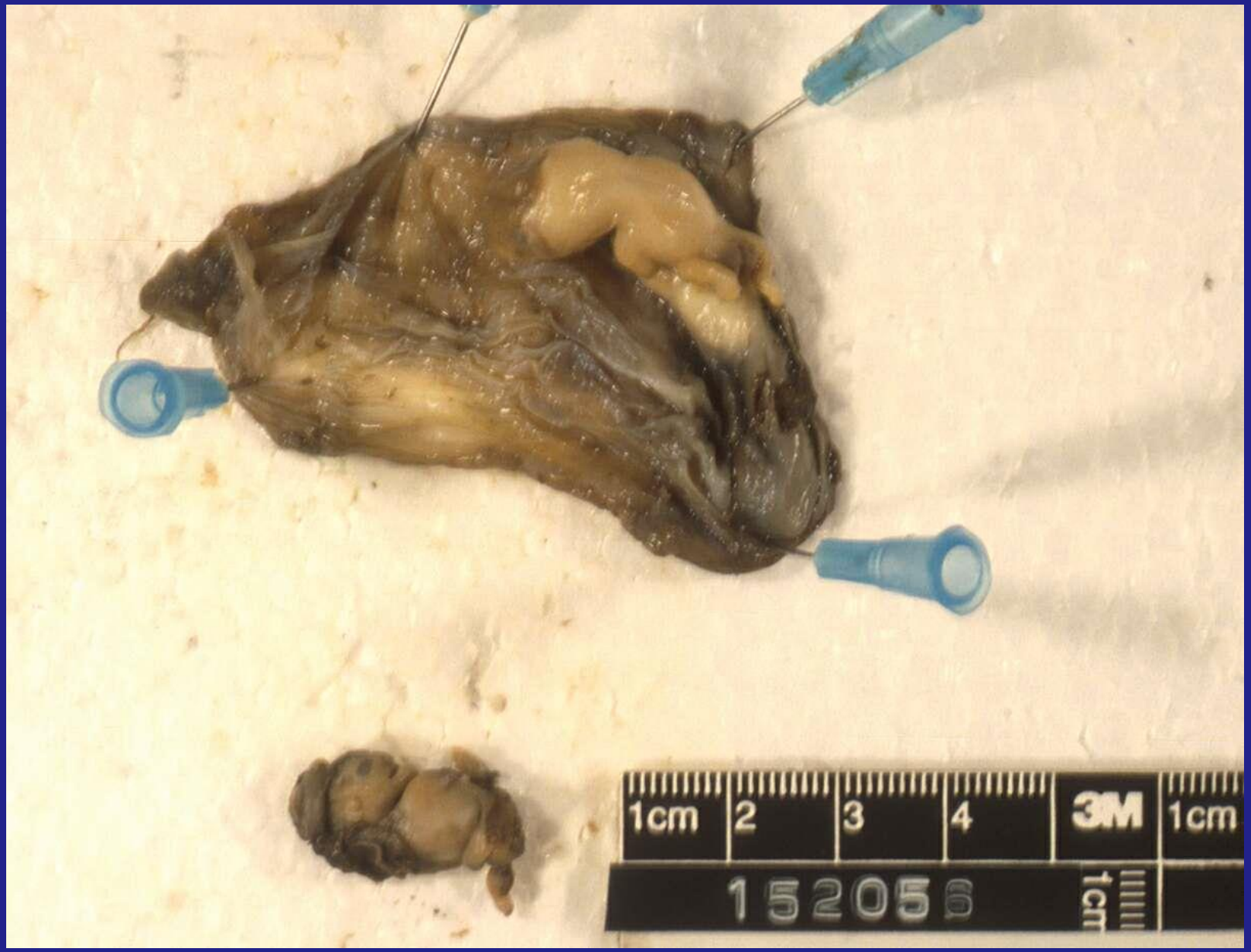
TRAP Sequence
(Twin-Reversed Arterial
Perfusion Sequence)

