Congenital disorders : hereditary and non-hereditary diseases

Congenital disorders (birth defects) are an important cause of pregnancy loss, premature death and life-long disability. The pathological conditions arise before birth, become evident at birth or become manifest later in life. Some hereditary disorders with a dominant trait may manifest in adults, and the patients may have children. Risk factors for congenital disorders include genetic, environmental and wider societal factors. Pathology of hereditary or non-hereditary congenital disorders is summarized herein.

Ref.: Moorthie S, et al. An overview of concepts and approaches used in estimating the burden of congenital disorders globally. J Community Genet 2018; 9(4): 347-362. doi: 10.1007/s12687-017-0335-3

Congenital disorders

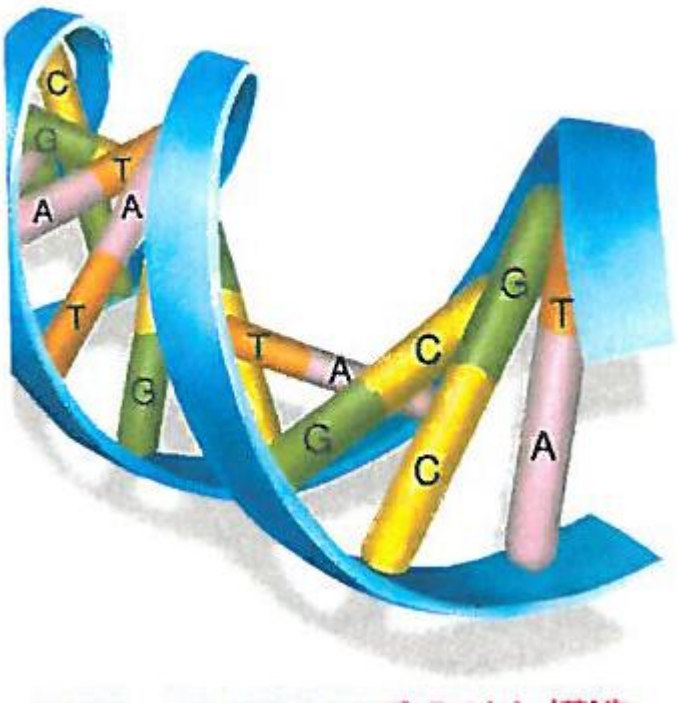
- Chromosomal abnormalities
- Single gene disorders

  1) dominant inheritance

  2) recessive inheritance

  3) X-linked inheritance

  4) mitochondrial inheritance
- Polygenic disorders
- Congenital anomalies



Mode of inheritance

- **Mendelian heredity (mendelism)**
  (Law of dominance and uniformity, law of segregation and law of independent assortment)
  1) Autodomal dominant inheritance
  2) Autosomal recessive inheritance
  3) X-linked inheritance

- **Non-mendelian heredity**
  1) Polygenic inheritance
  2) Cytoplasmic inheritance = mitochondrial inheritance
  3) Epigenetic mutant

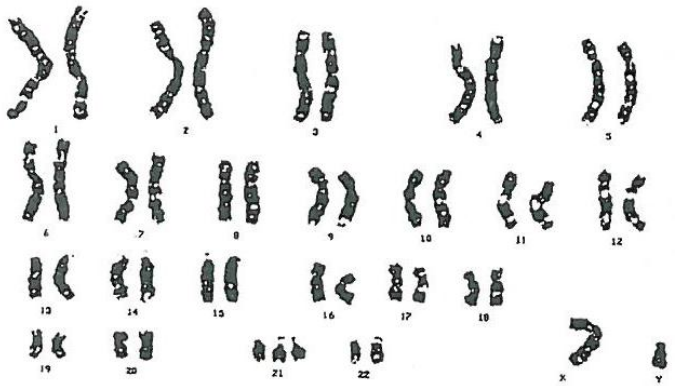
Hereditary disorders and genetic disorders

- **Hereditary disorders** ＝abnormalities in germ cells
  ～The abnormalities transmit from parents to child～

- **Genetic disorders**＝abnormalities in somatic cells
  ～The abnormalities are caused by acquired alterations of the gene, particularly in cancer～
  ～Not transmissible from the parents to child～

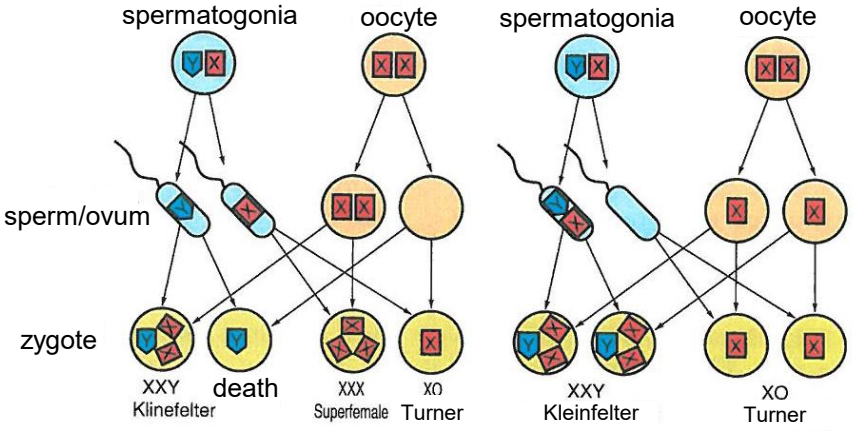
Chromosomal abnormalities

- Autosomal abnormalities
  1) Down syndrome (21 trisomy)
  2) Edwards syndrome (18 trisomy)
  3) Patau syndrome (13（D1) trisomy)
  4）Crying Cat Syndrome (deletion of the short arm of chromosome 5)

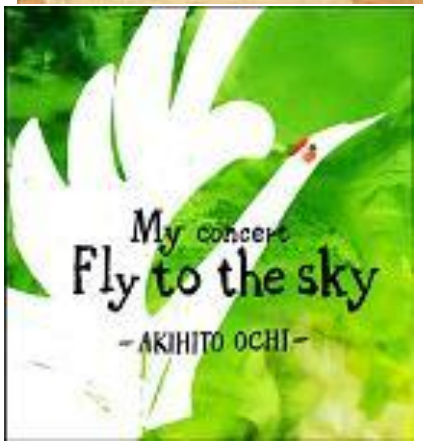


Karyotyping in Down syndrome

- Sex chromosome abnormalities
  1) Kleinfelter syndrome (XXY)
  2) Turner syndrome (XO)
  3) XYY syndrome
  4) XXX syndrome (superfemale)



Non-disjunction and abnormalities of sex chromosomes

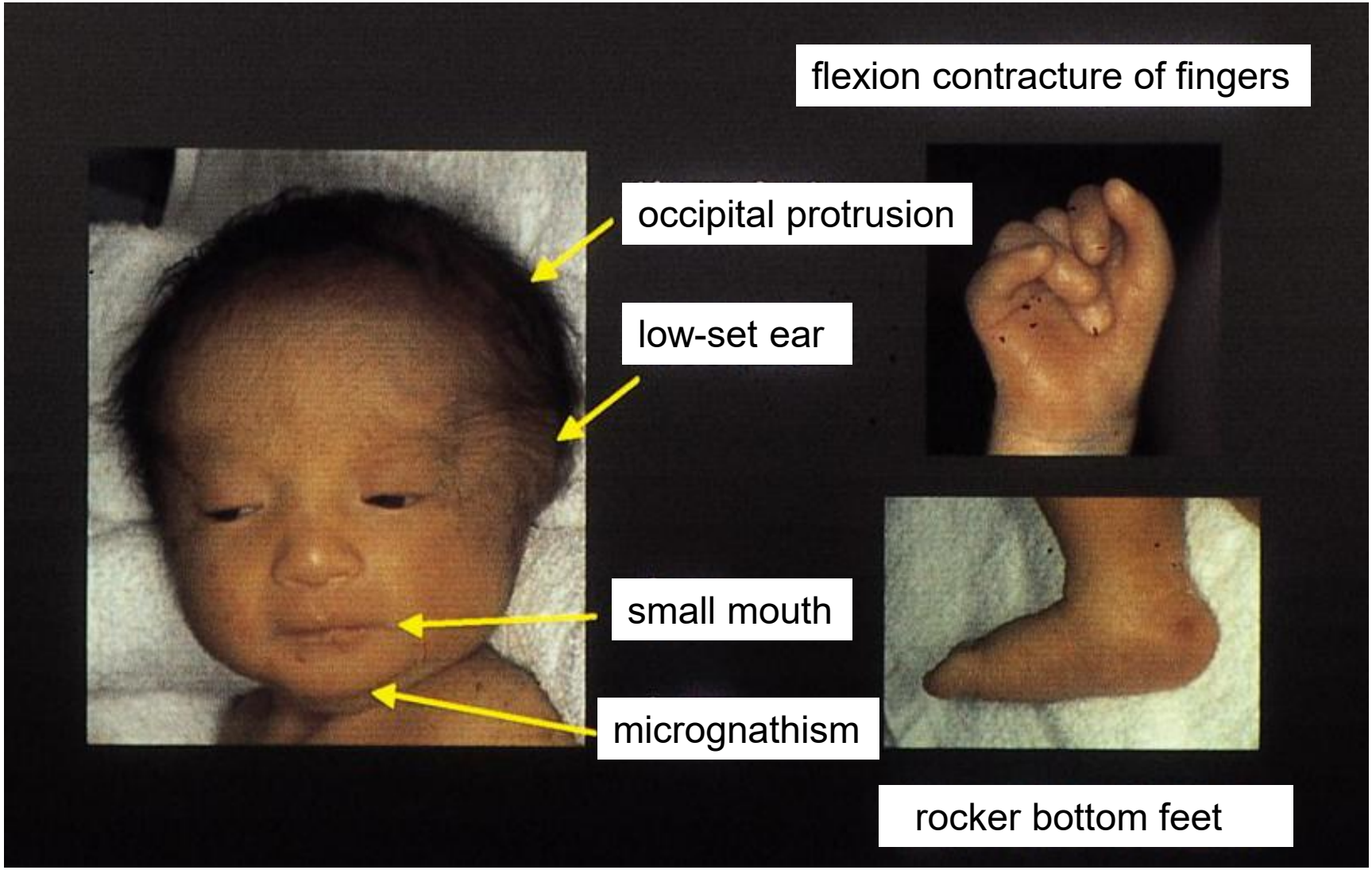


A heartful pianist with Down syndrome
～Mr. Akihito Ochi (越智章仁), having released 4 CDs～

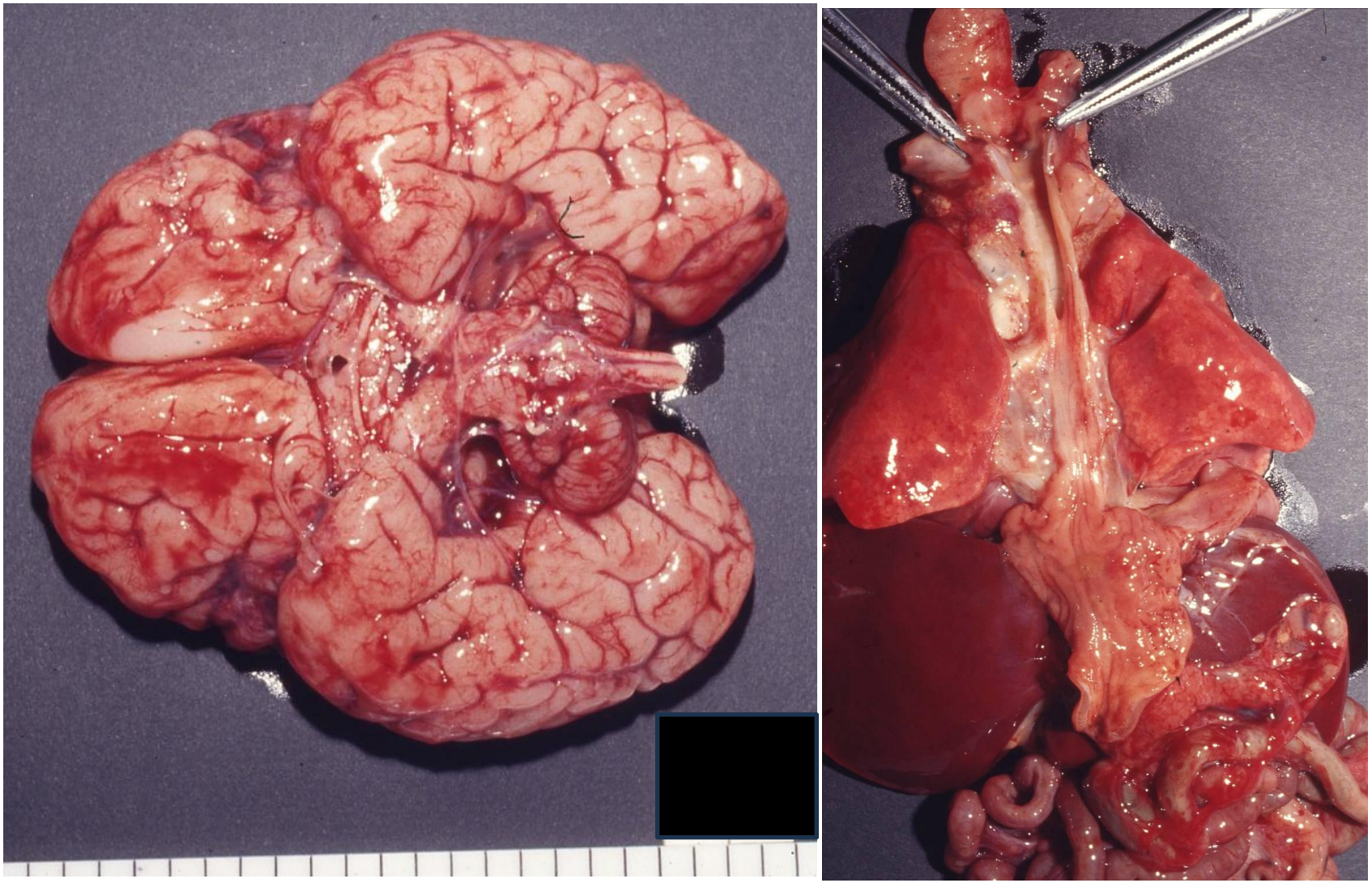
Down syndrome and leukemia

Transient abnormal myelopoiesis (TAM)

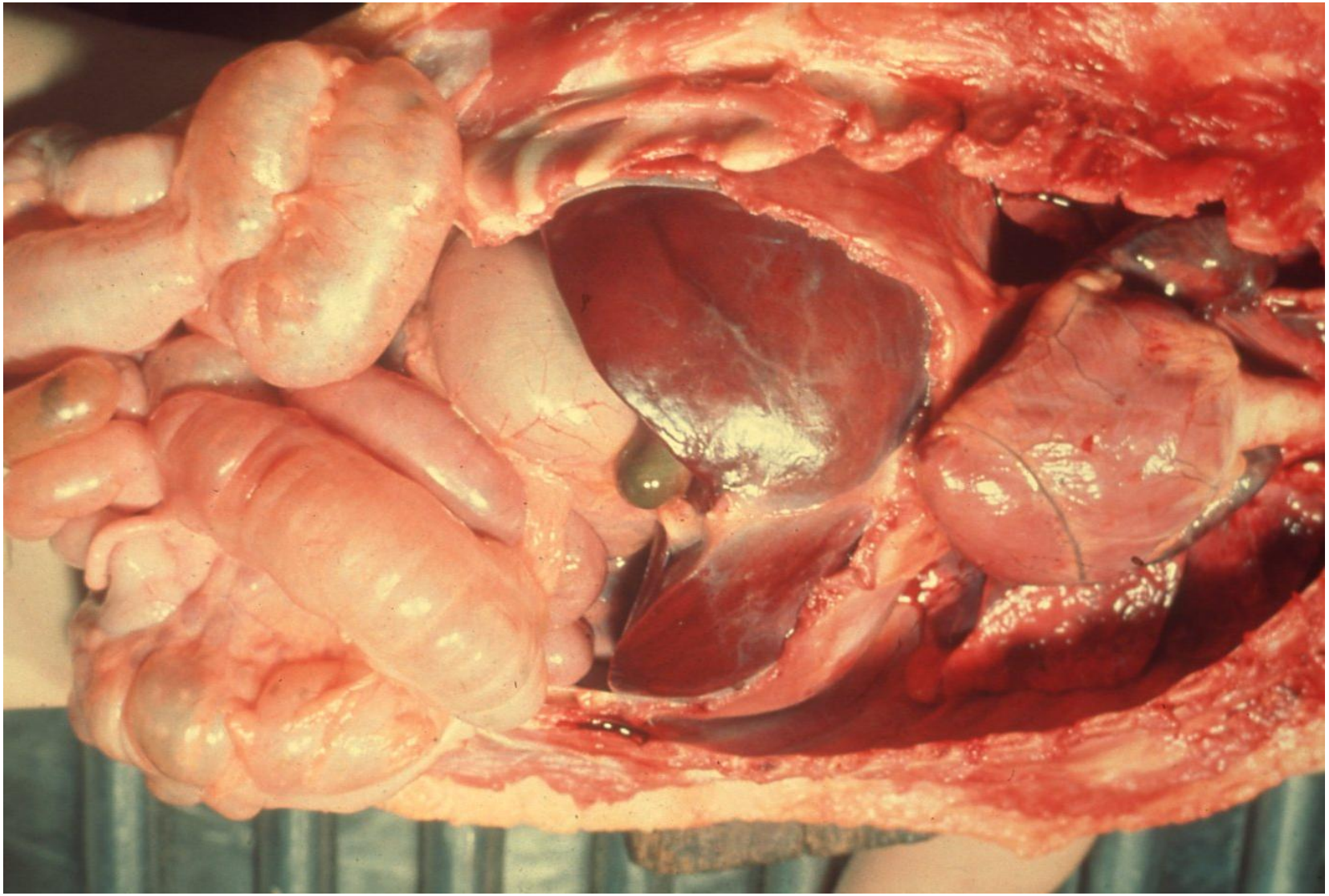
Acute megakaryoblastic leukemia (associated with liver fibrosis)