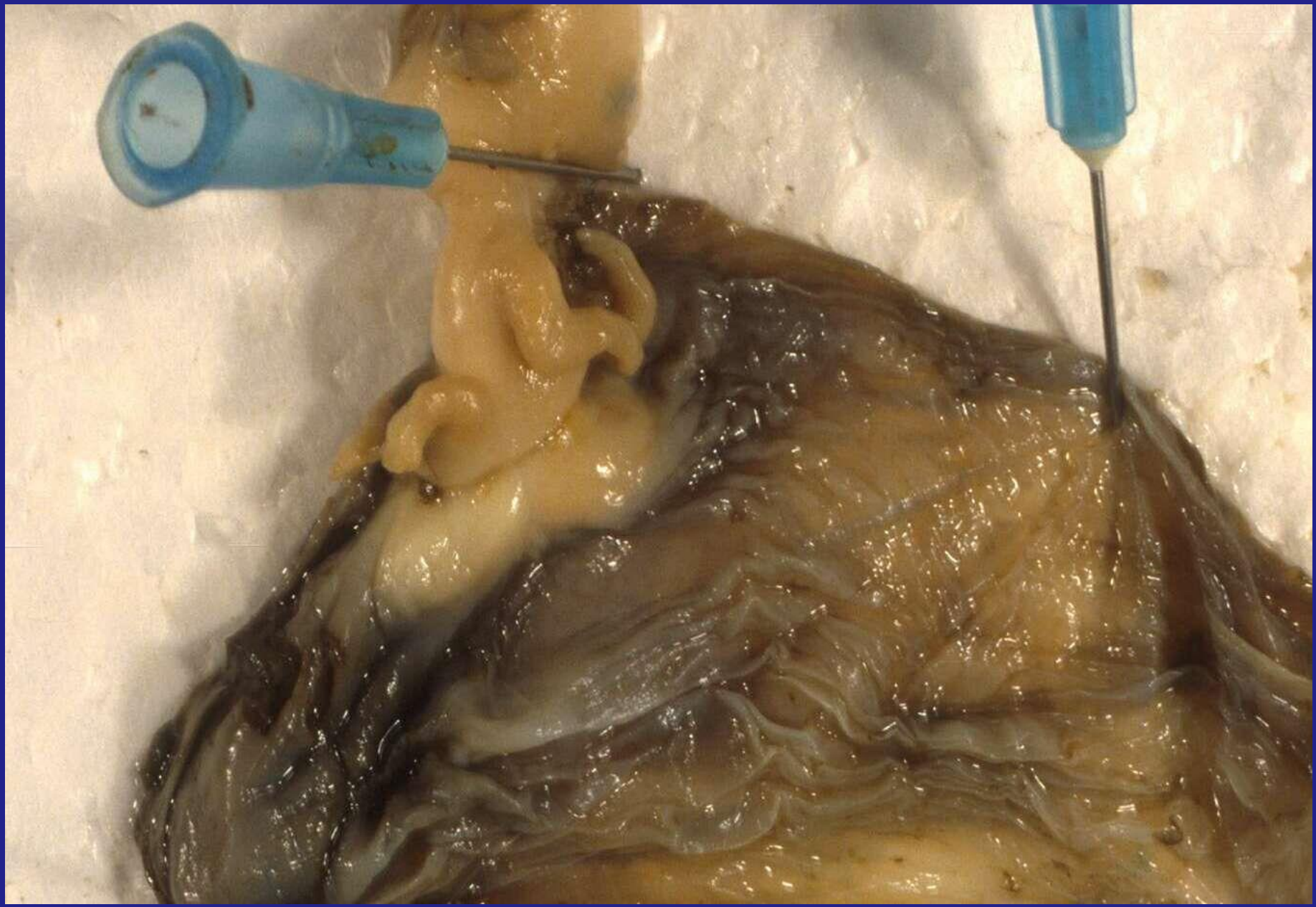
Body stalk anomaly

- Agenesis of umbilical cord

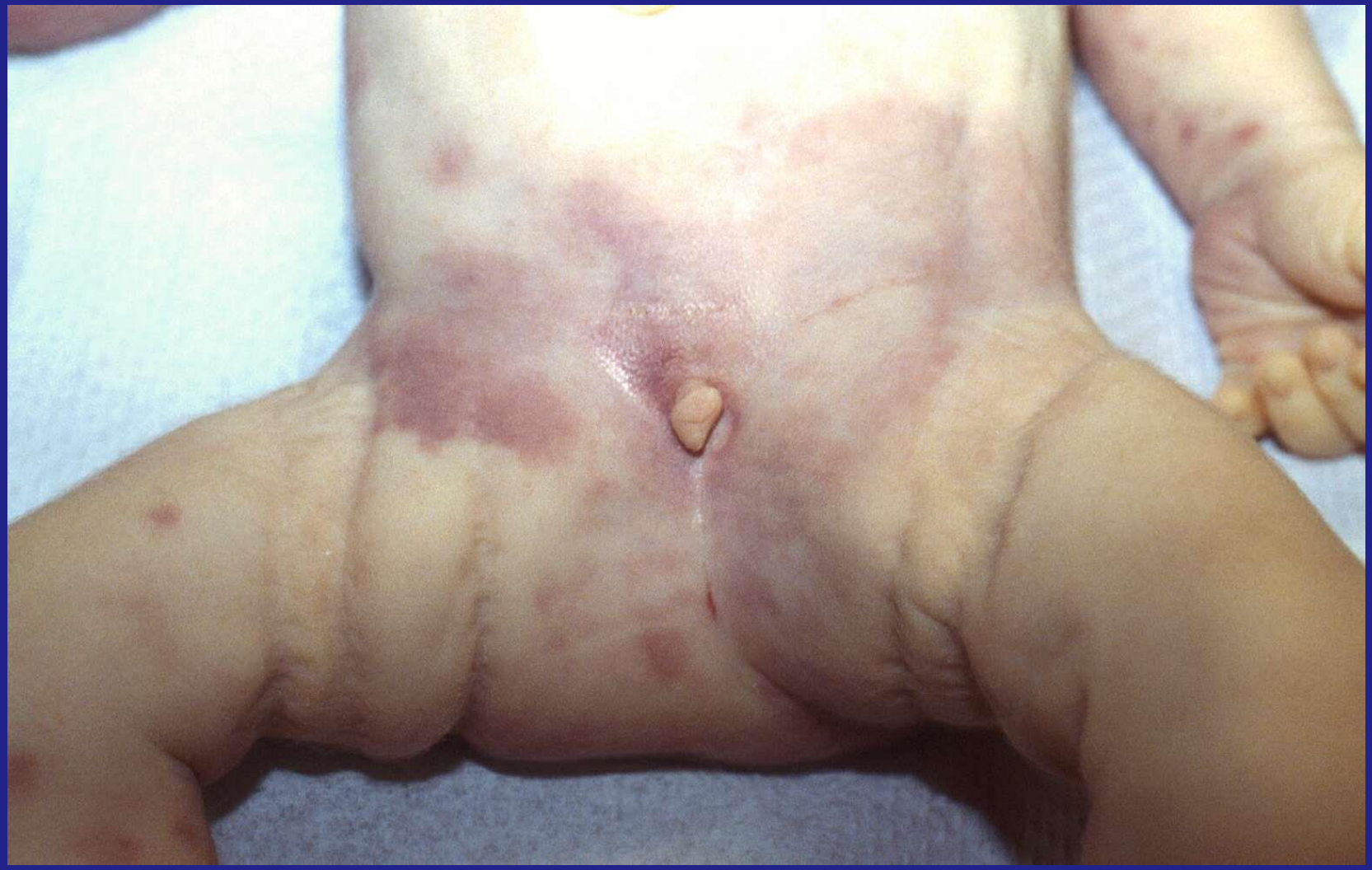


Body stalk anomaly (2)

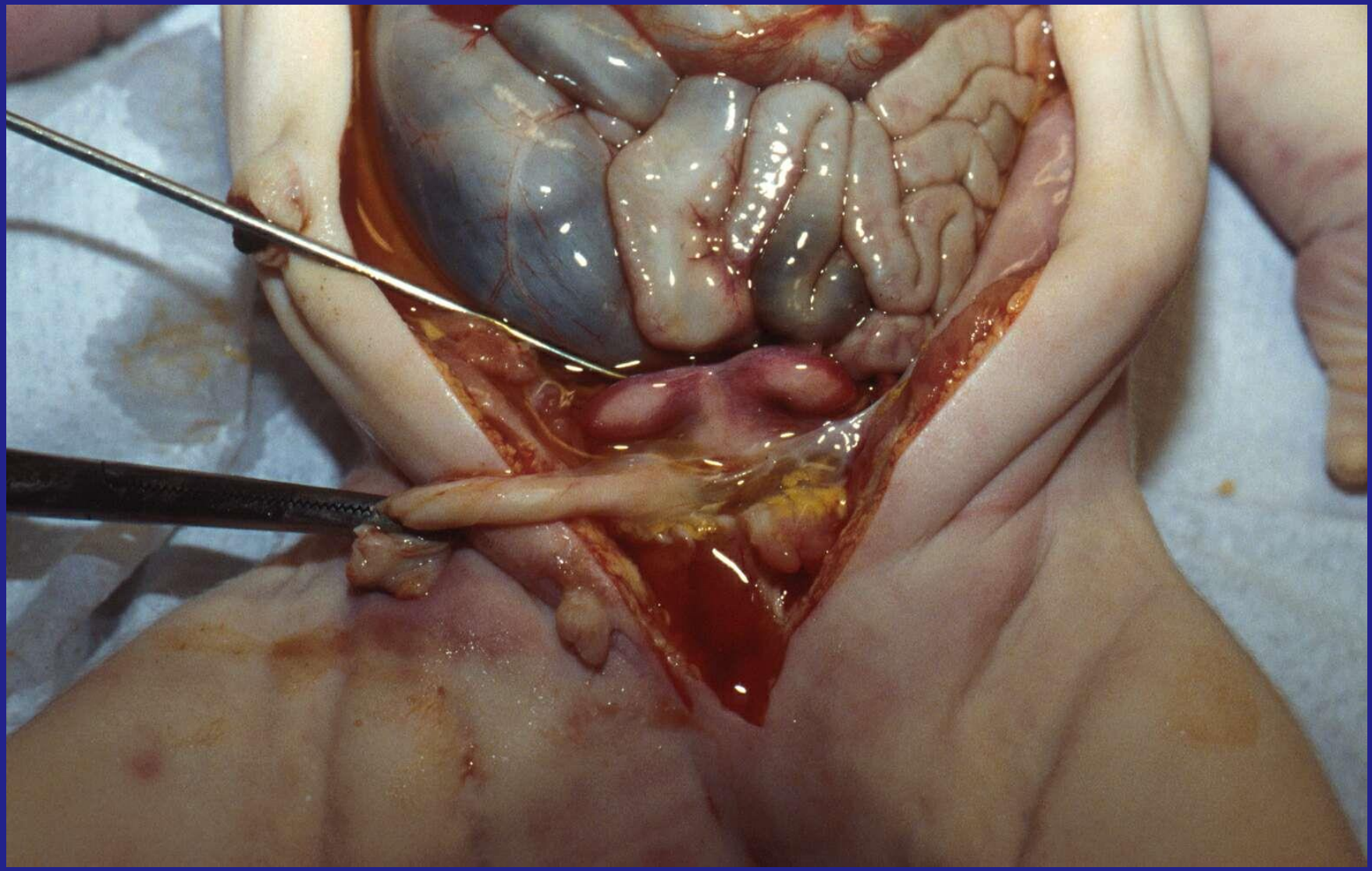




Caudal regression syndrome



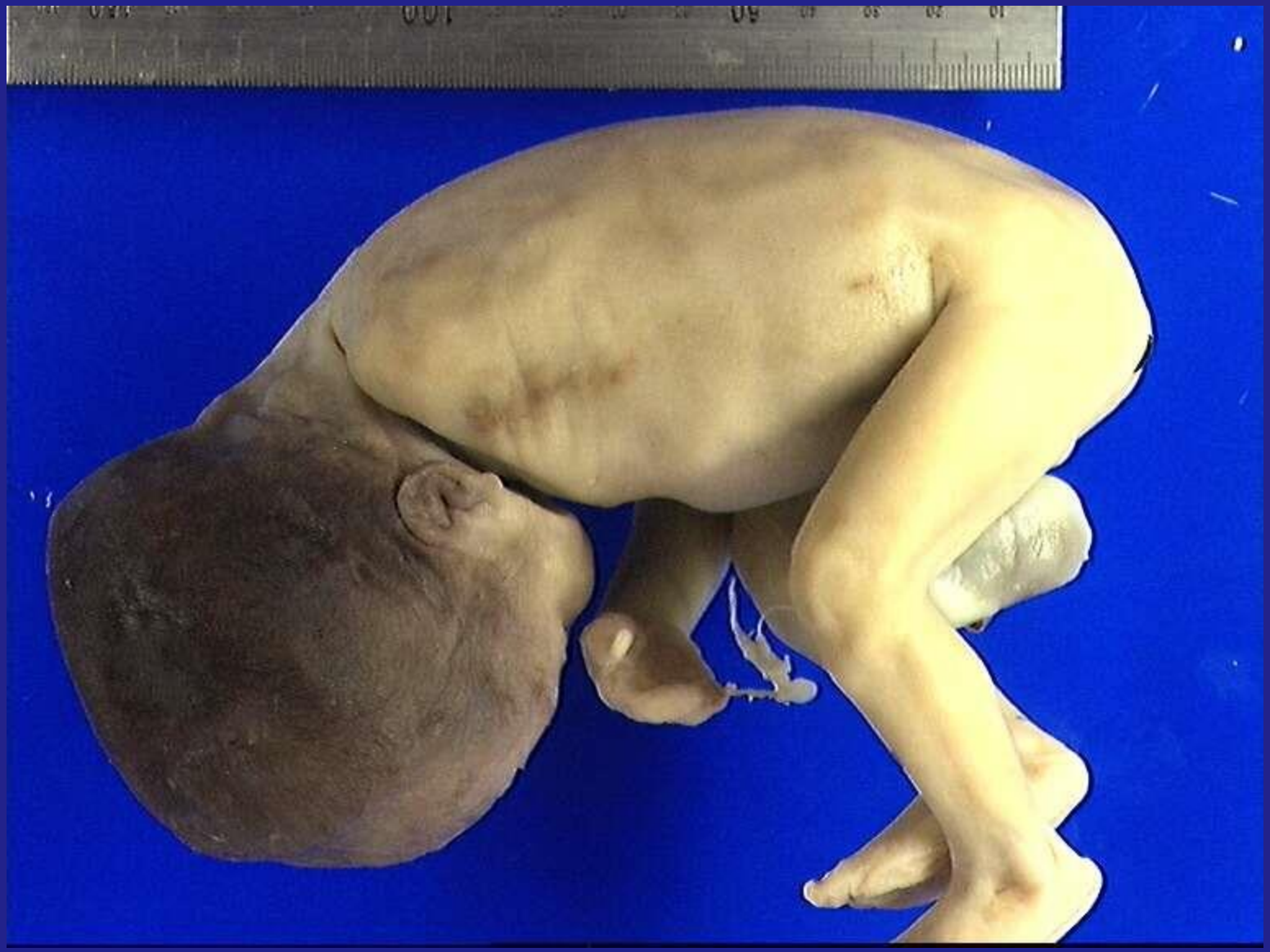
Caudal regression syndrome

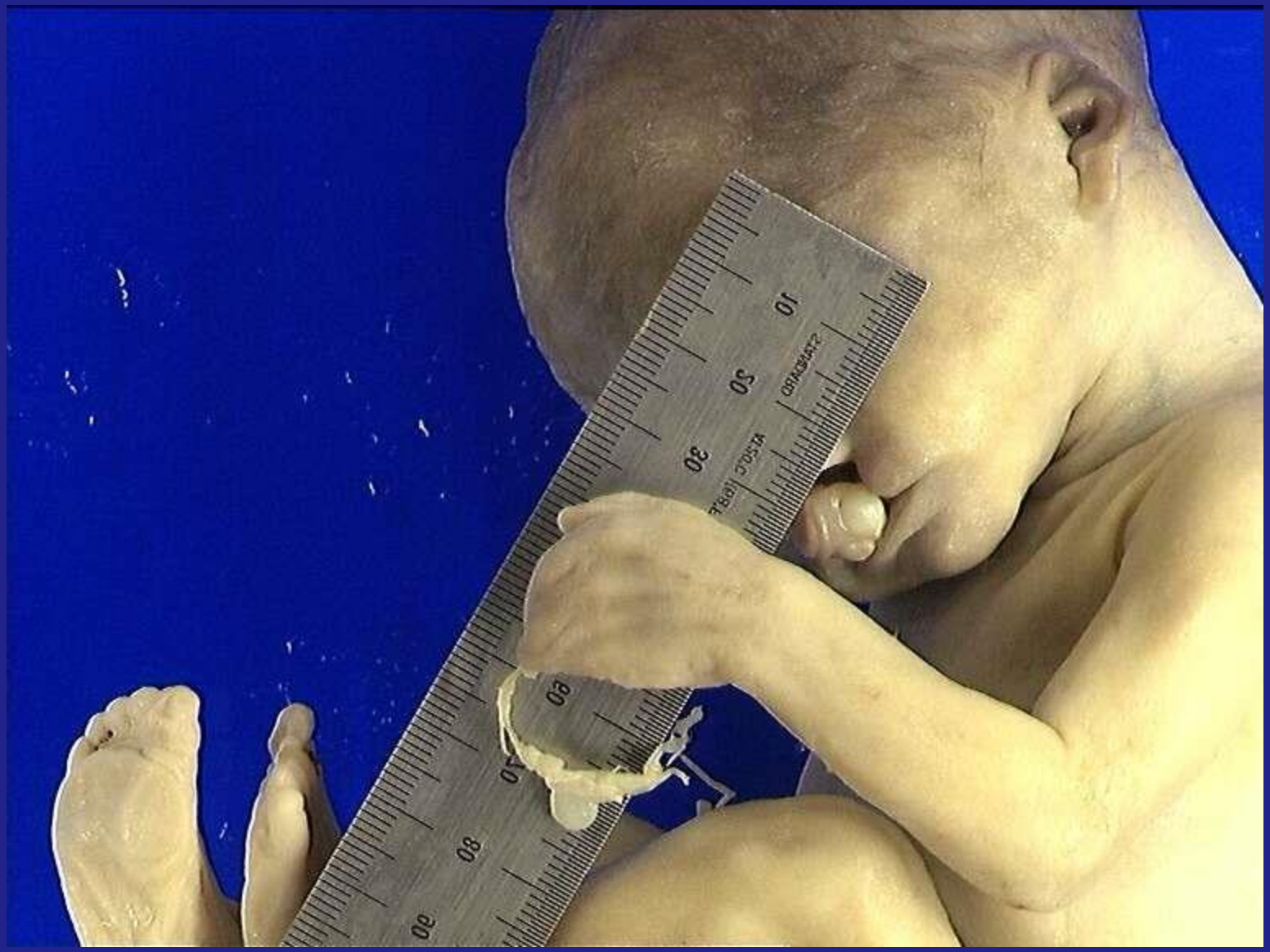


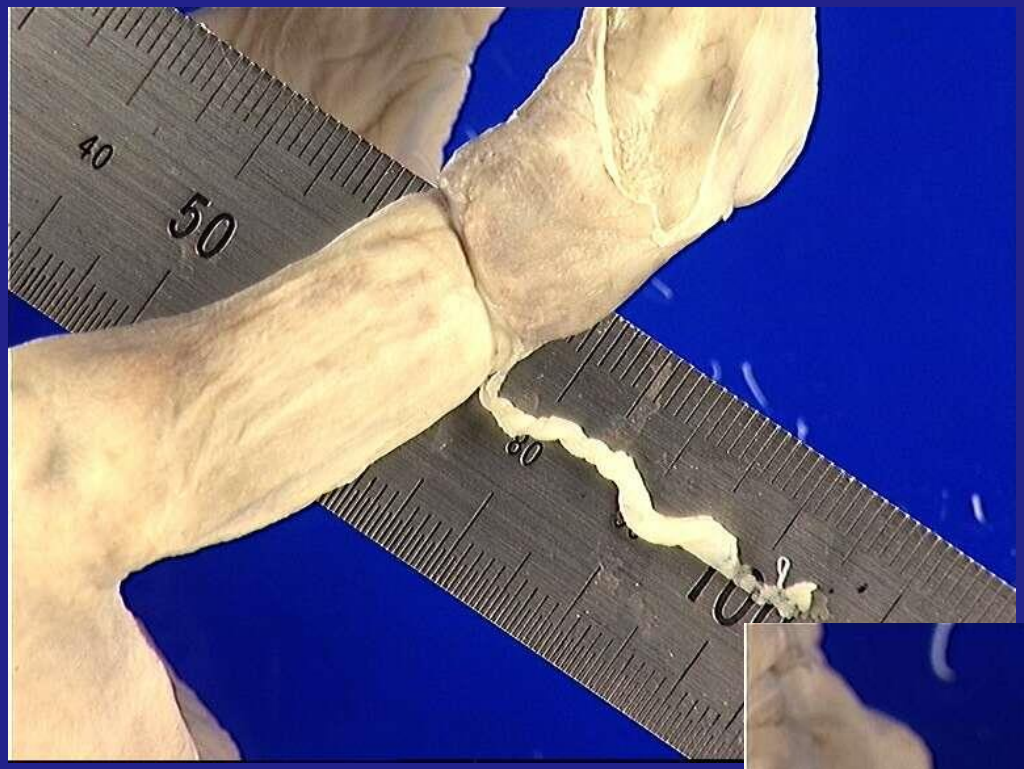
Sirenomely

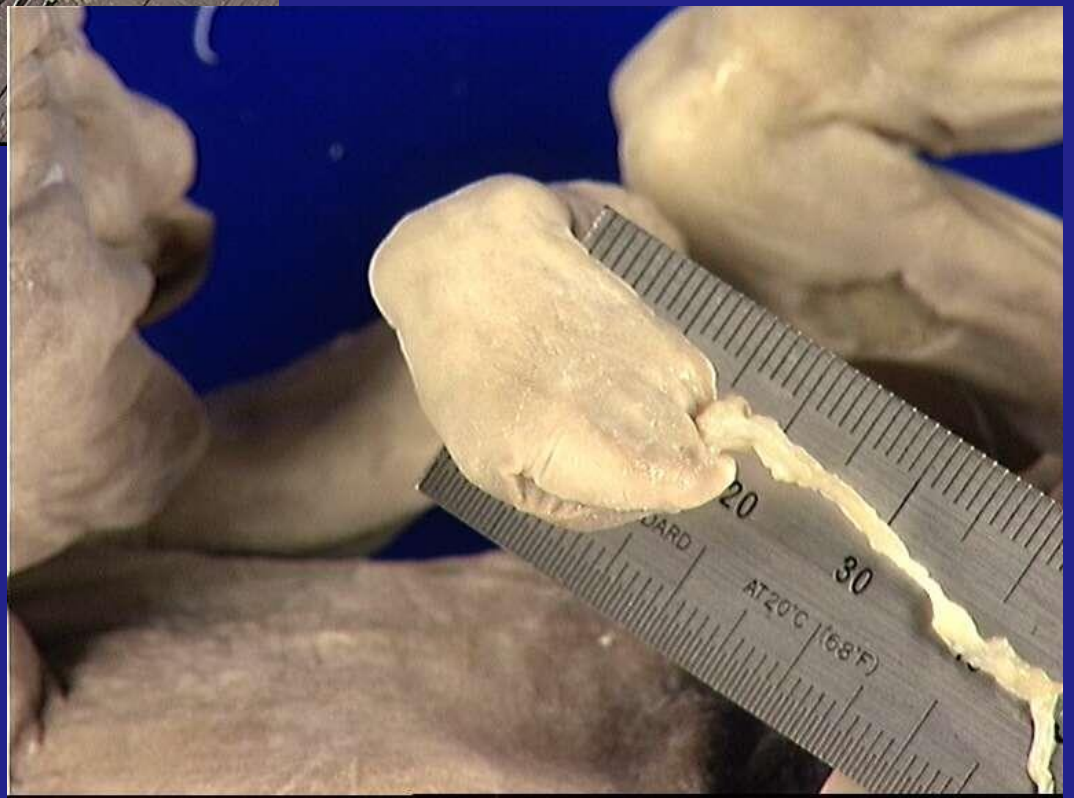
(extreme form of caudal regression)