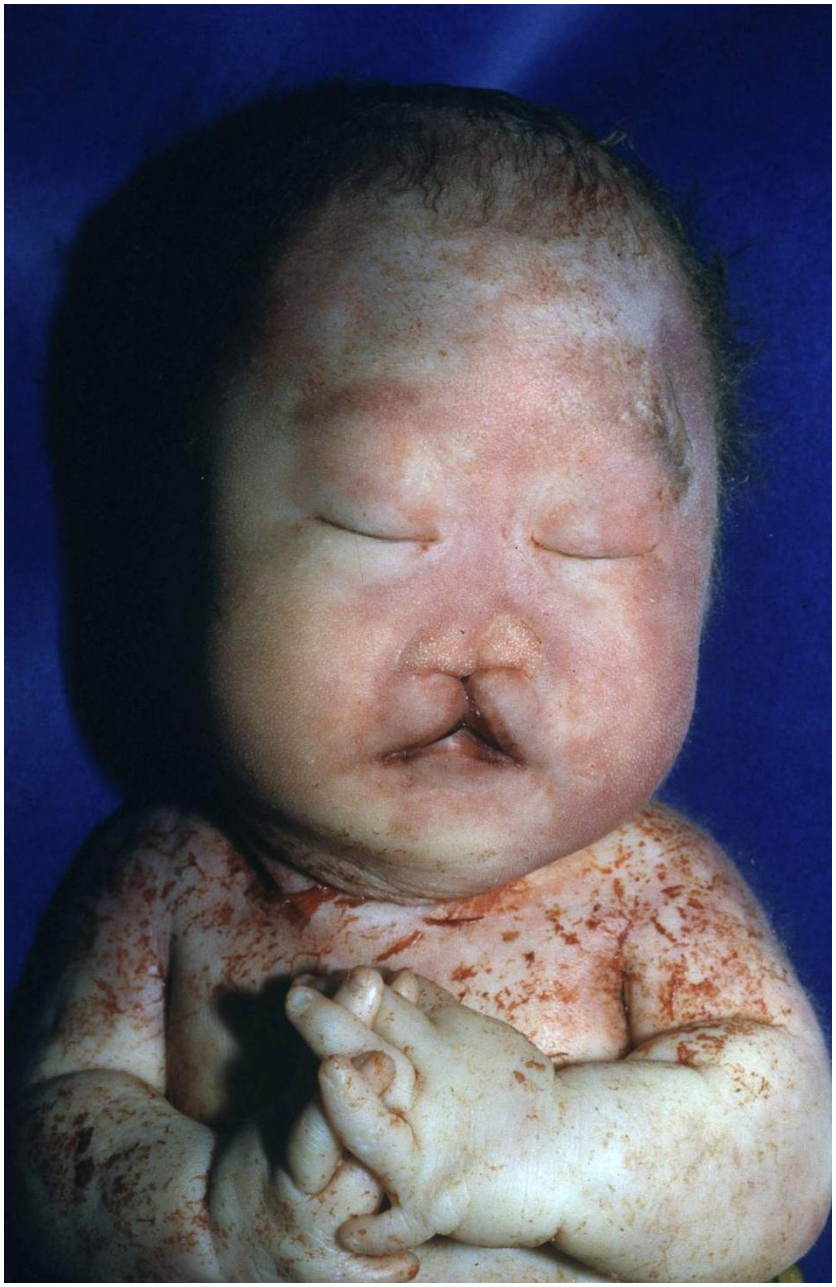
18 trisomy (Edwards syndrome)

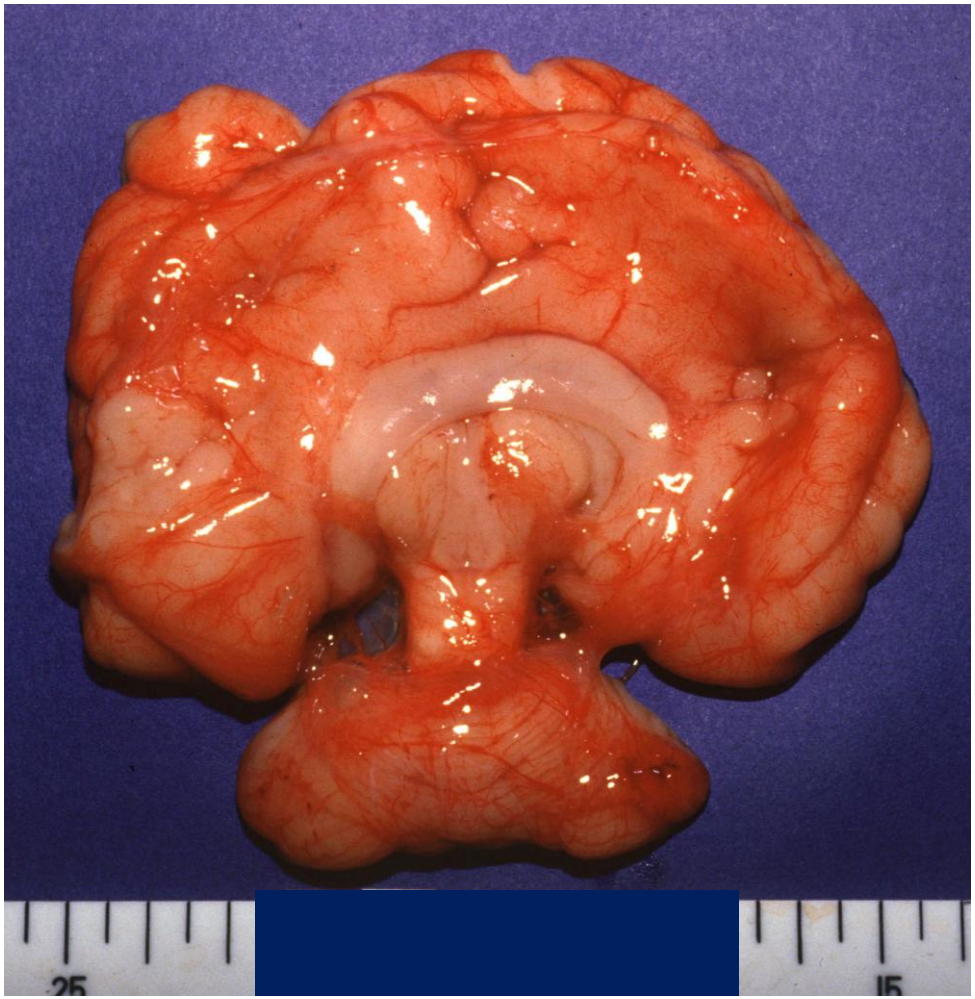


18 trisomy (Edwards syndrome) accompanying cerebellar hypoplasia (left) and esophageal atresia with connection to the trachea (right).



18 trisomy (Edwards syndrome) accompanying **asplenia syndrome** with situs ambiguous (right-isomerism). Note the symmetrical liver with centrally located gallbladder, malrotation of the intestine and truncus arteriosus (a single large blood vessel emerging from the heart).





13（D1）trisomy
Left: cleft lip and palate
Right: holoprosencephaly
(lack of separation of the cerebral hemispheres)

Single gene disorders

- **Hereditary disorders are not necessarily familial.**

  ～Mutations in germ cells may occur incidentally～

  ～The penetrance rate (incidence rate of gene abnormalities) is NOT 100%～

- **Autosomal dominant inheritance**

  A single copy of the mutated gene (from one parent) of the allele on a pair of the homologous chromosomes is enough to cause the disorder.

  ～The term of the disease with "familial" indicates autosomal dominant trait～

- **Autosomal recessive inheritance**

  Two copies of the mutated gene (one from each parent) are required to cause the disorder. The genetic carrier possesses one copy of the mutated gene.

  ～Most of the congenital metabolic disorders reveal autosomal recessive trait.～

- **X-linked recessive inheritance**

  The disorder is seen only in male patients

- **Mitochondrial inheritance**

  Maternal inheritance is observed.

  ～Mitochondria of the fertilized ovum are derived from the mother.～

Congenital metabolic disorders

Lysosomal diseases (deficiency of lysosomal enzymes)

Tay-Sacks disease, Gaucher's disease, Fabry's disease, Niemann-Pick's disease, Hurler syndrome, neuronal ceroid lipofuscinosis, I-cell disease

Glycogen storage diseases (glycogenosis)

von Gierke disease (type I), Pompe disease (type II), Cori disease (type III), Anderson disease (type IV), McArdle disease (type V), Hers disease (type VI), Tarui disease (type VII)

liver form＝types Ⅰ&Ⅵ, muscle form＝types Ⅴ&Ⅶ

liver/muscle form＝types Ⅲ&Ⅳ, systemic form＝type Ⅱ

Disorders of carbohydrate metabolism

galactosemia, fucocidosis, alpha-mannosidosis

Disorders of amino acid metabolism

phenylketonuria, alkaptonuria, homocystinuria, maple syrup disease

Congenital metabolic disorders and the mode of transmission

Autosomal dominant	von Recklinghausen's disease, tuberous sclerosis von Hippel Lindau's disease, Huntington's disease, familial hypercholesterolemia, familial amyloid polyneuropathy, Marfan's syndrome, adult-type polycystic kidney disease, hereditary spherocytosis, sickle cell anemia, familial polyposis coli, multiple endocrine neoplasia, hereditary retinoblastoma
Autosomal recessive	Gaucher's disease, Niemann-Pick's disease, Hurler's syndrome, glycogen storage disease, phenylketonuria, maple syrup disease, homocystinuria, galactosemia, Wilson's disease, xeroderma pigmentosum, hemochromatosis, cystic fibrosis, severe immunodeficiency syndrome
X-linked recessive	hemophilia, color vision deficiency, Duchenne-type muscular dystrophy, Fabry's disease, Hunter's syndrome, adrenoleukodystrophy, glucose-6-phosphate dehydrogenase (G6PD) deficiency

Diagnosis of congenital disorders

- **Prenatal screening**
  - Diagnosis using a fertilized ovum
  - Amniotic diagnosis
  - Genetic screening using mother's peripheral blood
  - Imaging diagnosis by echography and CT scan
- **Mass screening for the neonate**
- **Postnatal genetic screening using polymerase chain reaction**

Right to know and right not to know

Adult onset-genetic diseases without treatment choice can be diagnosed by examining peripheral blood.

22 target disorders of the tandem mass screening for the neonate in Japan

1) Disorders of amino acid metabolism (8)
   phenylketonuria, maple syrup disease, homocystinuria, citrullinemia-type 1, argininosuccinic aciduria, tyrosinemia-type 1, argininemia, citrin deficiency
2) Disorders of organic acid metabolism (7)
   methylmalonic acidemia, propionic acidemia, isovaleric acidemia, 3-methylglutaconic aciduria, 3-hydroxy-3-methylglutaric acidemia, multiple carboxylase deficiency, glutaric acidemia type 1
3) Disorders of fatty acid metabolism (5)
   medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, very long chain acyl-CoA dehydrogenase (VLCAD) deficiency, 3-hydroxy acyl-CoA dehydrogenase (HADH)/trifunctional protein deficiency, carnitine palmitoyltransferase I deficiency, carnitine palmitoyltransferase 2 deficiency
4) Congenital endocrine disorders (2)
   congenital hypothyroidism (cretinism), congenital adrenocortical hyperplasia

A small aliquot of peripheral blood is sampled from the plantar part of the foot. Filter paper adsorbed with the blood is sent for evaluation.

Adult-onset genetic disorders

1) The patients often have children.
2) The disease transmits with an autosomal dominant trait.
3) There is no specific treatment for the disorder.
4) The diagnosis can be confirmed during children (in a presymptomatic stage).
5) The right not to know should be kept.

(examples)

- Huntington's disease
- Spinocerebellar degeneration
- Myotonic dystrophy
- Adrenoleukodystrophy (peroxisome disease with X-linked trait)
- Familial amyloid neuropathy (treatable with liver transplantation)
- Adult-type polycystic kidney disease (treatable with renal transplantation)

Genetic disorders may protect the patient from malaria

Sickle cell anemia (hemoglobin S disease)

7% of African-American and 30% of inhabitants in certain African areas have Hb S disease.

Hb S disease shows the resistance to falciparum malaria.

Antimalaria resistance

1) sickle cell anemia (autosomal dominant trait)
2) thalassemia (autosomal recessive trait)
3) glucose-6-phosphate dehydrogenase (G6PD) deficiency (X-liked recessive trait)
4) pyruvate kinase (PK) deficiency (autosomal recessive trait)
5) loss of Duffy-type blood group antigen Fy(a-b-) : the resistance to tertial (vivax) malaria

Representative autosomal dominant disorders

Familial amyloid neuropathy

Huntington's disease

Phacomatosis

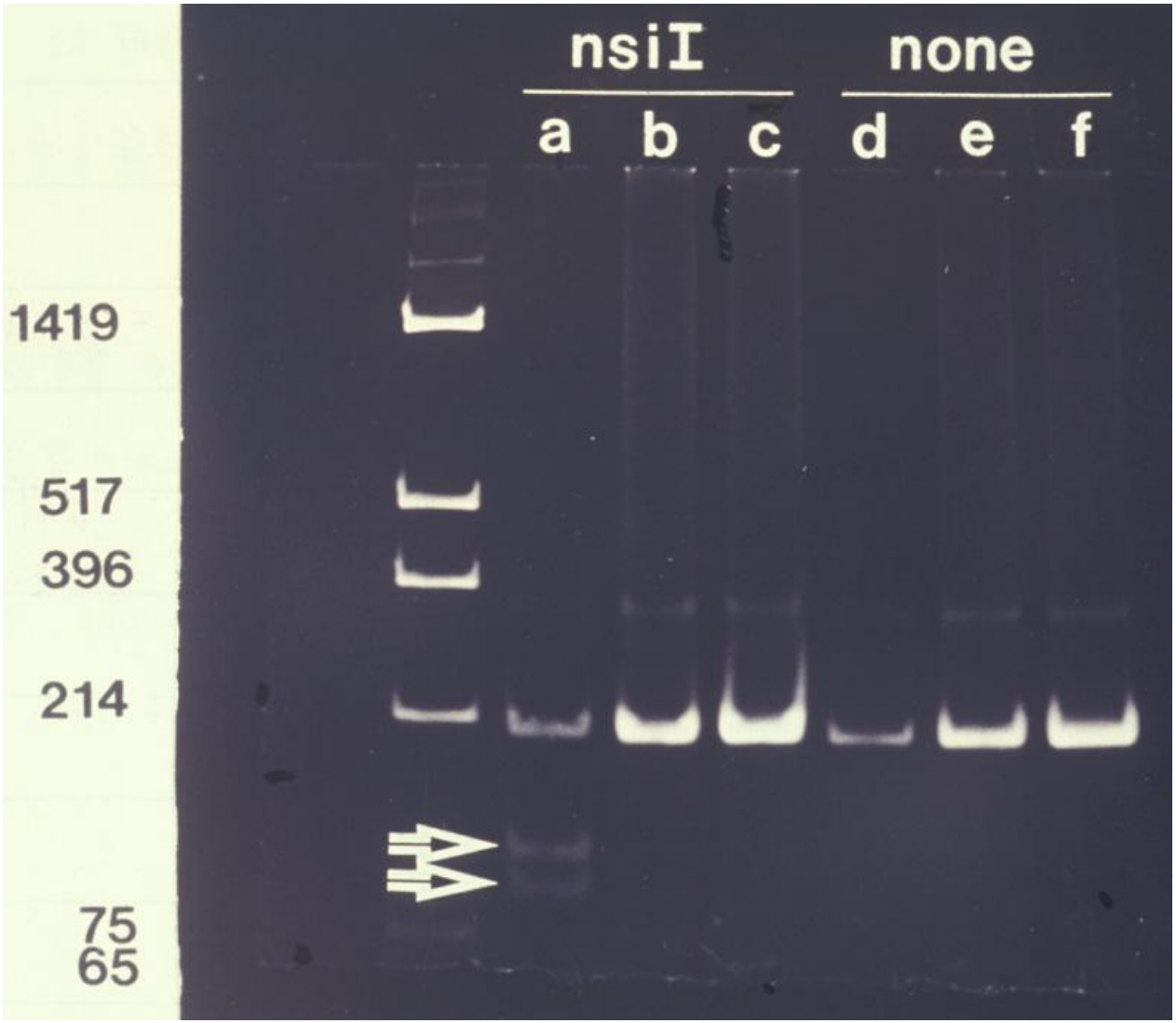
- von Recklinghausen's disease
- Kasabach-Merritt syndrome