Amniotic band syndrome






40
50
60


20
30
AT 20°C (68°F)

Twin-Twin transfusion syndrome

Siamese Twins

Chromosomal anomaly

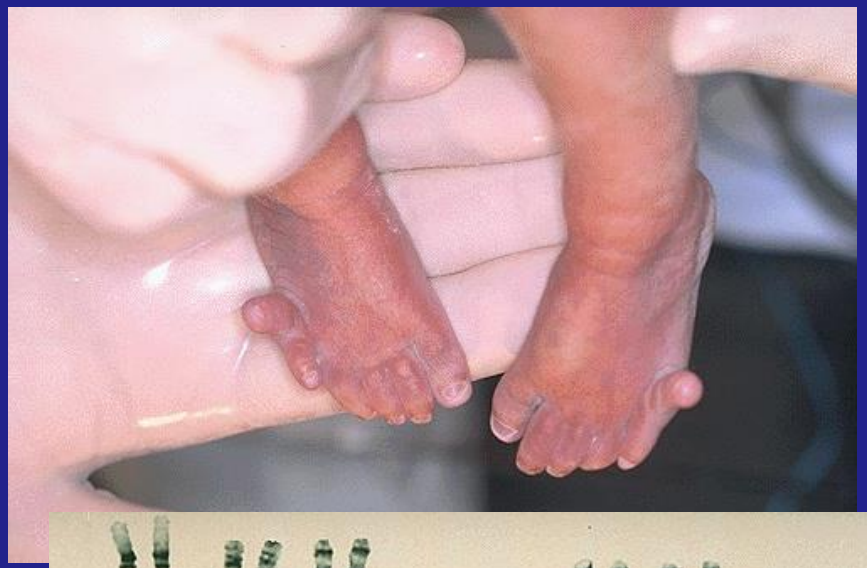
- Trisomy 13
- Trisomy 18
- Trisomy 21

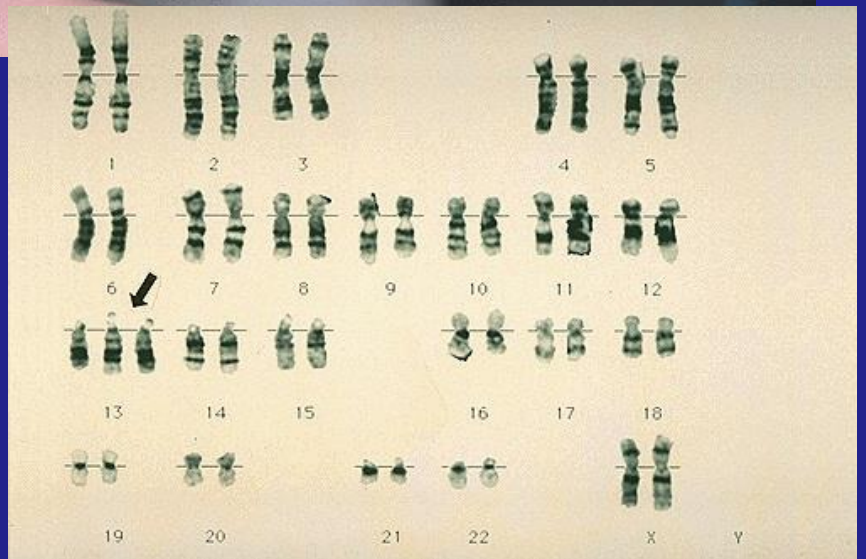
- Turner syndrome(X0)

- Triploïdy

Trisomy 13 (Patau Syndrome)