Adult-type polycystic kidney disease

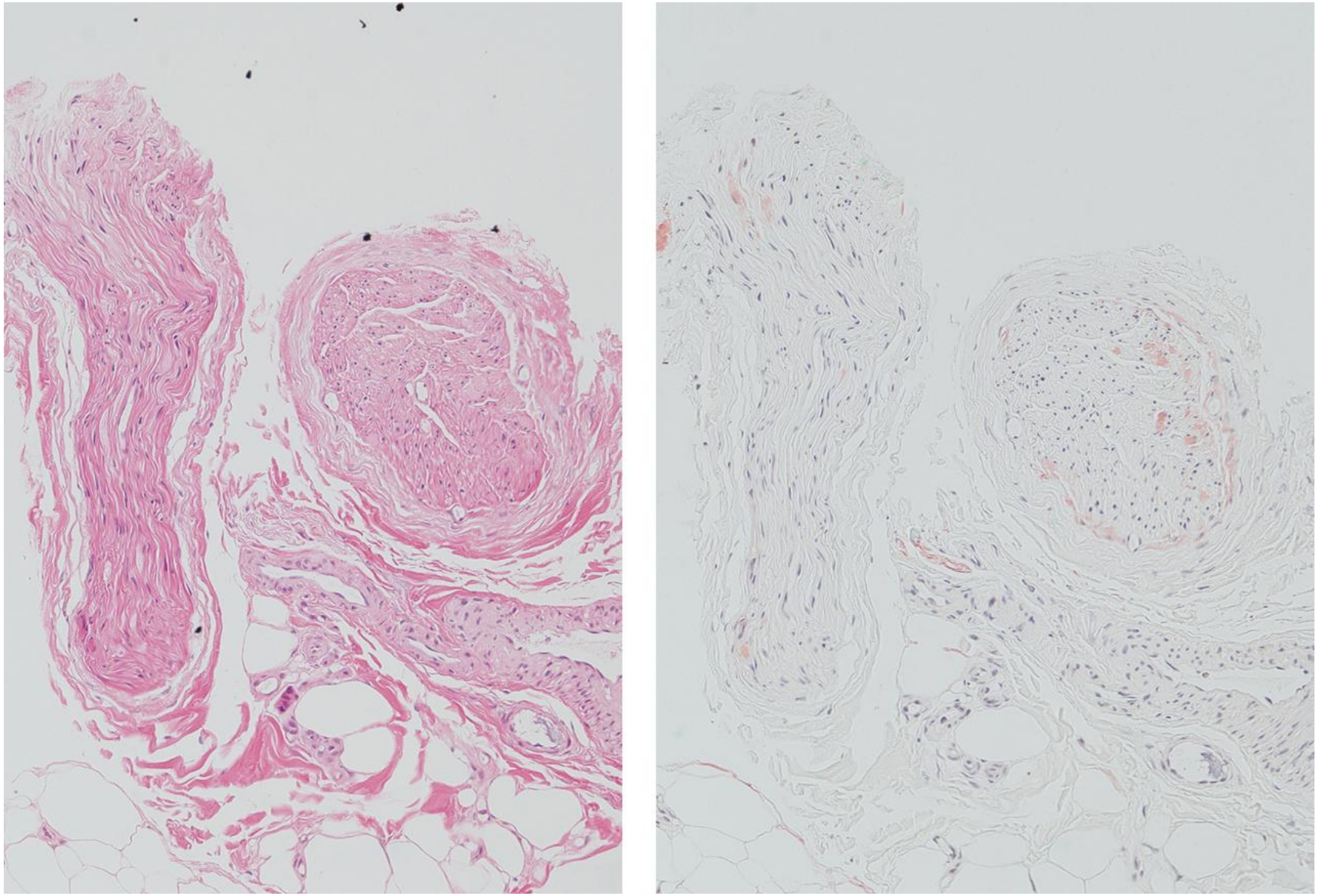
Marble bone disease

Osteogenesis imperfecta

Achondroplasia

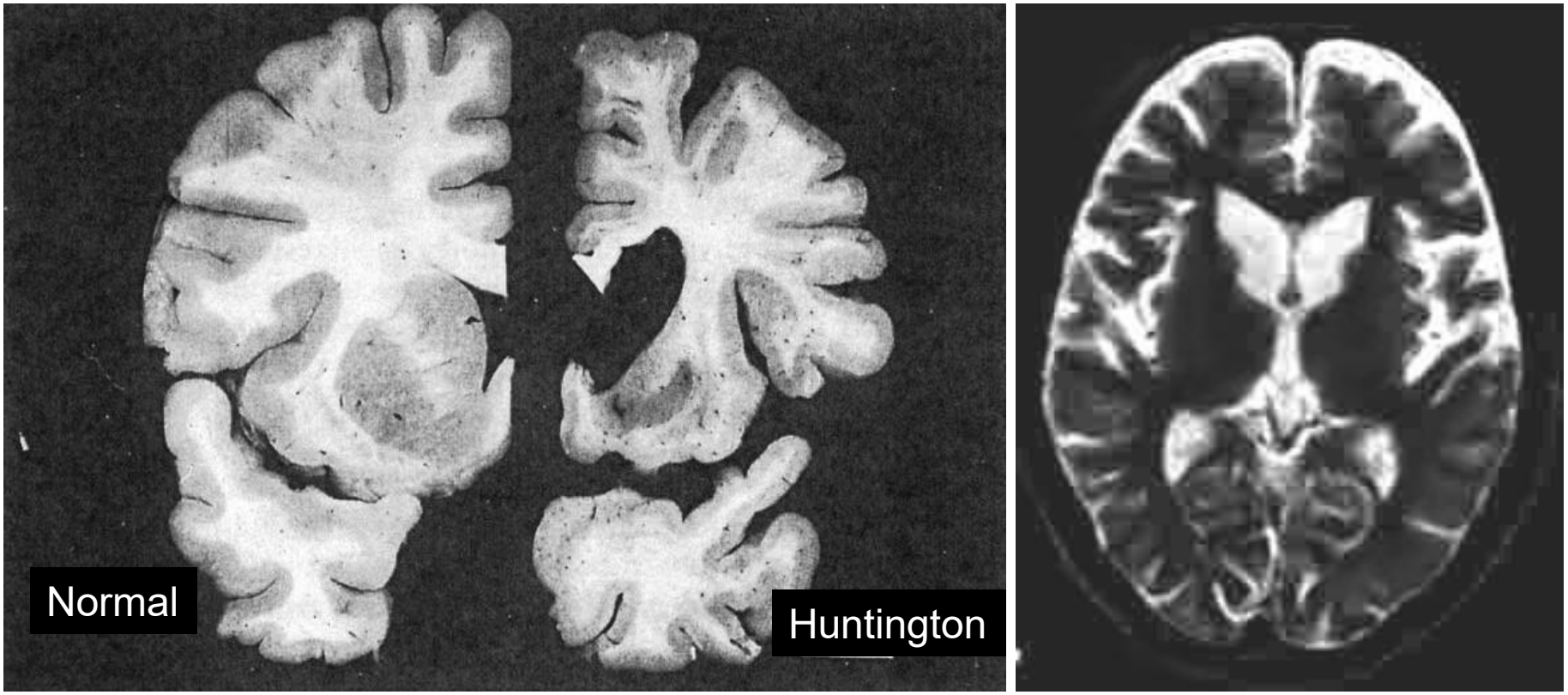


Genetic diagnosis of familial amyloid neuropathy
（PCR analysis of the peripheral blood DNA:
abnormal DNA is cleaved to smaller fragments
by the restriction enzyme nsil：lane a）



Familial amyloid neuropathy

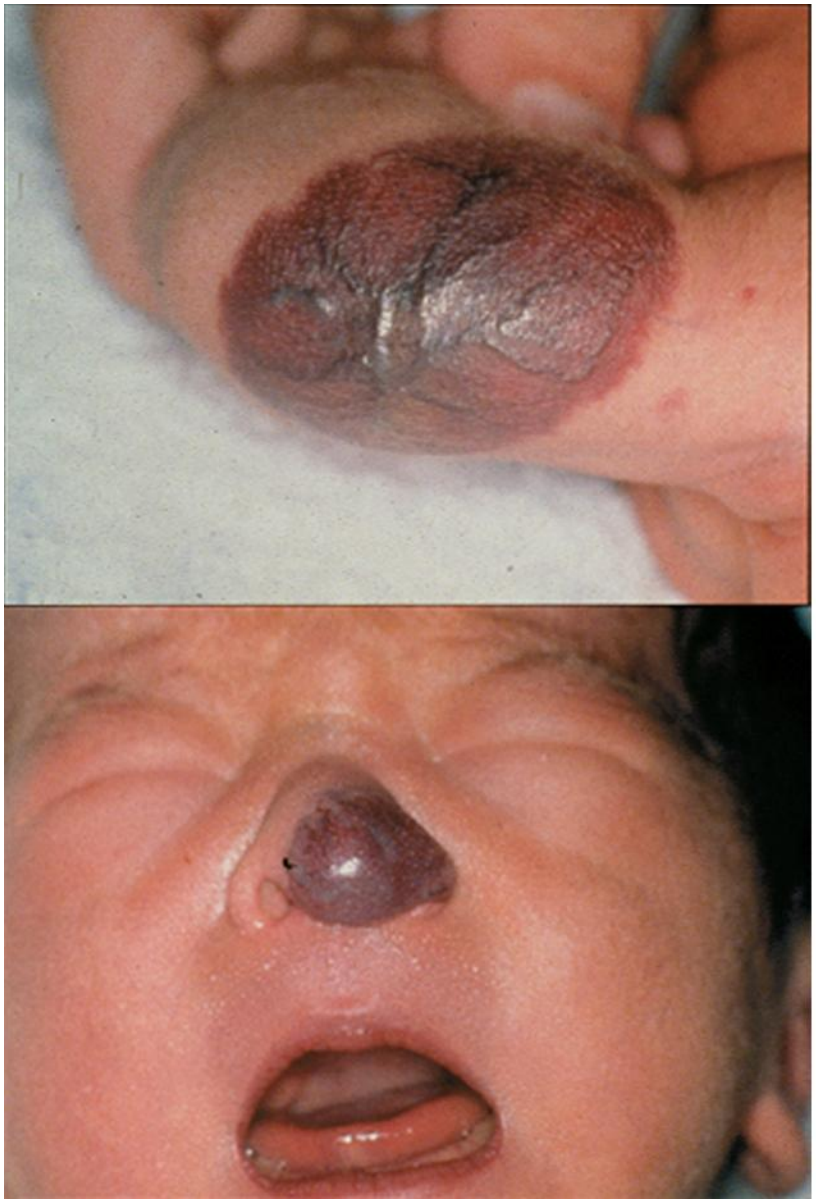
(amyloid deposition to the biopsied sural nerve, left : H&E, right: Dylon stain)

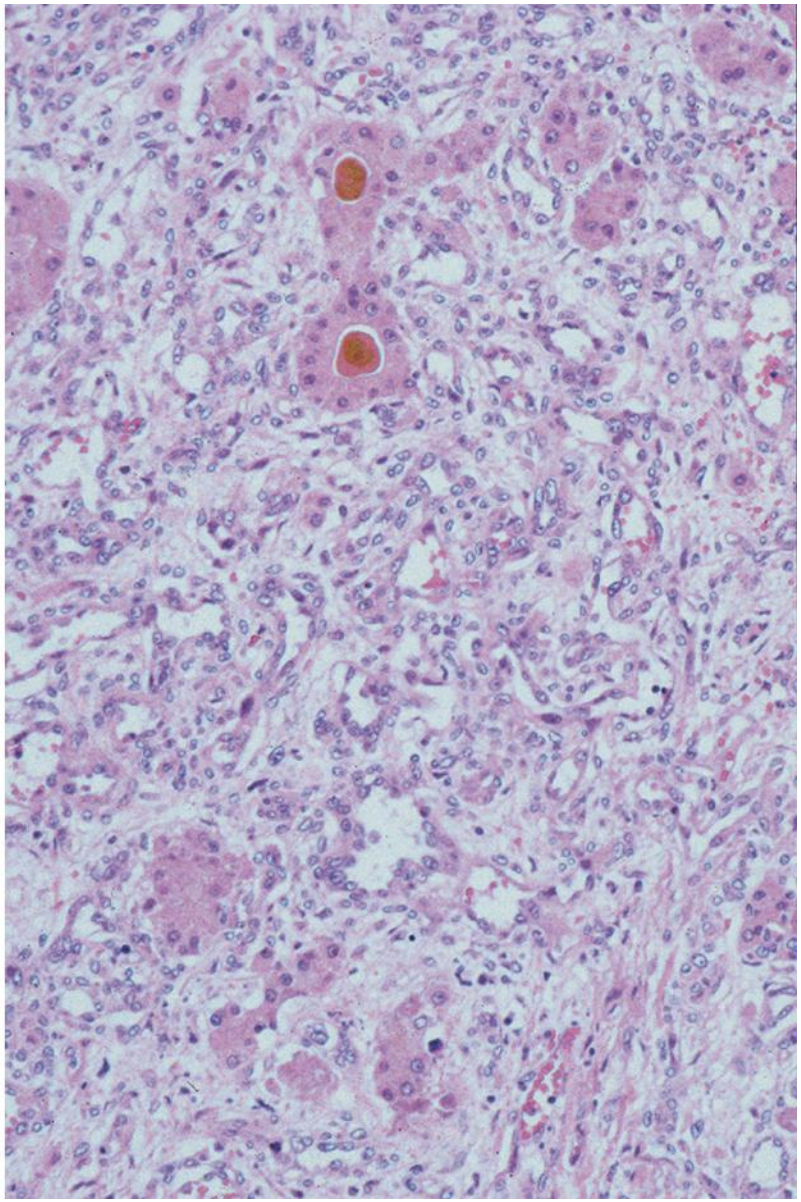


Huntington's disease（left: frontal sections, normal vs Huntington's disease showing marked atrophy of the caudate nucleus and dilatation of the lateral ventricle, right: MRI image)

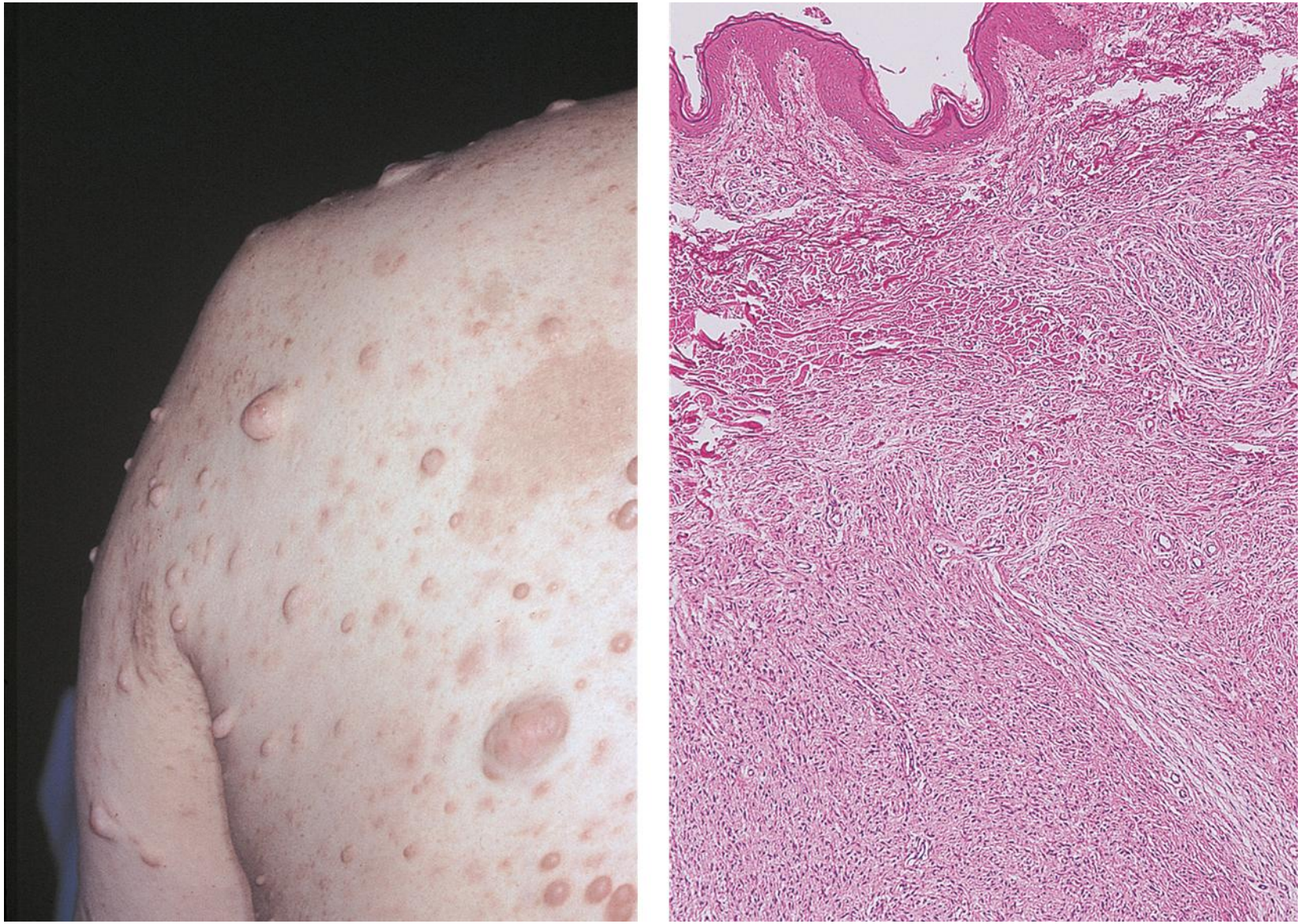
Adult onset genetic neuronal disorders

① Huntington's disease, ② spinocerebellar degeneration, ③ adrenoleukodystrophy, ④ familial amyloid neuropathy

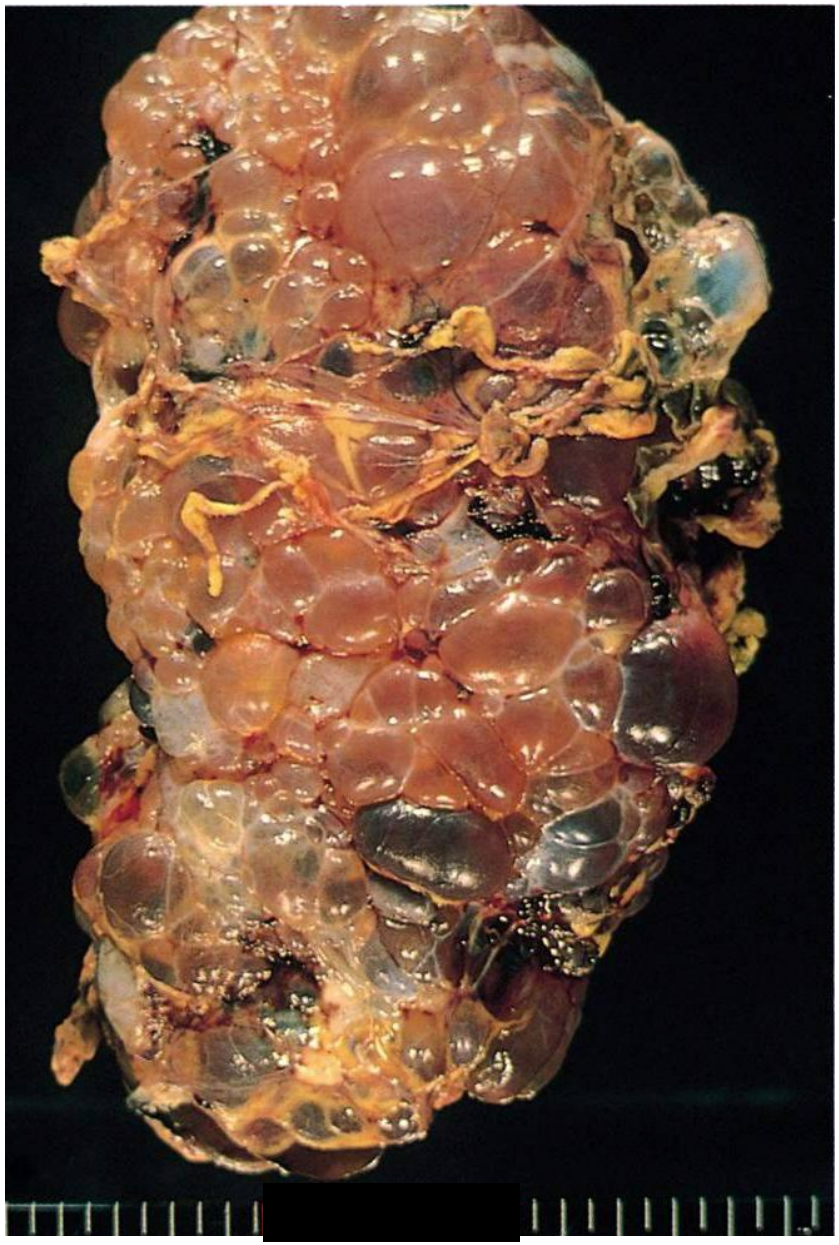


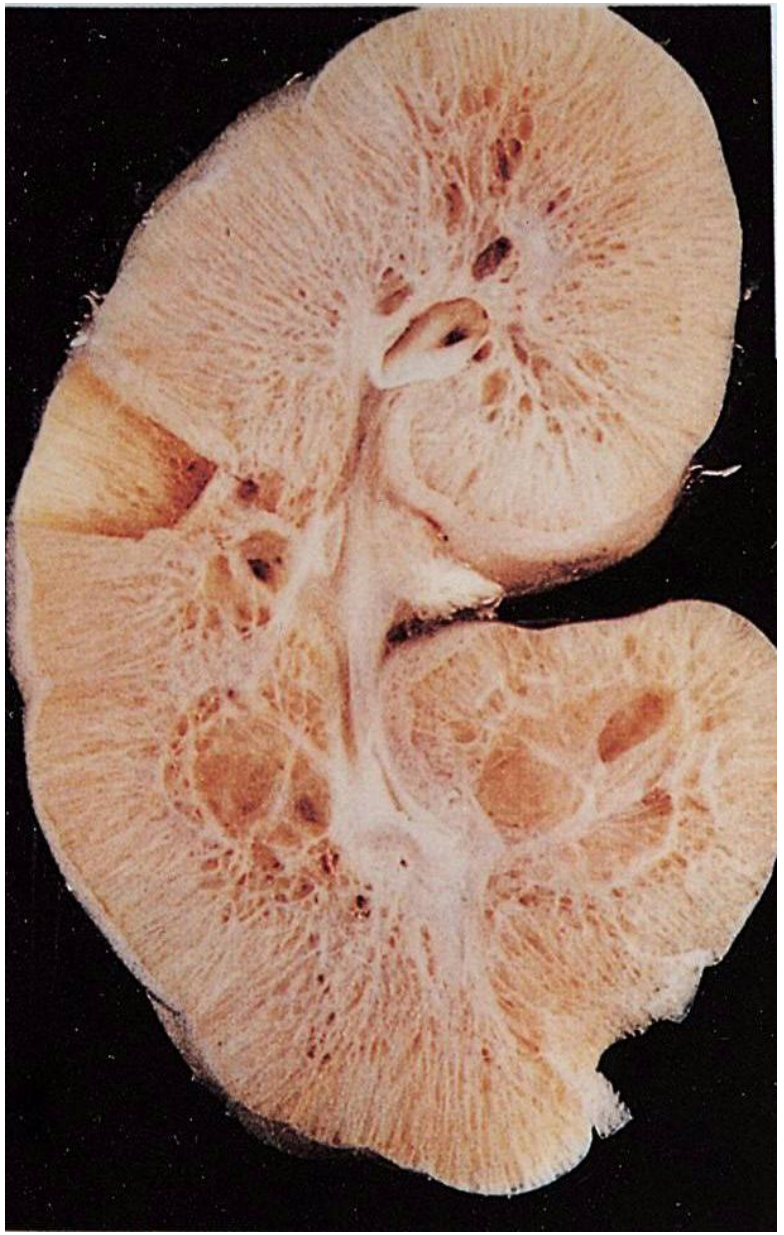


Kasabach-Meritt syndrome showing multiple skin hemangiomas (left) and hepatic capillary hemangioma stained with H&E (right)