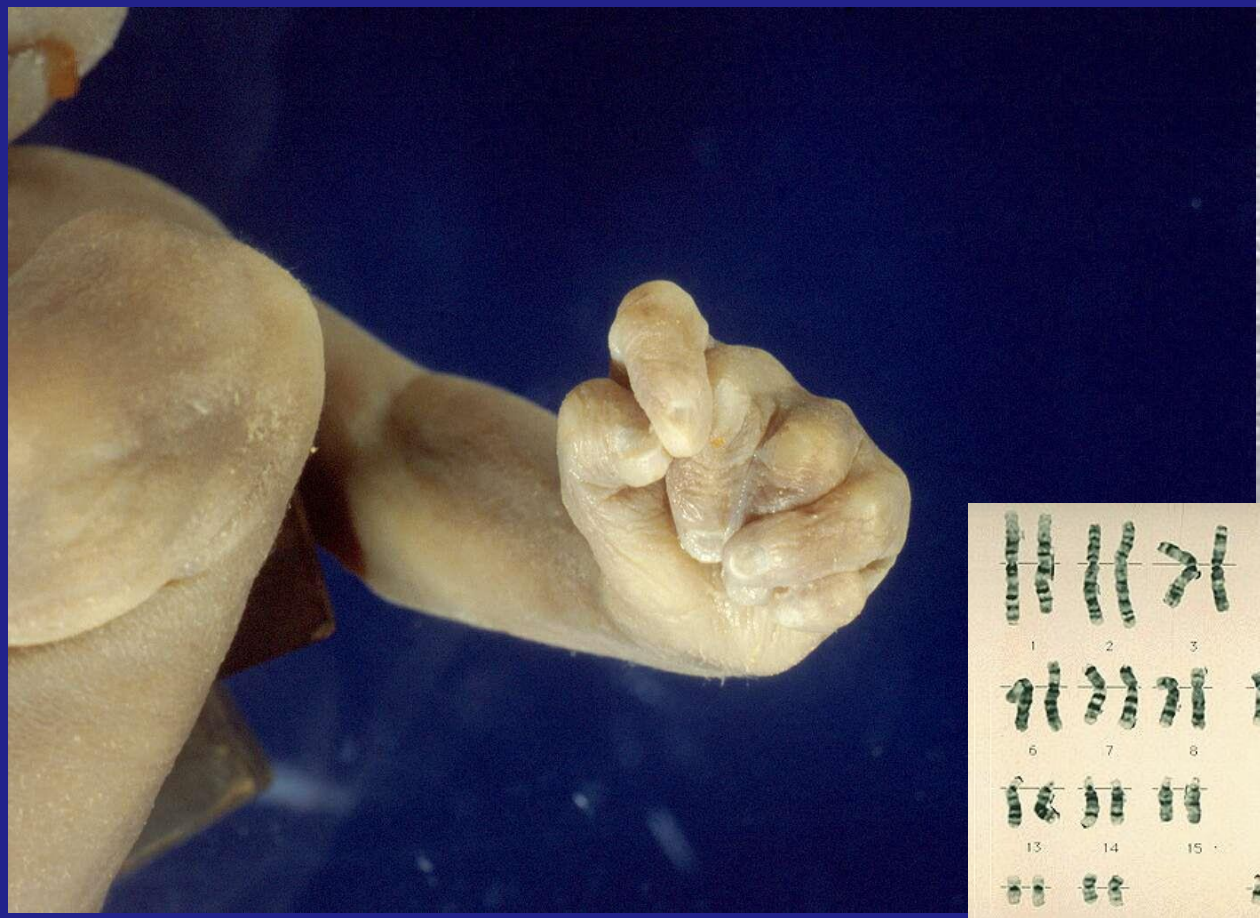
- 1/4000 - 1/10.000 birth
  - dysmorphy, cleft lip / palate, polydactyly, microphtalmy

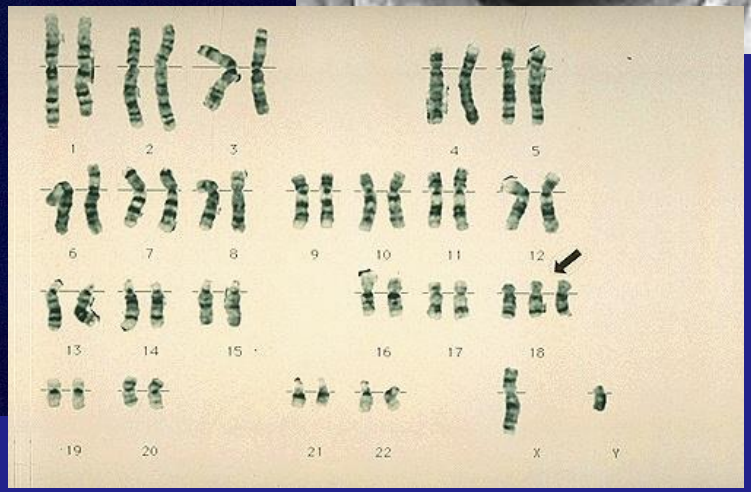




Trisomy 18 (Edwards Syndrome)

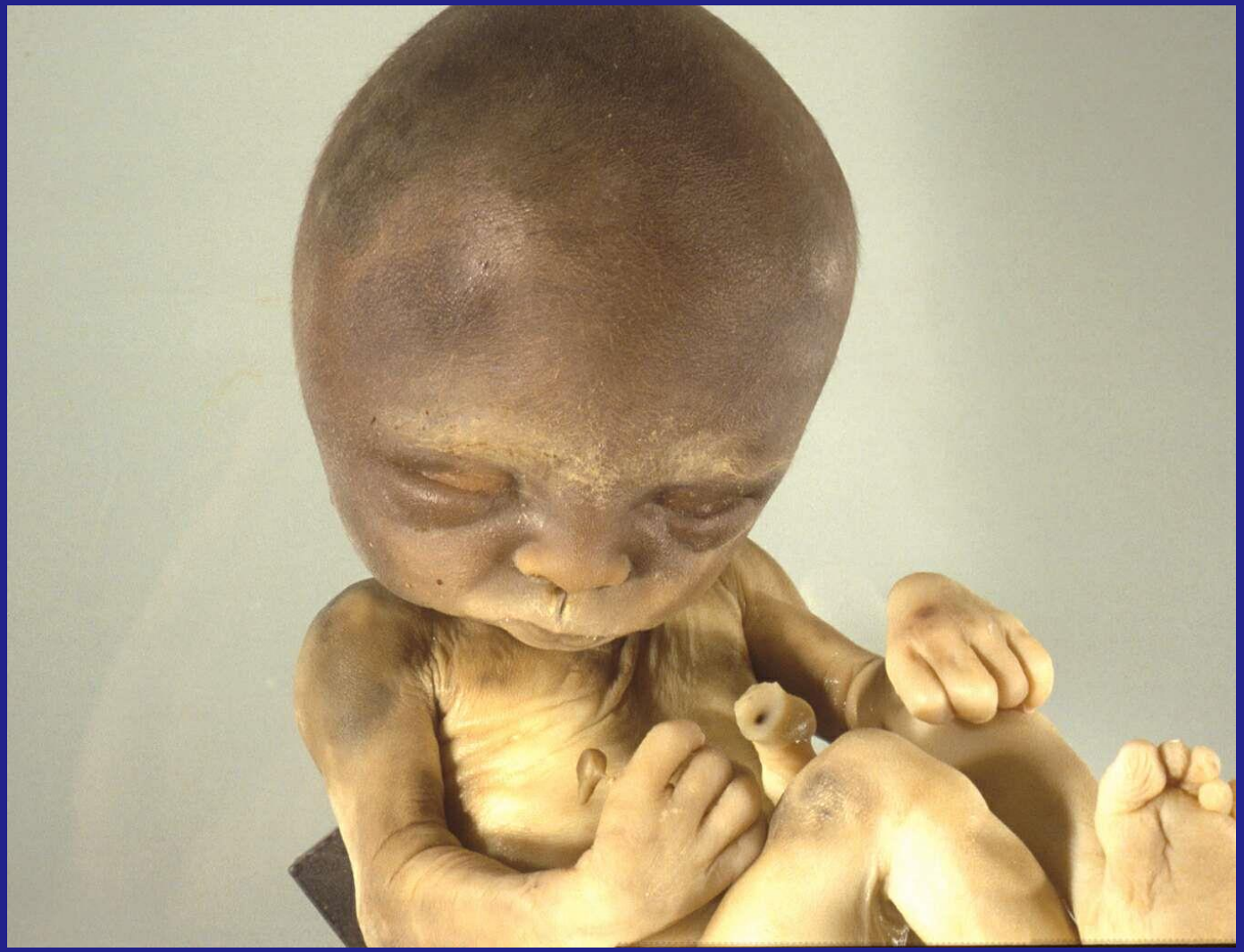
- 1/8.000 birth ! Sex ratio 4F / 1M
  - dysmorphy, microcephaly, micrognathia, arthrogryposis,
  - visceral malformations are frequent