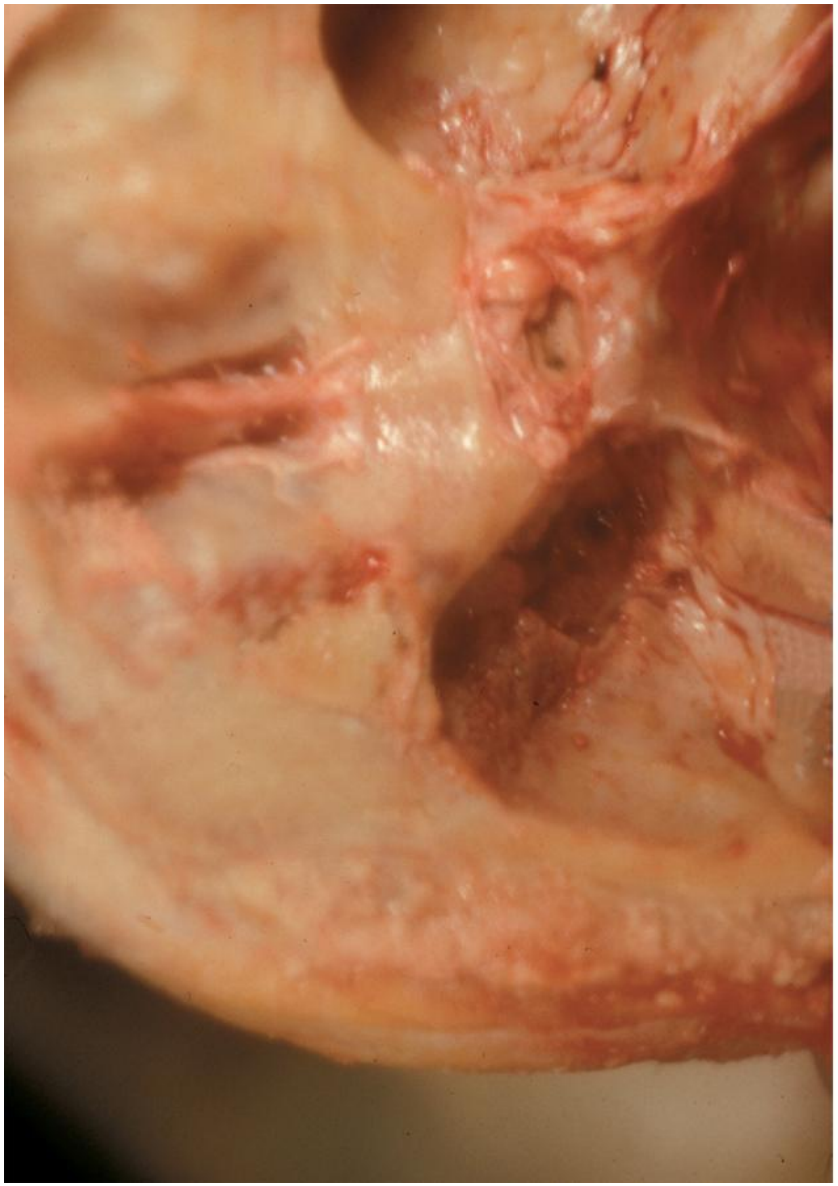


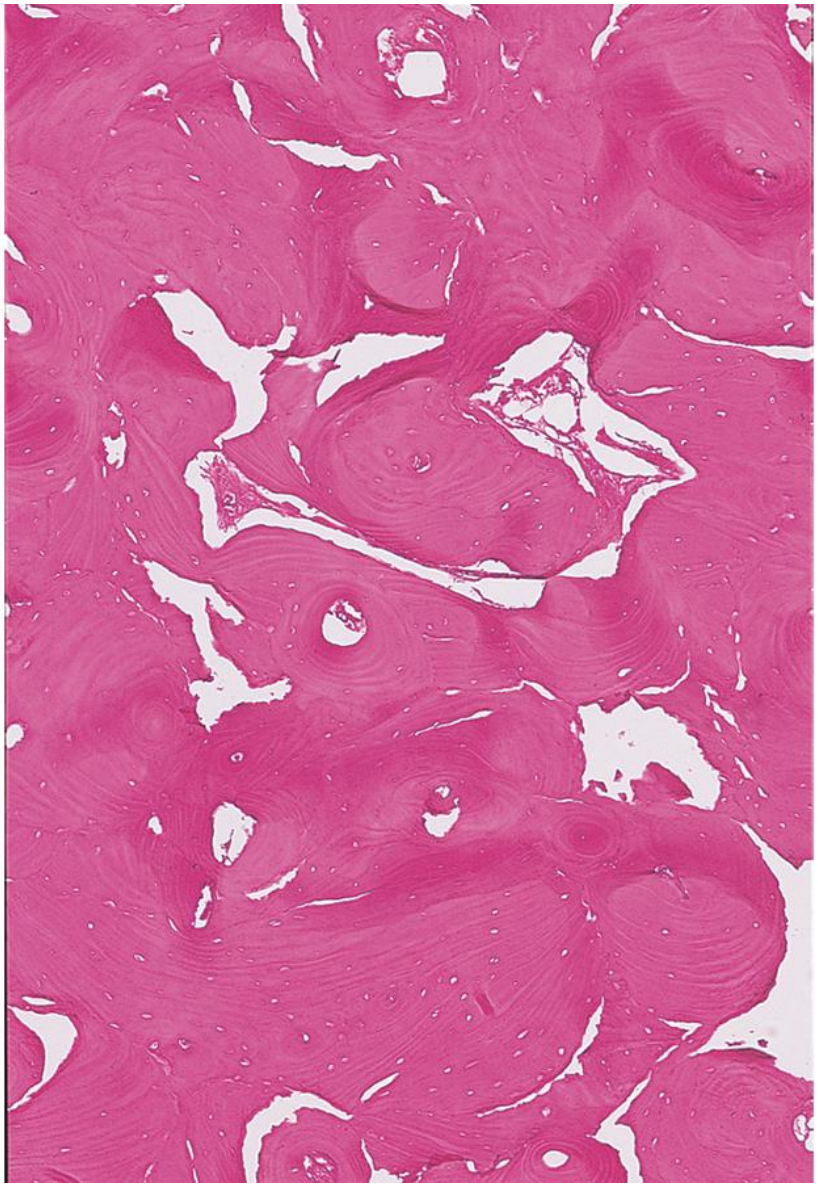
von Recklinghausen's disease (neurofibromatosis). Left: multiple neurofibromas with cafe au lait spots, Right: skin neurofibroma (H&E)



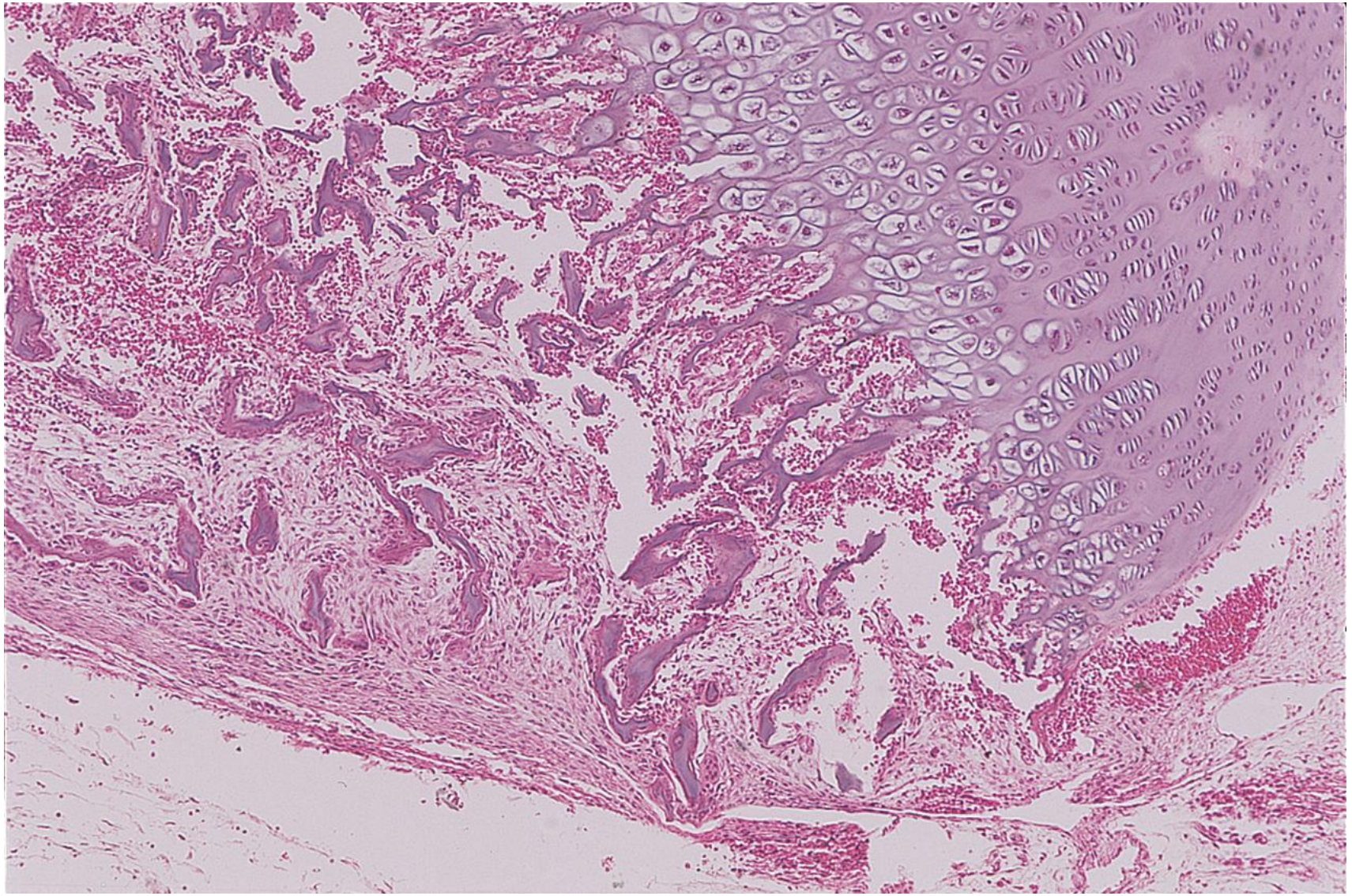


Left: **Adult-type polycystic kidney disease** (huge sized, weighing 1 kg)
Right: **Infantile polycystic kidney disease** (spongy kidney) without size enlargement

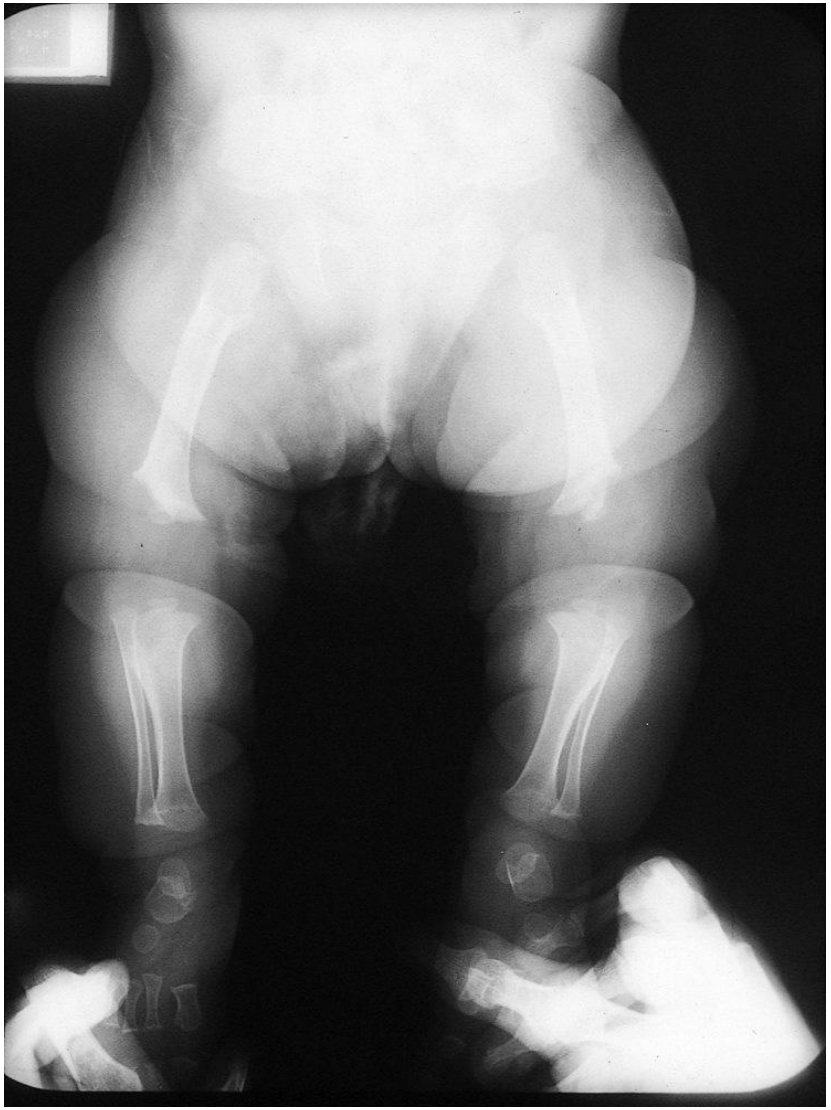


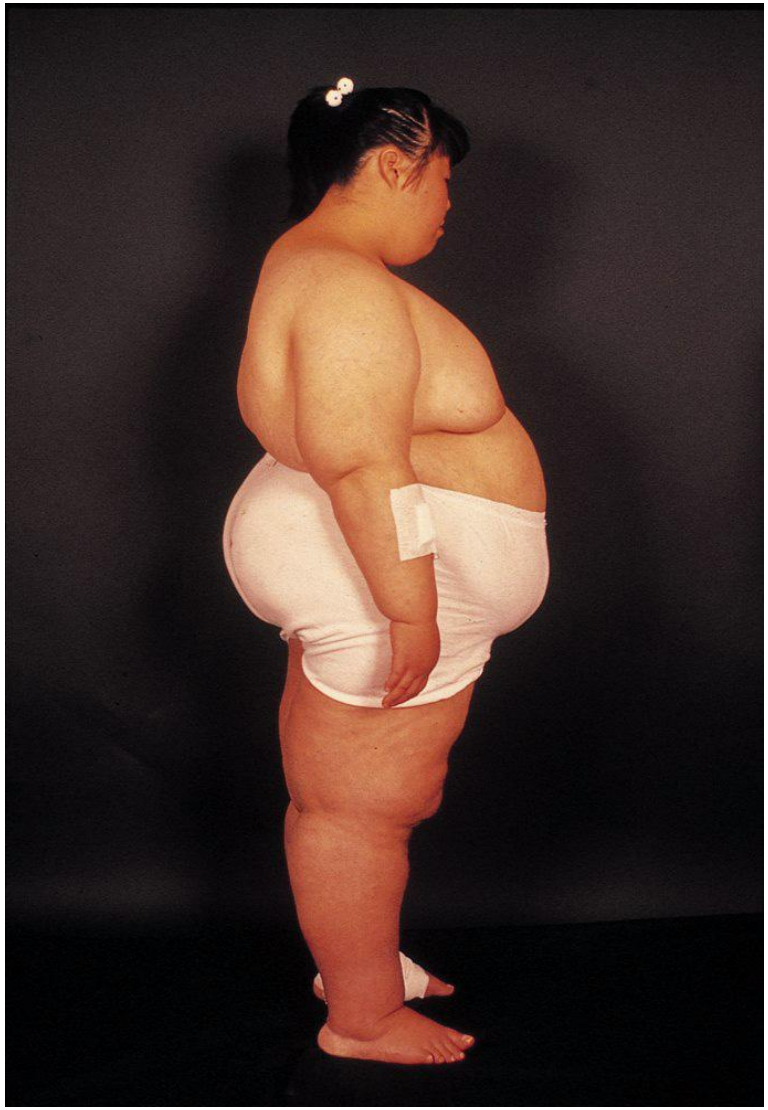


Marble bone disease. Left: gross appearance of the skull base, Right: thickening and fusion of the bone trabeculae (H&E)