Trisomie 18

- Phenotype may vary!!! In this case macrocephaly

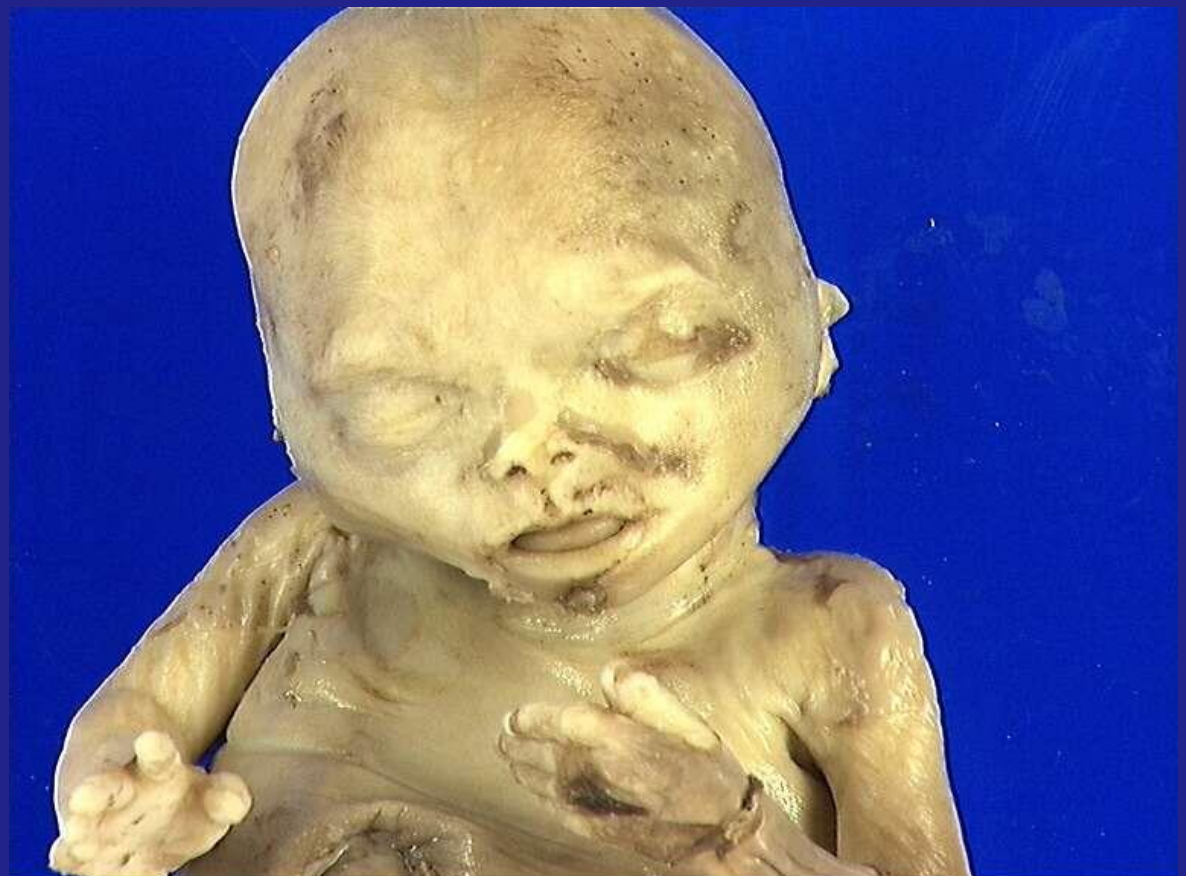


Trisomy 21 (Down Syndrome)

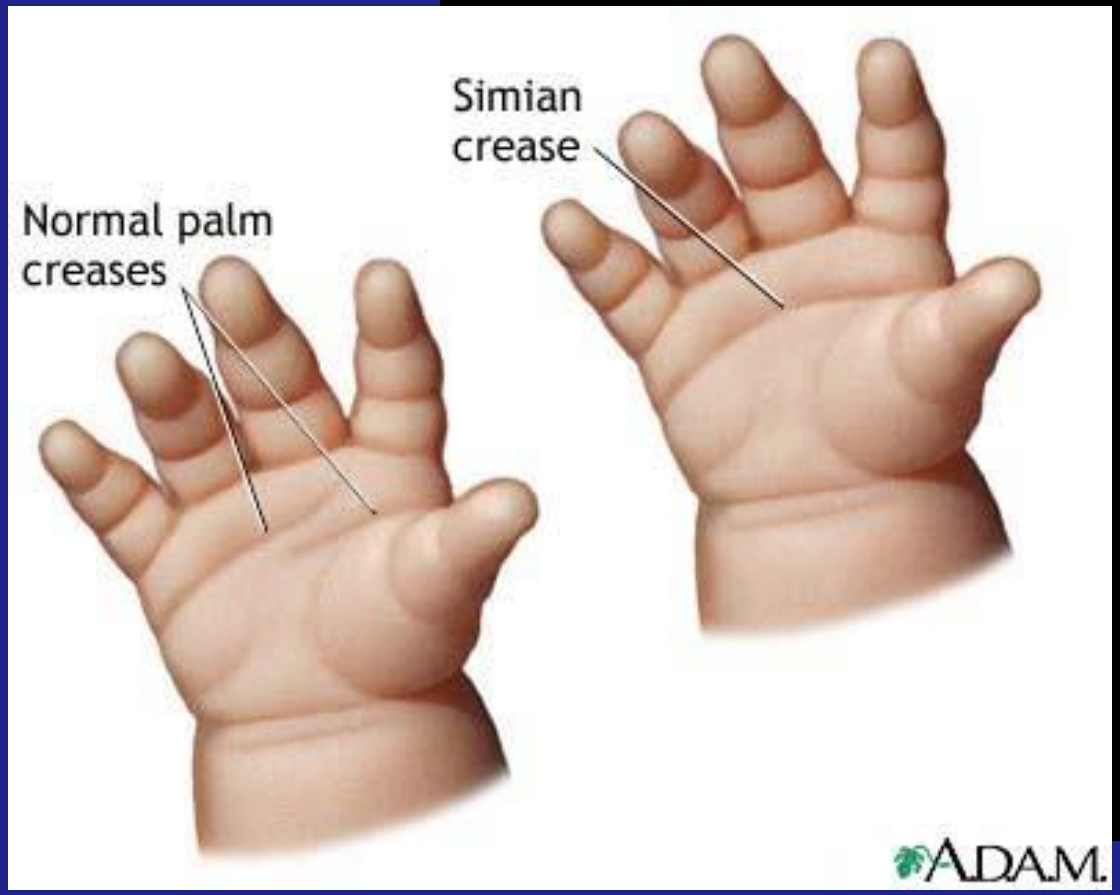
- Frequency is highly related to maternal age:

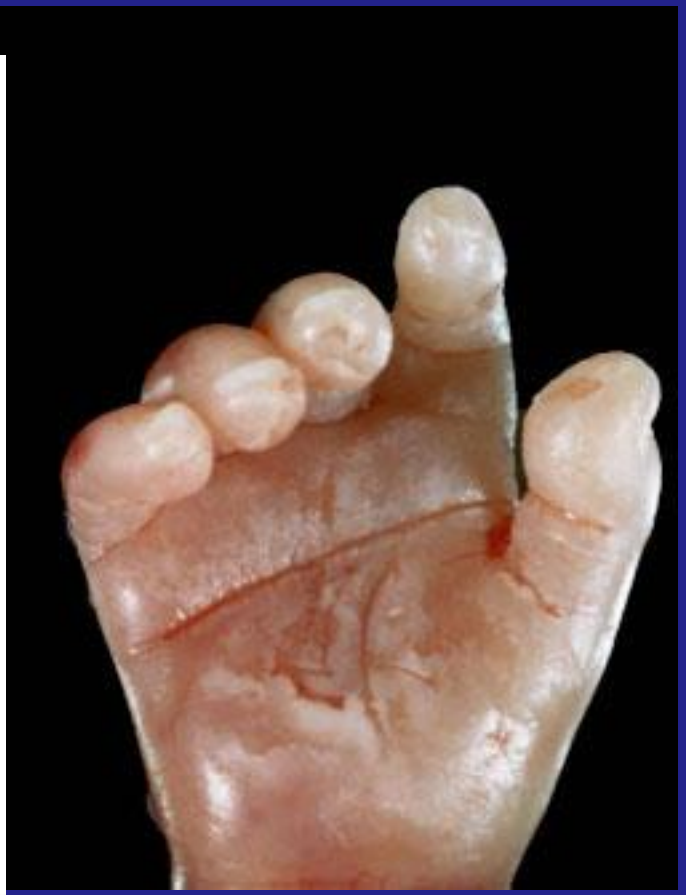
1/700 birth at 20 > 1/13 at 45 !