Osteogenesis imperfecta (malformation of the cortical bone with pathological fracture formation, H&E)

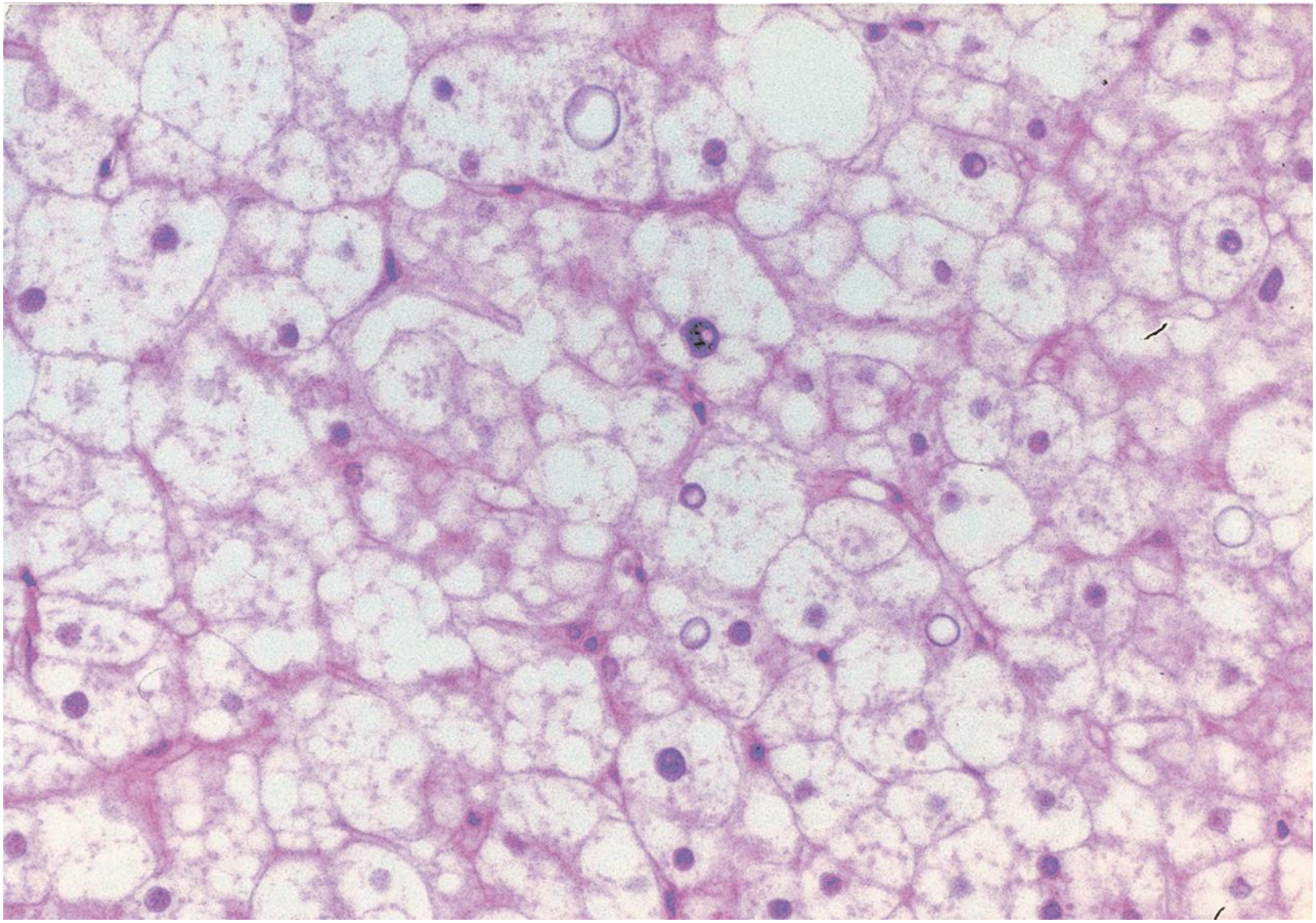




Left: **Achondroplasia** (low statue with shortening of limbs
Right: **Prader-Willi syndrome** with marked obesity (abnormality in chromosome 15)
(low myotonia, gonadal maldevelopment and intellectual disability also associated)

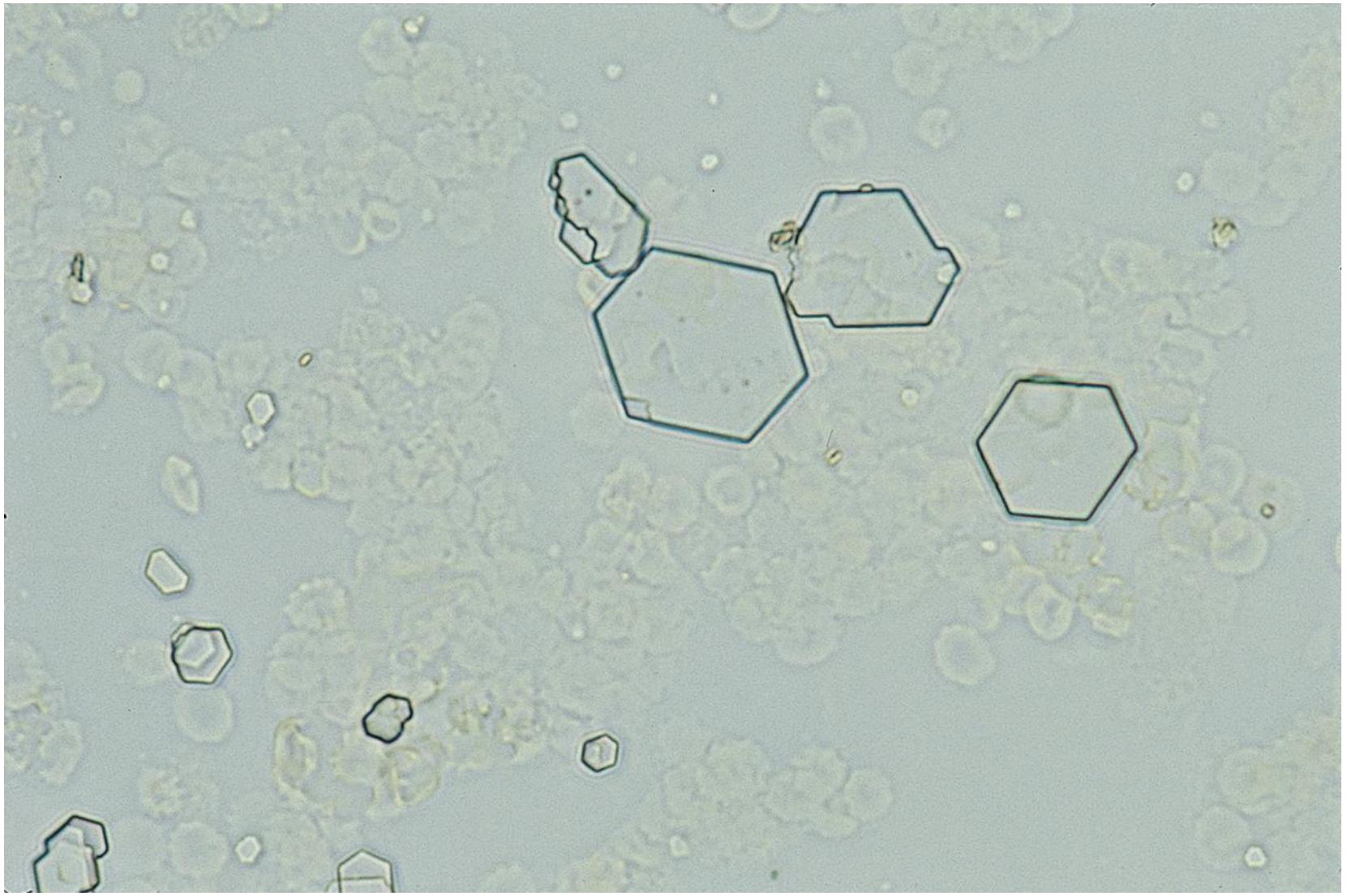
Representative autosomal recessive disorders

Glycogen storage disease
  von Gierke's disease (glycogenosis type 1)
Disorders of amino acid metabolism
    cystinuria and tyrosinemia
Ichthyosis (recessive form)
Prader–Willi syndrome
  (see the previous slide)

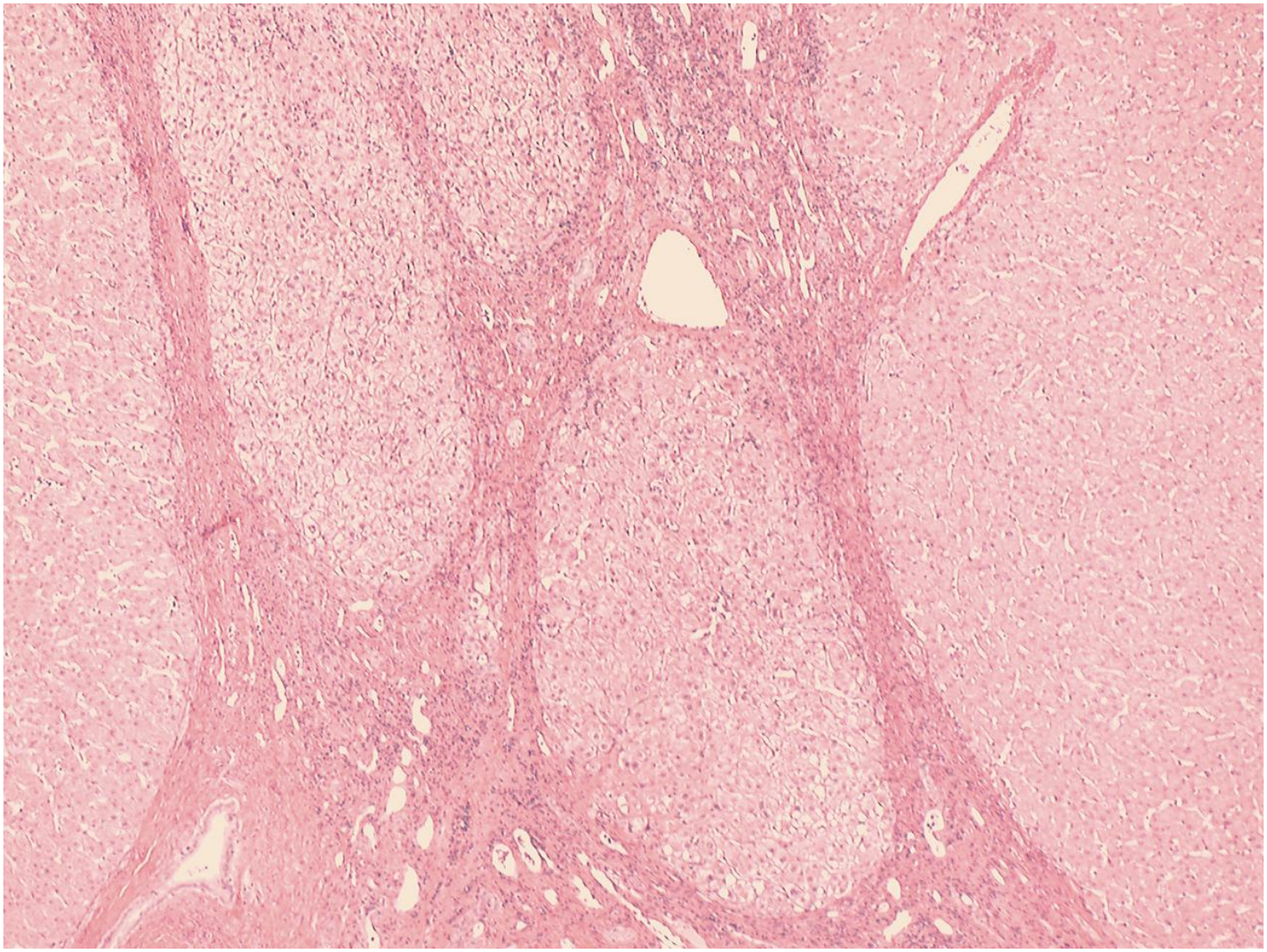


von Gierke's disease

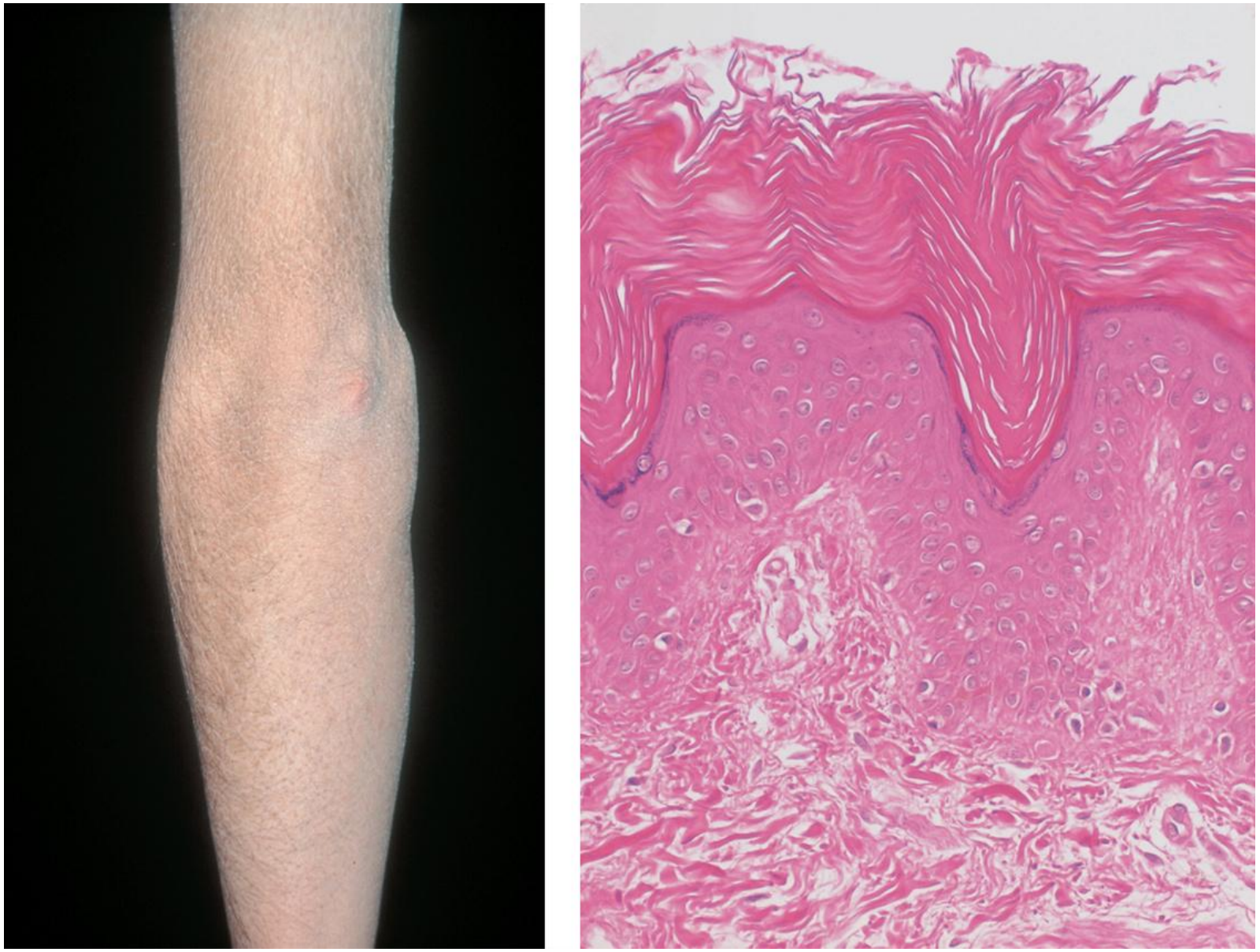
Glycogen deposition is pronounced in the hepatocytes (H&E).



Cystinuria (cystine crystals in urine sediments)
The patient presents with hematuria and urinary stones. The intellectual level is normal.



Tyrosinemia with liver cirrhosis in a 5-year-old boy: Hepatocellular carcinoma is complicated, H&E