• Large Protruding tongue , upward-slanting palpebral fissures, flat nasal bridge , low set ears, single transverse palmar crease, short fifth finger with clinodactyly, cystic hygroma, heart defect.



Trisomy 21
single transverse palmar crease

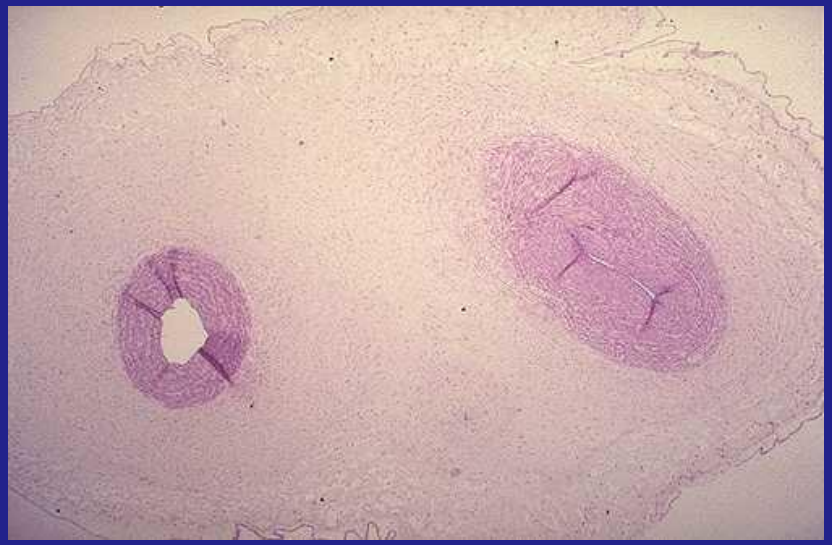




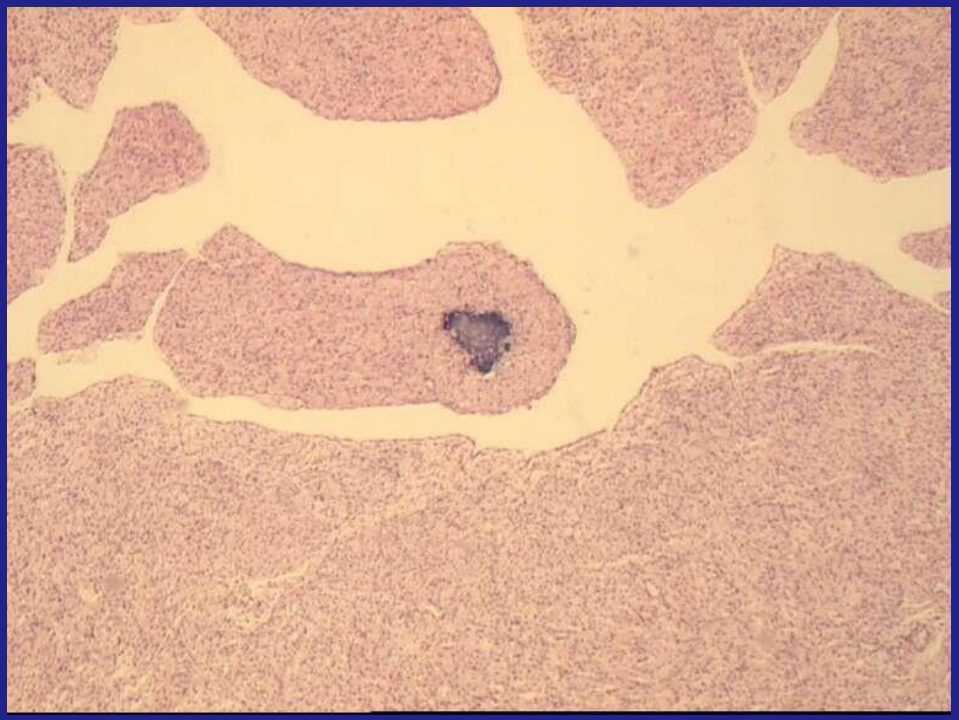
Trisomy 21

- Secondary signs:

Single umbilical artery



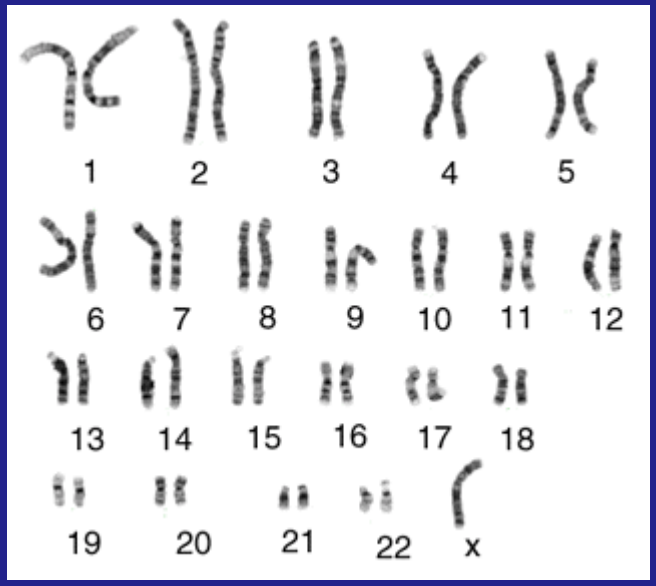
isolated myocardic calcification

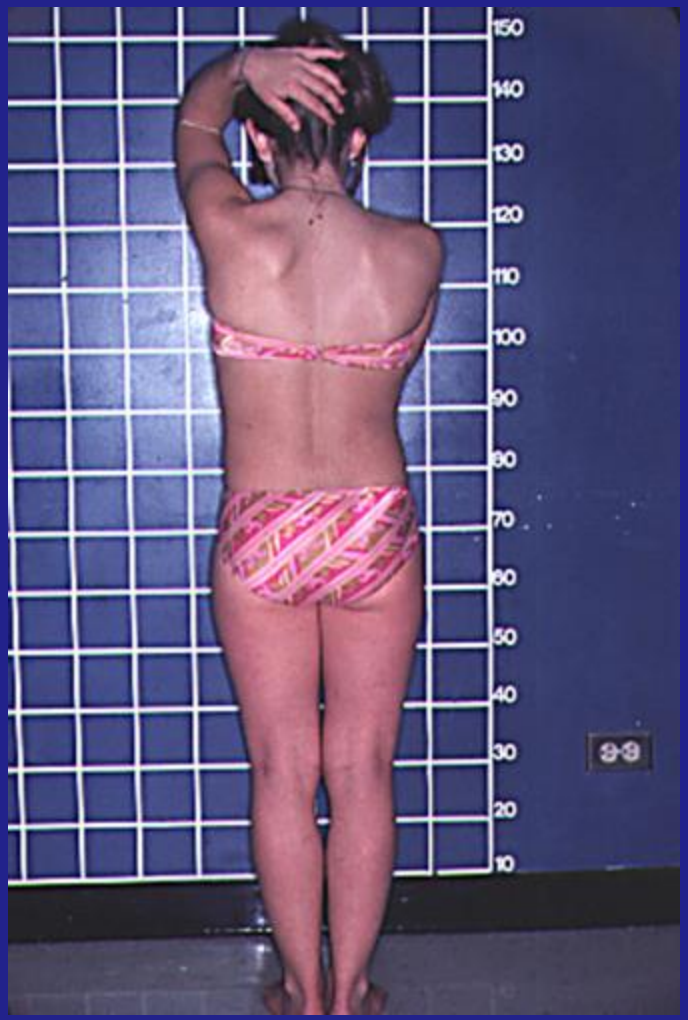


Turner Syndrome (X0)

- 0,4 / 1000 female birth
- (Real frequency is higher, elevated miscarriage rate)
- Short stature, short neck , cystic hygroma, loss of ovarian function.