Ichthyosis. left: gross appearance of the goose skin, right: hyperkeratosis, H&E

Representative X-linked recessive disorders

Duchenne-type muscular dystrophy

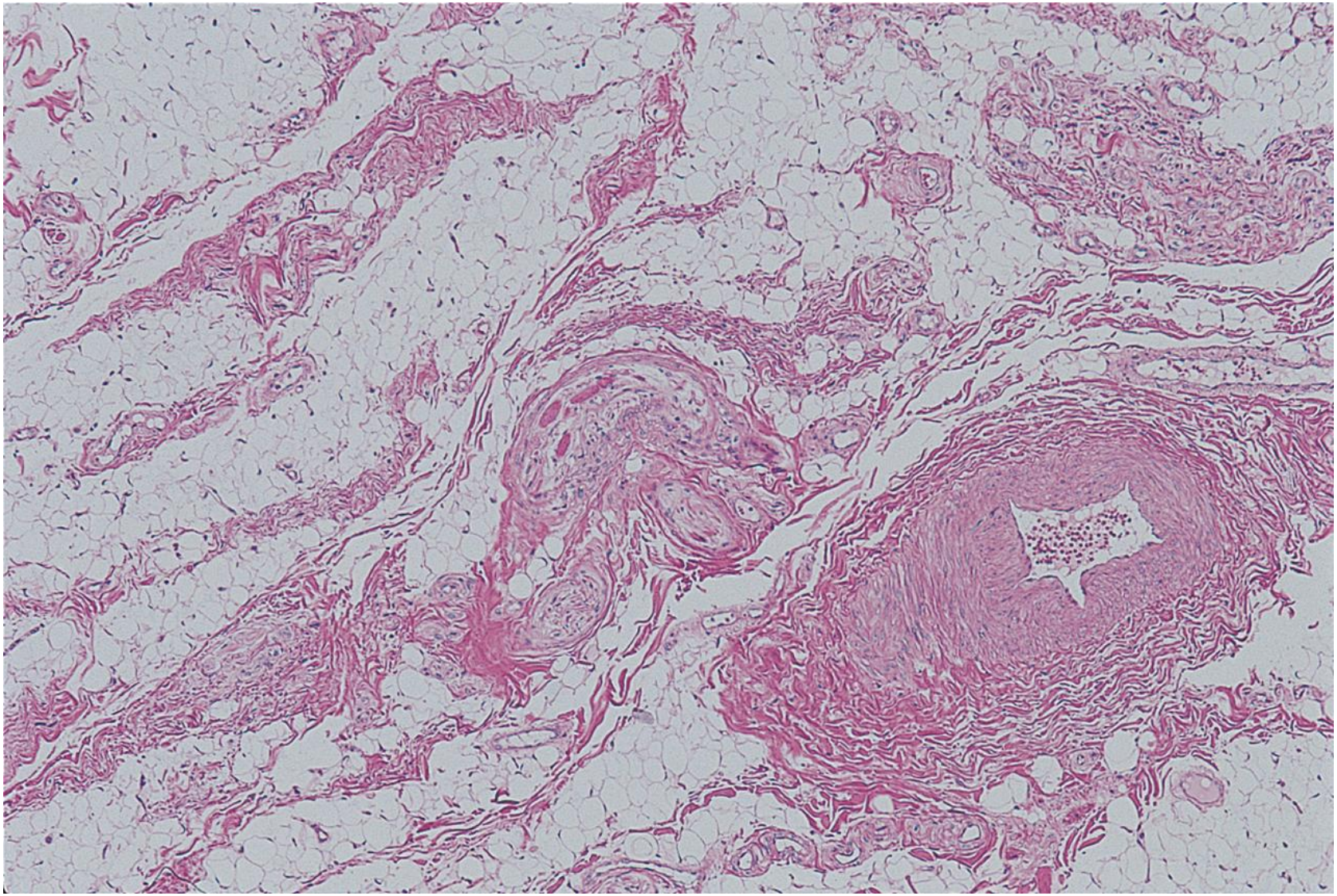
Fabry's disease

Hunter's syndrome

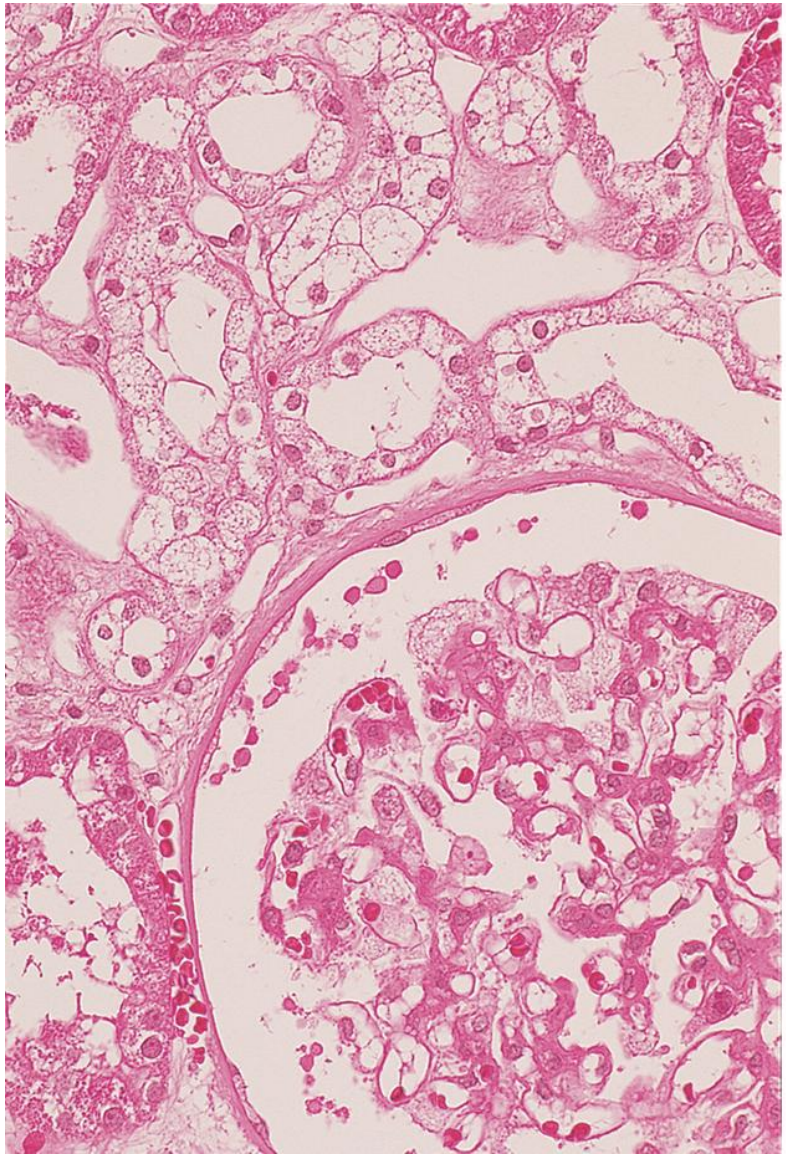
Mitochondriopathy

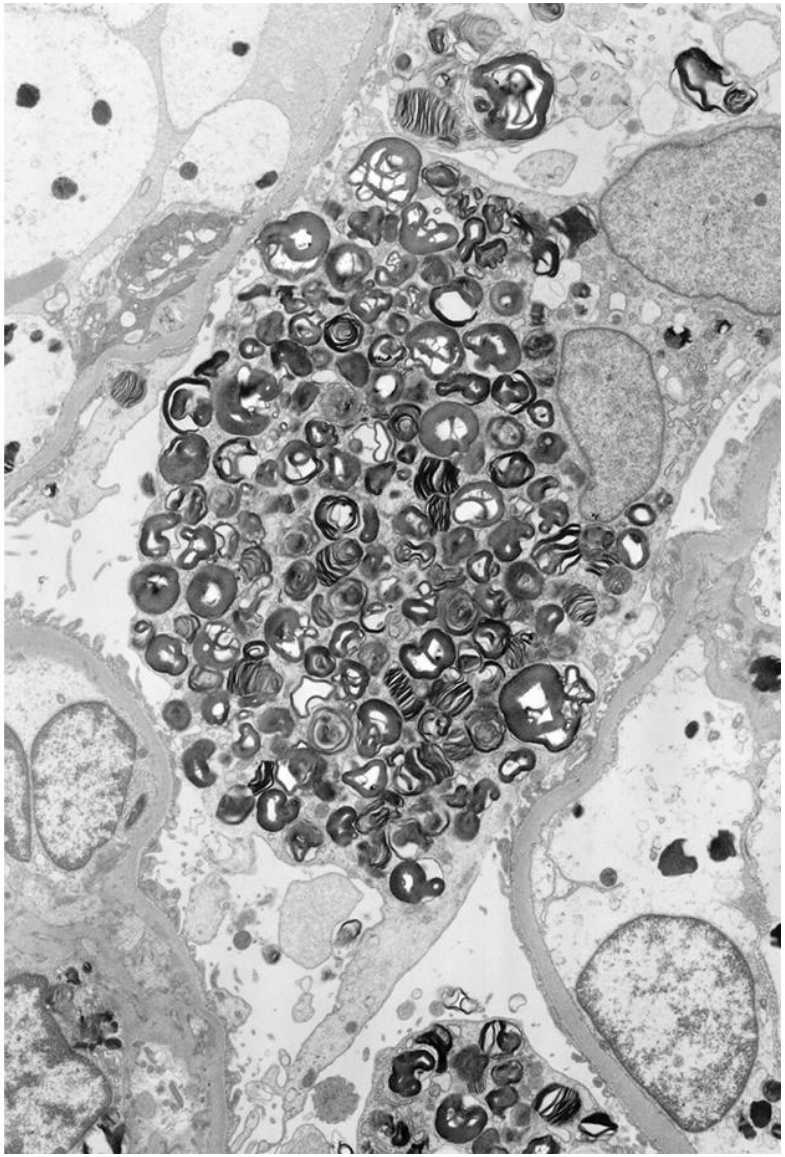
Mitochondrial cerebromusculopathy:

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes)

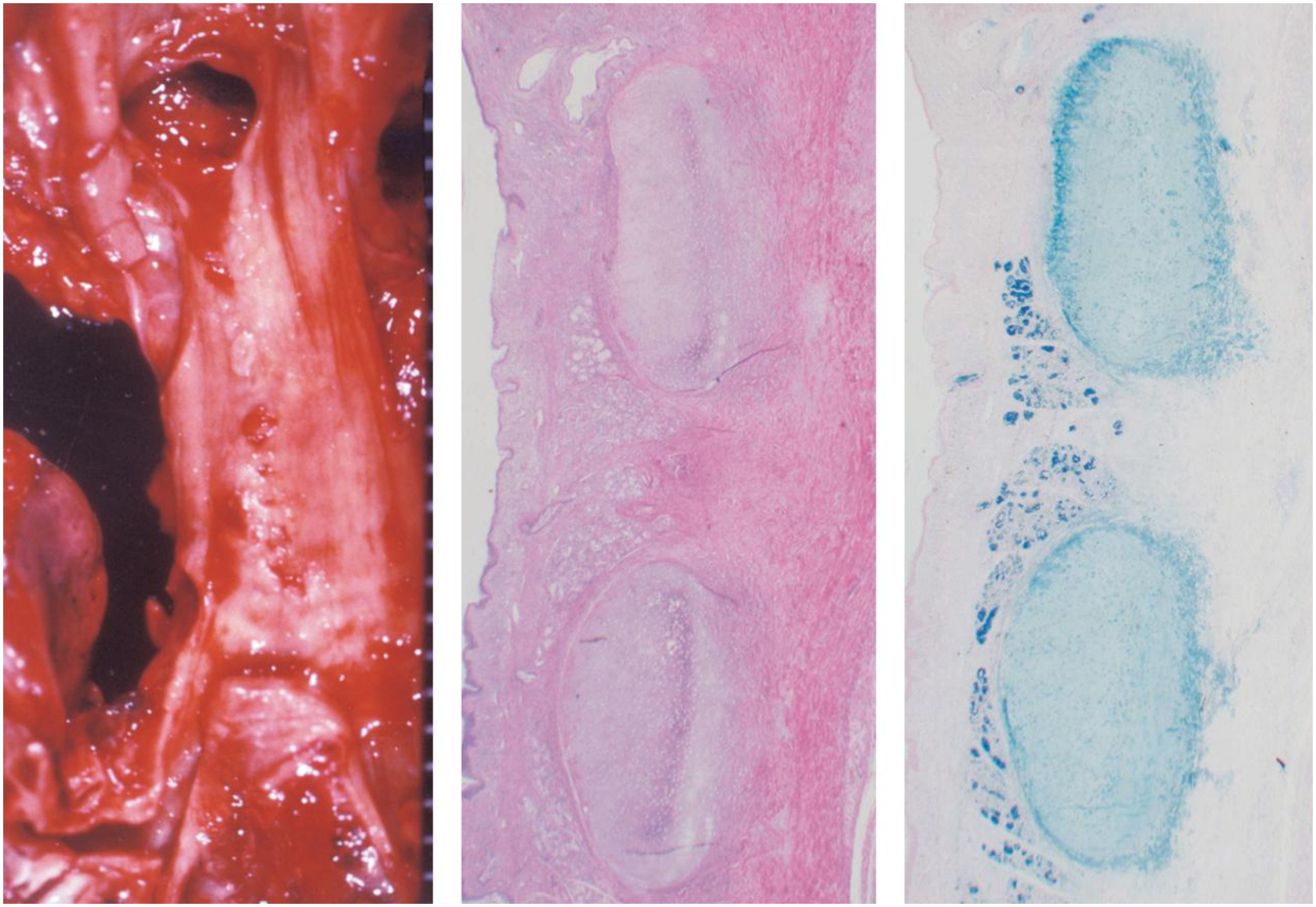


Duchenne-type muscular dystrophy.
Marked loss of muscle cells with lipomatosis (H&E):
A muscle spindle is retained.

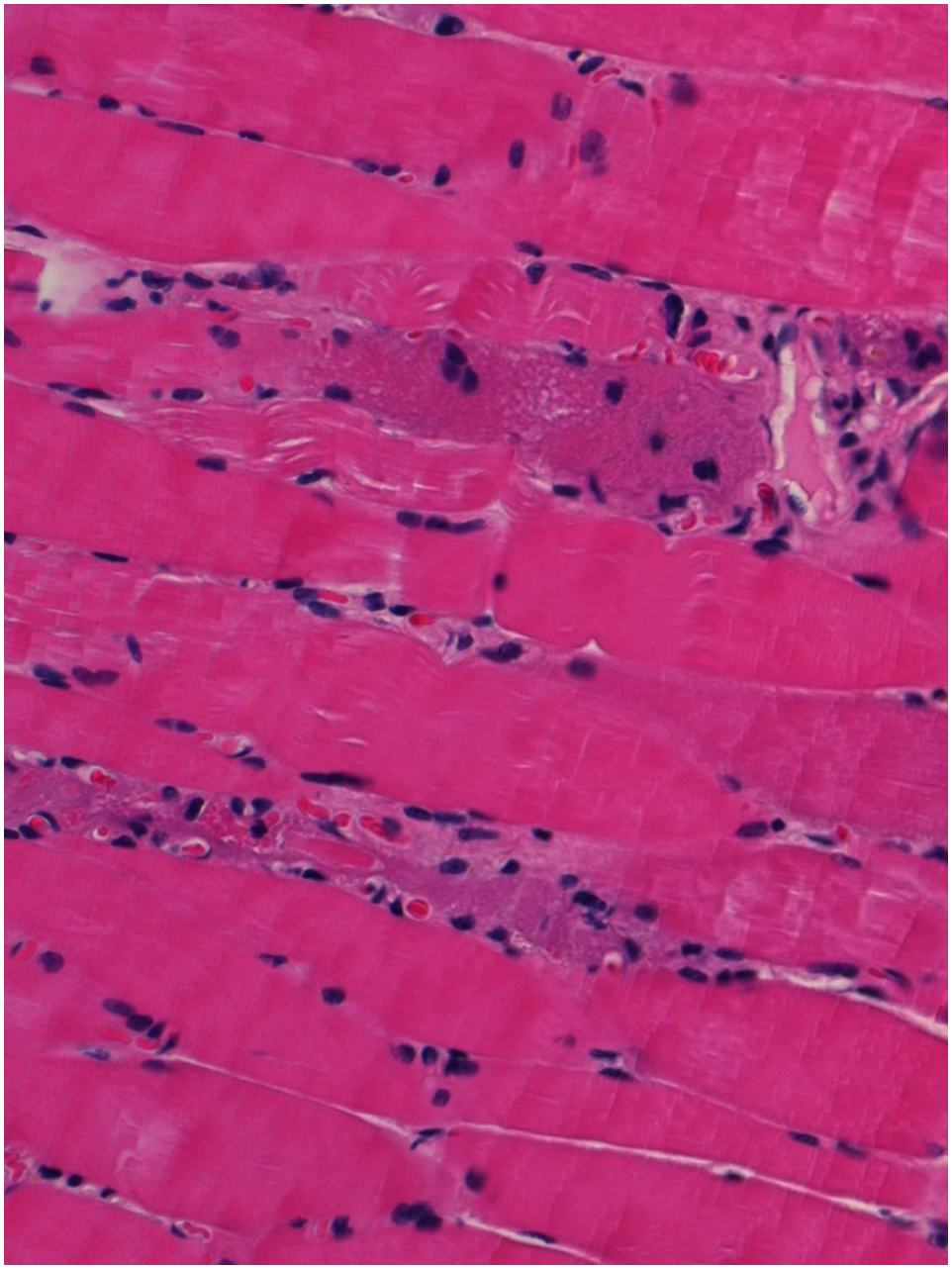


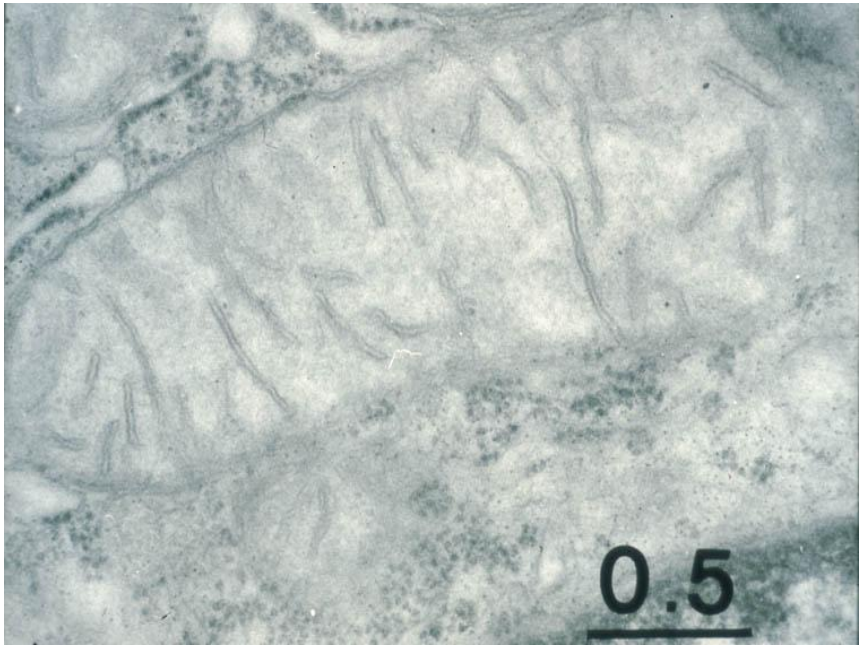


Fabry's disease (left: renal biopsy showing vacuolar swelling of the podocytes, right: electron micrograph showing deposition of zebra bodies in the podocytes)



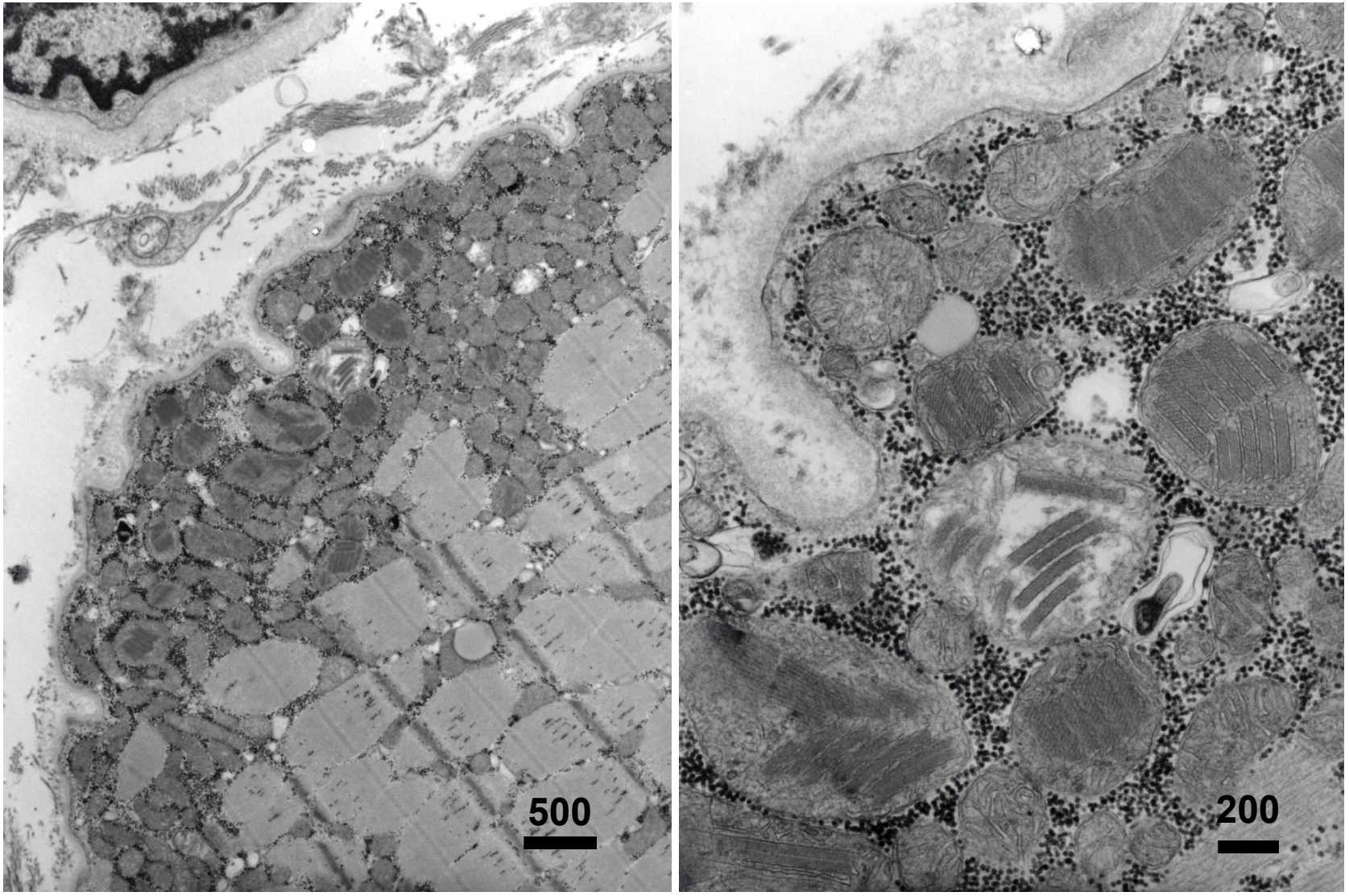
Hunter's syndrome in a male college student aged 20's (left: gross appearance of deformed tracheal cartilage, middle (H&E)/right (alcian blue): deposition of mucopolysaccharides in the deformed cartilage)





normal mitochondrion in a hepatocyte

Mitochondrial cerebromusculopathy: **MELAS** (a 36-year-old lady, striated muscle biopsy, H&E)



Mitochondrial cerebromusculopathy: MELAS (muscle biopsy reveals accumulation of morphologically abnormal mitochondria (electron micrographs)

Polygenic disorders

Multiple genes are involved in the disease process.