Turner Syndrome (X0)



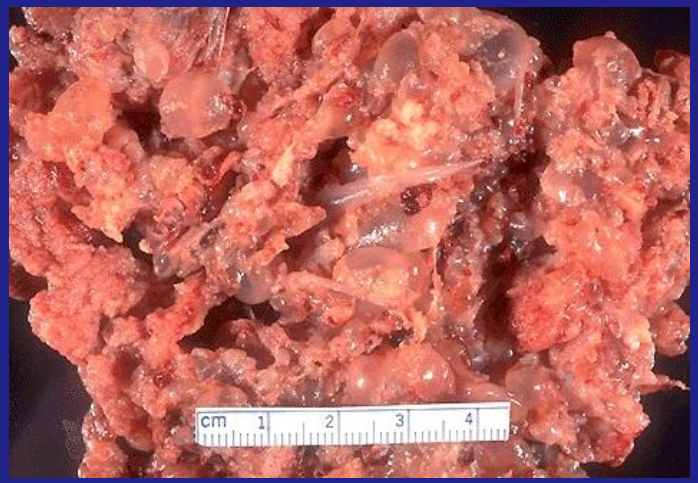


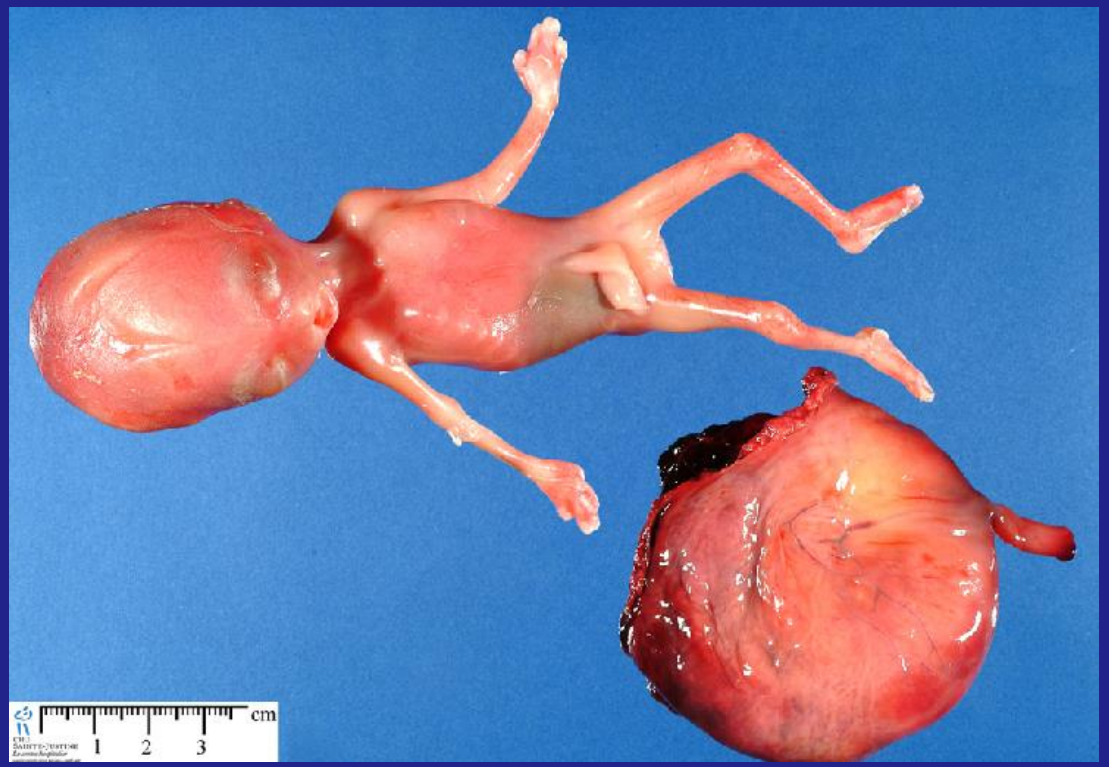
Triploïdy

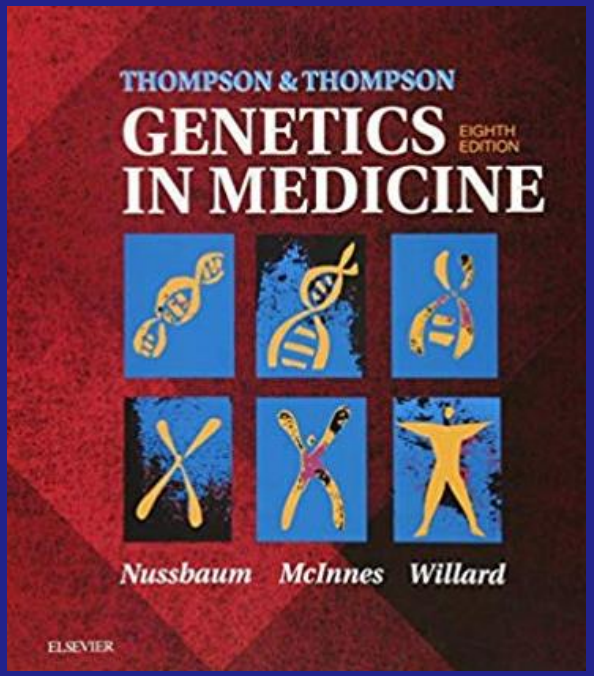
- Up to 10% in first trimester spontaneous abortion, rare at birth
- Typical syndactyly III-IV, cleft lip/palate, omphalocele, CNS anomalies (50%), cardiac malformation (30%)

Triploïdy

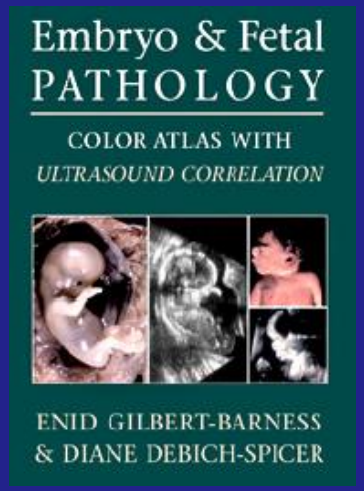
	fetus size	Adrenals	Placenta
Diandric	Nl / Light IUGR	Nl	partial hydatiform
Digynic	Marked IUGR	hypoplastic	small, non molar

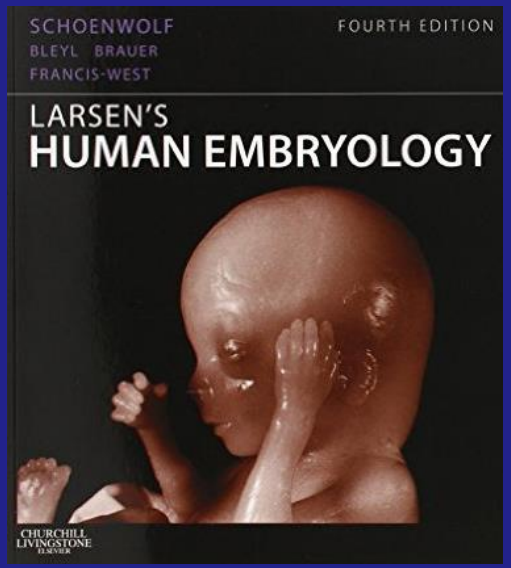






LONDON MEDICAL DATABASES





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