The incidence is higher than single gene disorders.

The severity of the disease is dependent on the number of genes involved.

Environmental factors modify the disease.

There is a certain degree of familial aggregation.

The involved genes are called as disease-susceptibility genes.

Combination of single nucleotide polymorphism (SNP) (or gene polymorphism) may cause the disease.

Interactions of the disease-susceptibility genes consist of physical makeup or constitution.

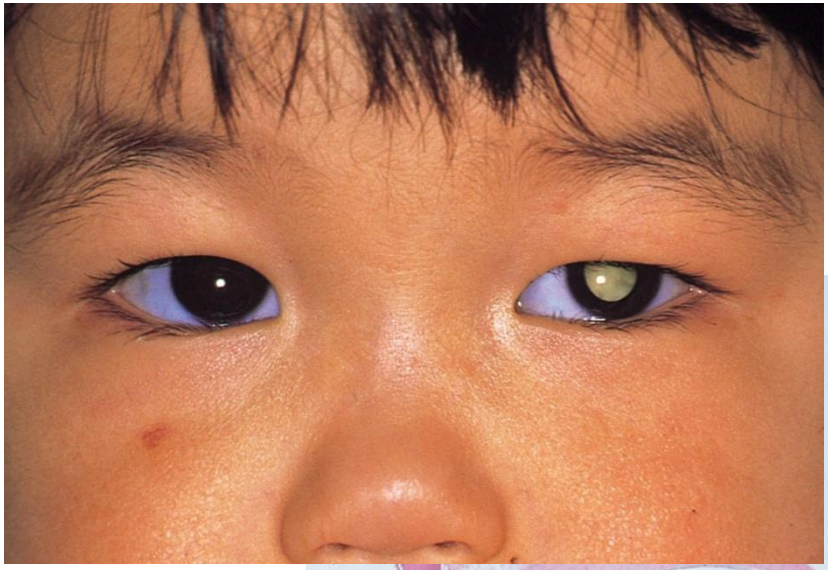
Pathogenic mechanisms are not clear.

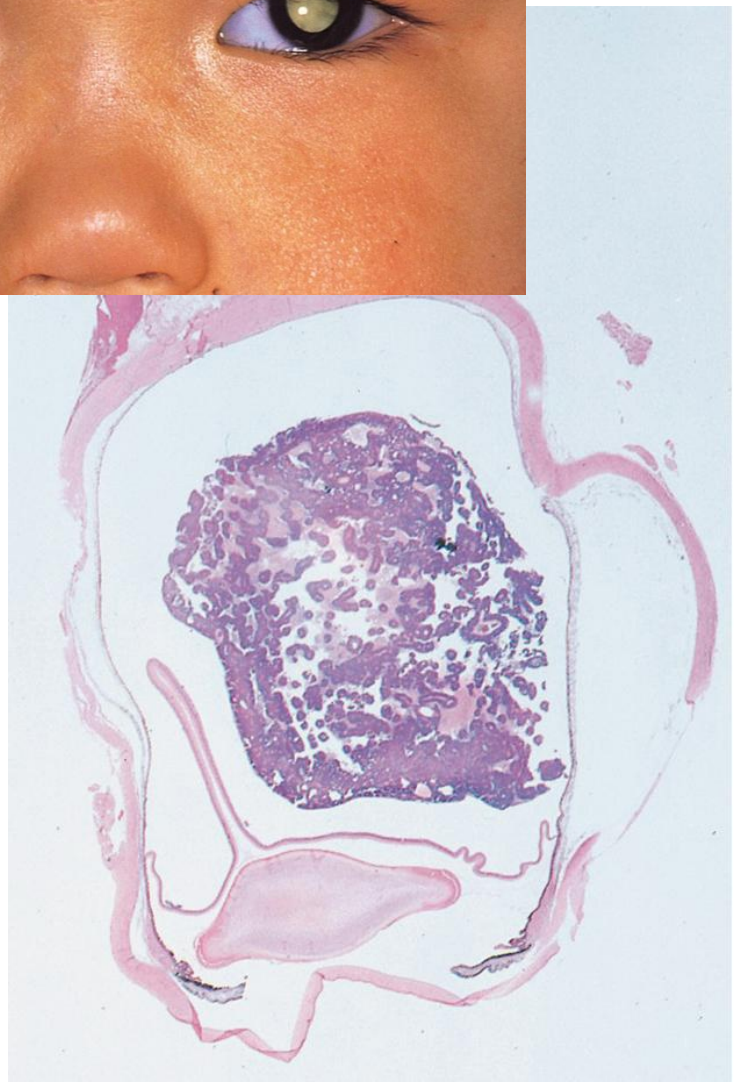
Examples : life style-related diseases (diabetes mellitus, gout, essential hypertension), so-called cancer family, psychiatric diseases (schizophrenia, mood disorder) , cleft lip/palate, and hearing loss

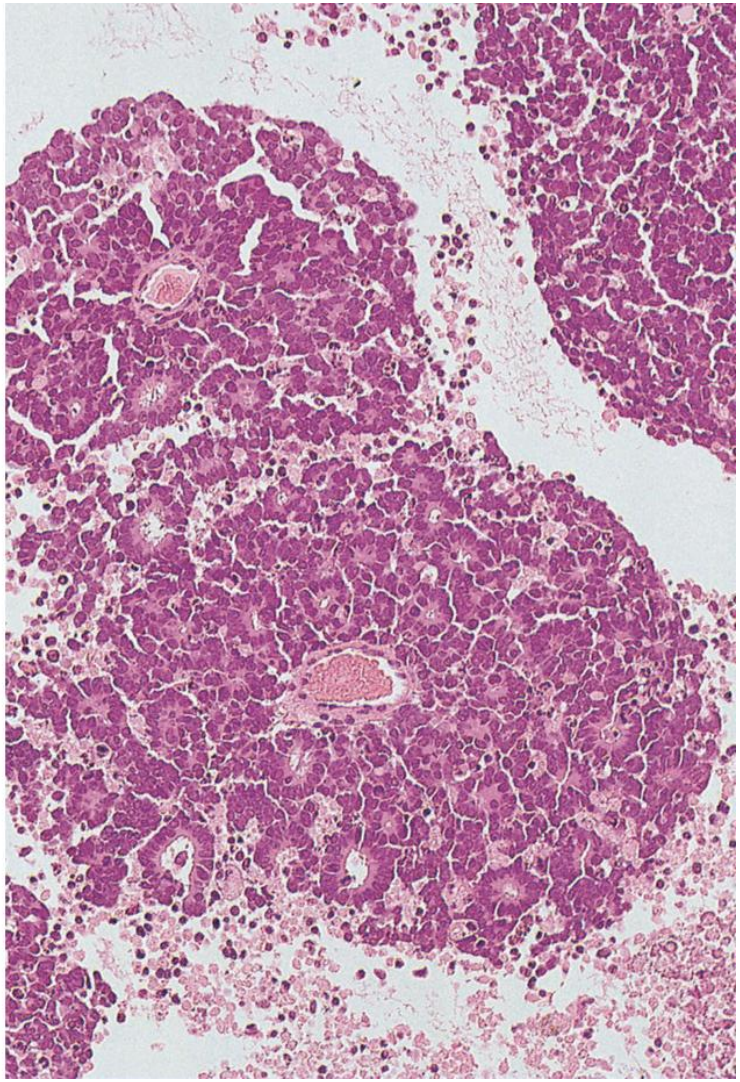
Hereditary human neoplasms

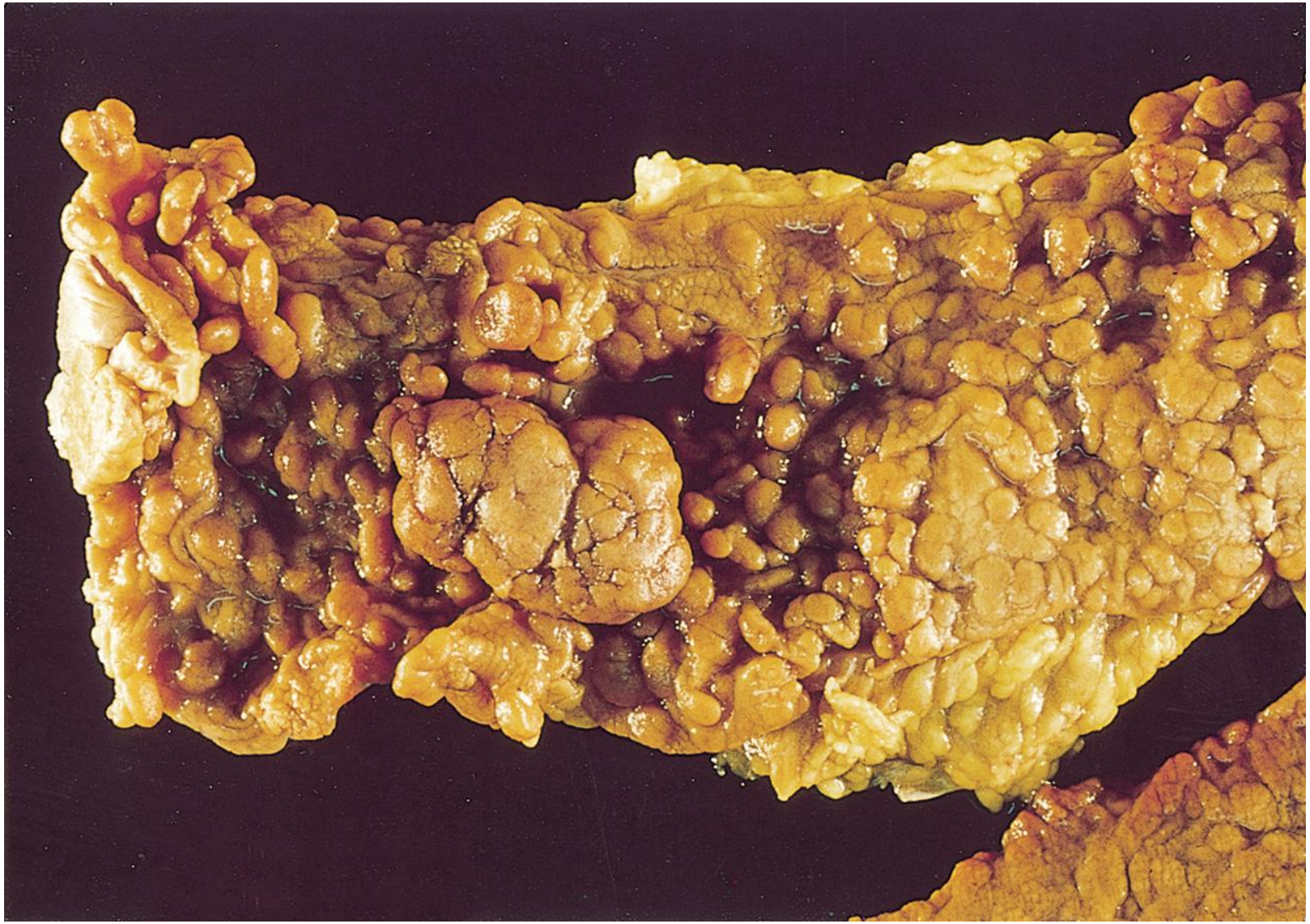
- Retinoblastoma — Rb gene
- Wilms' tumor — WT gene
- Familial polyposis coli — APC gene
- Hereditary non-polyposis colon cancer (HNPCC) — DNA-repairing enzyme genes
- Multiple endocrine neoplasia, type I (Wermer's dyndrome) — MEN1 gene
- Multiple endocrine neoplasia, type II (Sipple's syndrome) — Ret gene
- von Recklinghausen's disease — NF1 gene
- Xeroderma pigmentosum — DNA-repairing enzyme genes
- Werner's syndrome (progeria) — DNA helicase gene

Retinoblastoma（leukocoria and H&E features showing rosette formation）



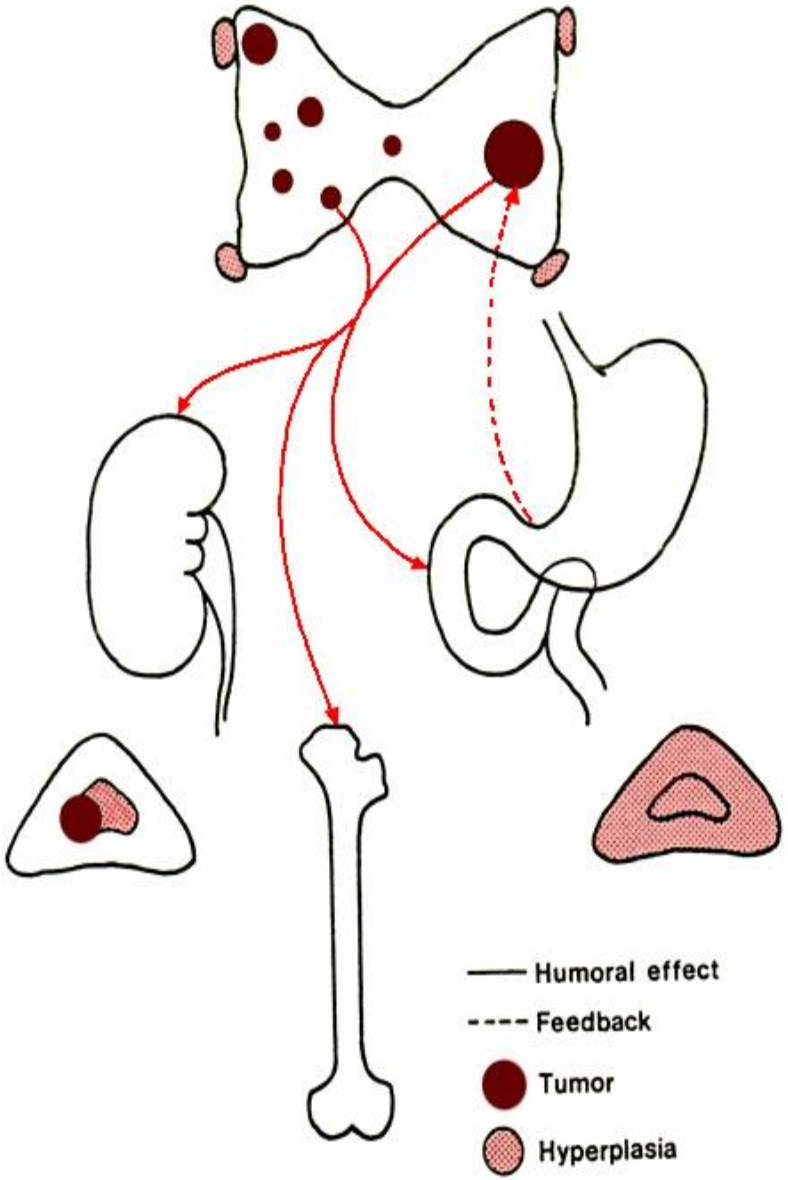




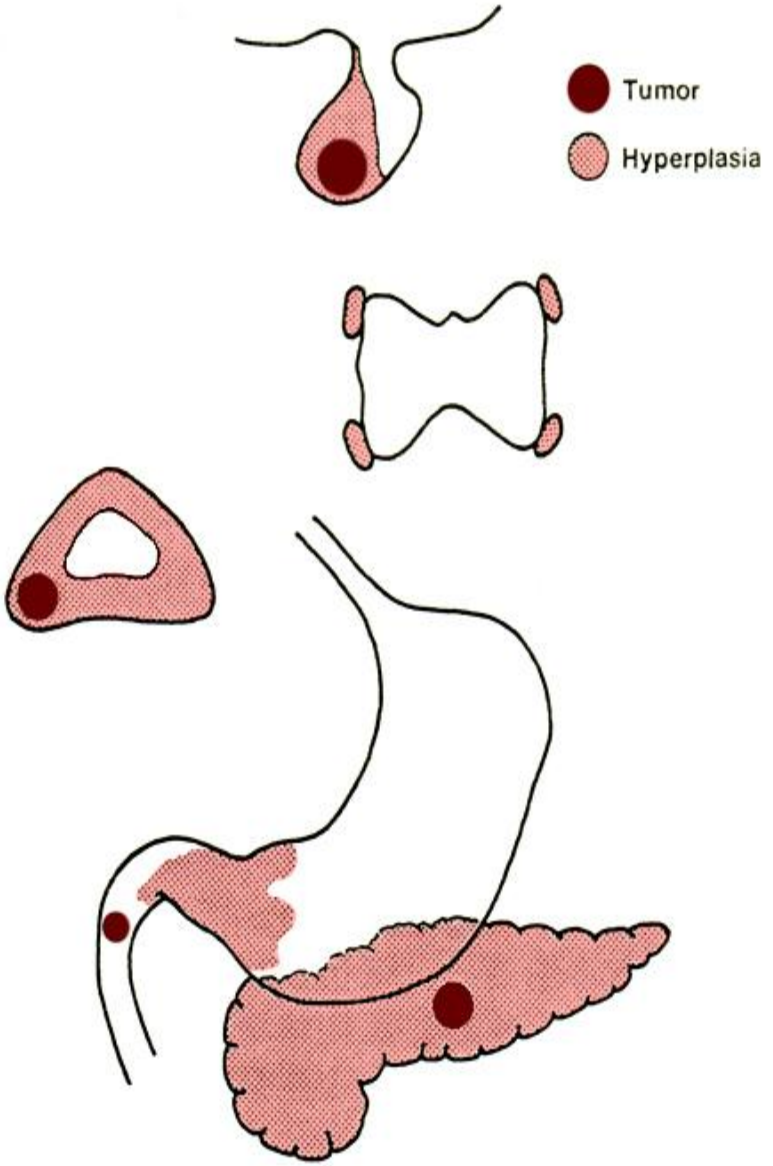


Familial polyposis coli (gross appearance of the colon after formalin fixation: Numerous adenomas are seen.

MEN, type II



MEN type I



Responsible genes in multiple endocrine neoplasia (MEN)

MEN-I (Wermer's syndrome)

MEN1 gene (autosomal dominant trait)

MEN-II (Sipple's syndrome)

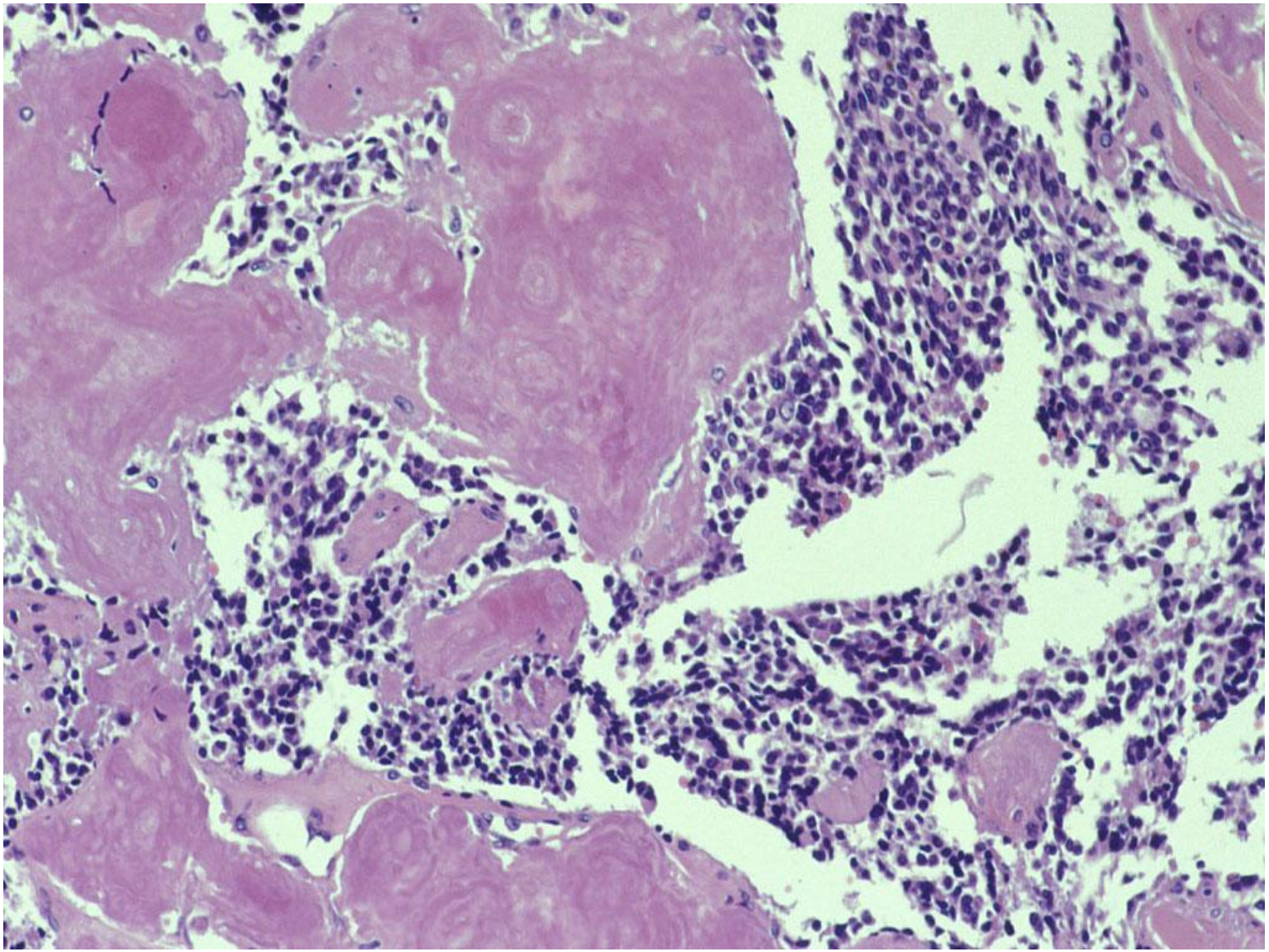
ret gene (autosomal dominant trait)

Ret gene-related disorders

1) Point mutation (activating mutation)→MEN2A、MEN2B

2) Gene rearrangement (transposition to form ret/PTC chimeric gene) →papillary thyroid carcinoma

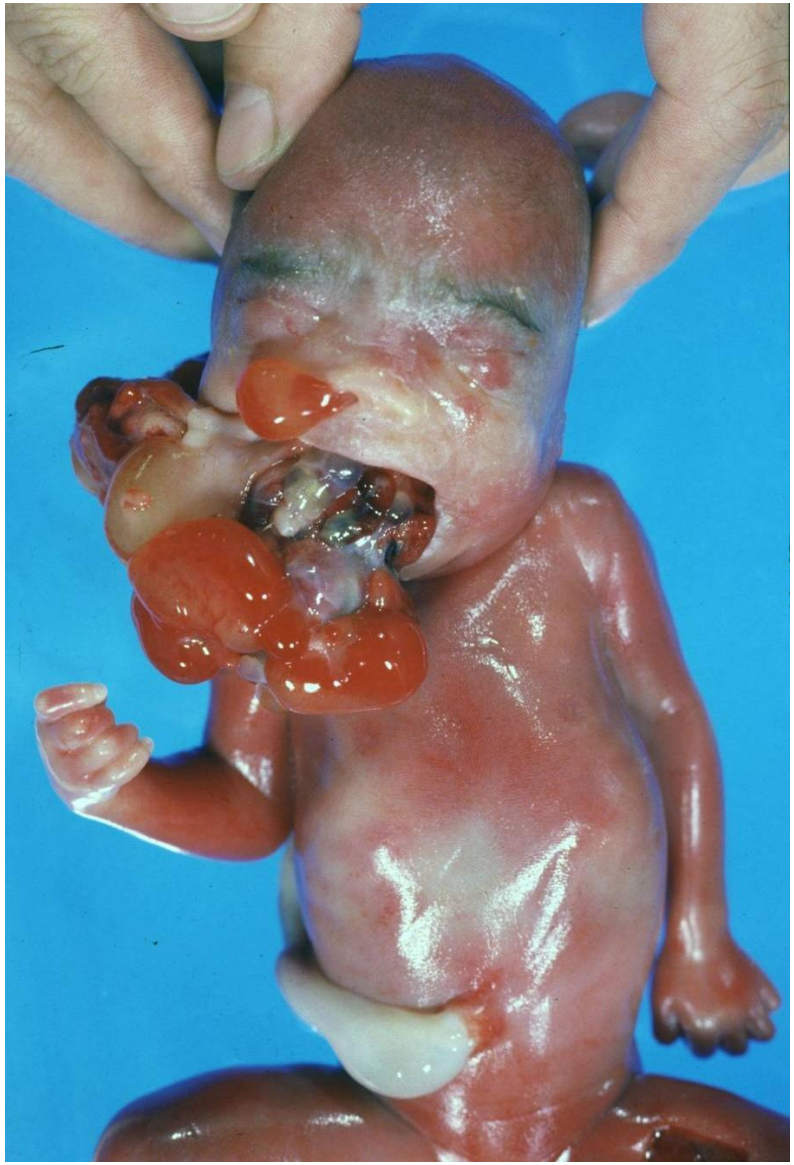
3) Gene deletion (inactivating mutation)→Hirschsprung's disease

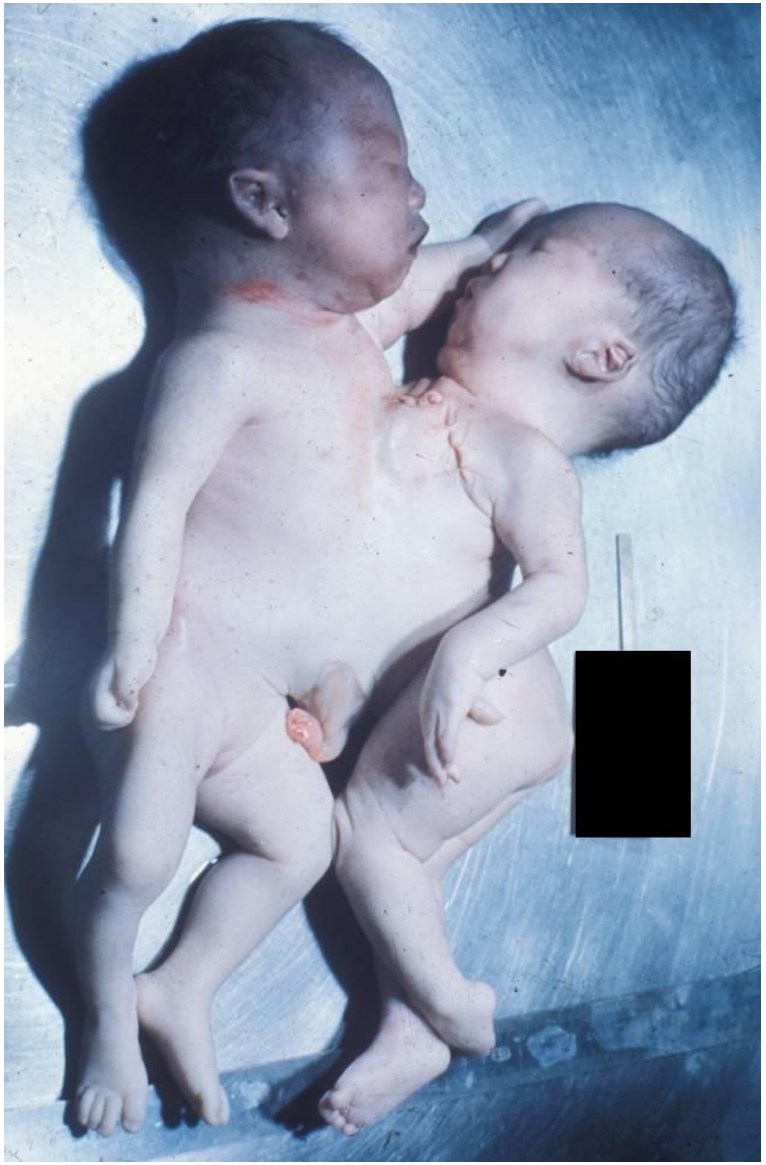


Medullary thyroid carcinoma with amyloid deposition (H&E)

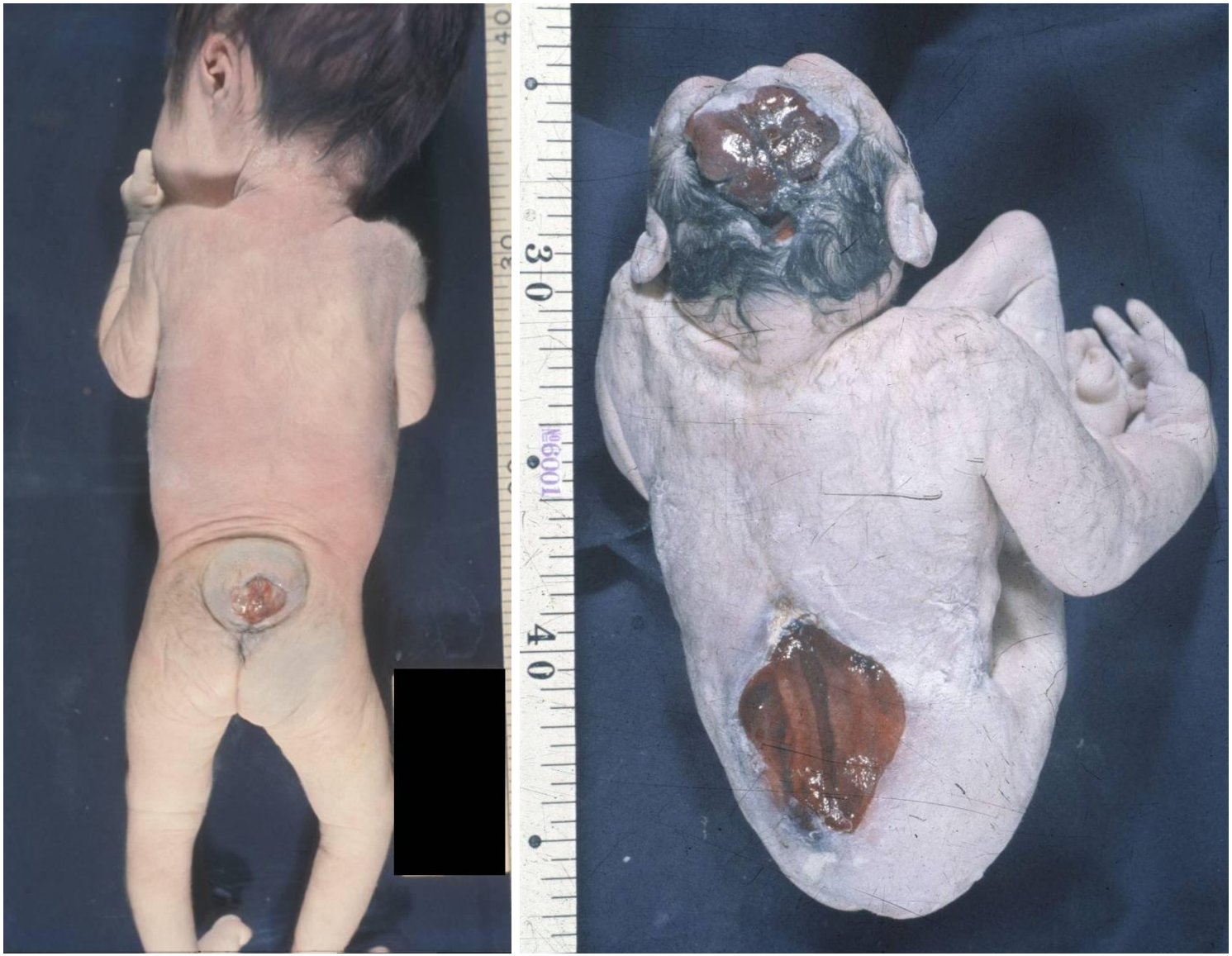
Congenital malformations

- Chromosomal abnormalities
- Segregation distortion of the fertilized ovum
  conjoined twins (Siamese twin)
  epignathus (differentiated mature teratoma)
- Abnormalities in early pregnancy
  Congenital rubella syndrome
  TORCH syndrome (infection by Toxoplasma、Others、Rubella、CMV、HSV)
  Hydrops fetalis caused by parvovirus B19 infection (erythema infectiosum)
  Irradiation
  Adverse effects of drugs
    (thalidomide, hormones, lithium carbonate and anticonvulsants)
  Methylmercury intoxication (congenital Minamata disease)
  Folate deficiency (neural tube defect, anencephaly)
- Unknown etiology
  Cardiac anomalies, anomalies in the urogenital and digestive tracts
  Remnants of fetal structures
  (Meckel's diverticulum, urachal remnants, thyroglossal duct cyst, etc)

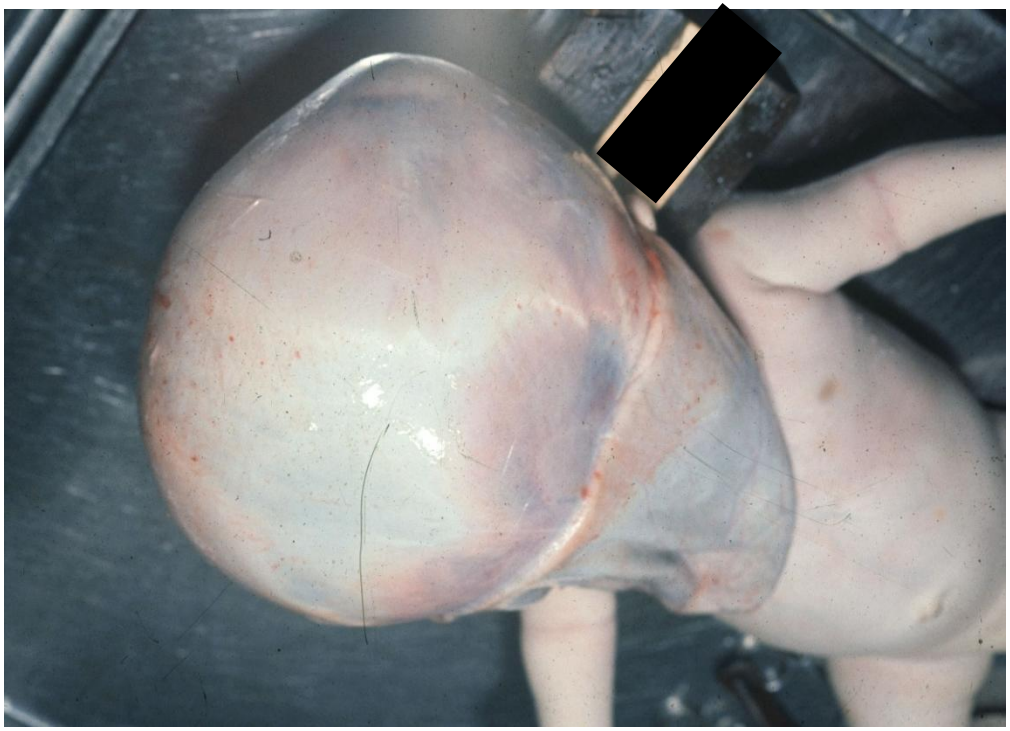


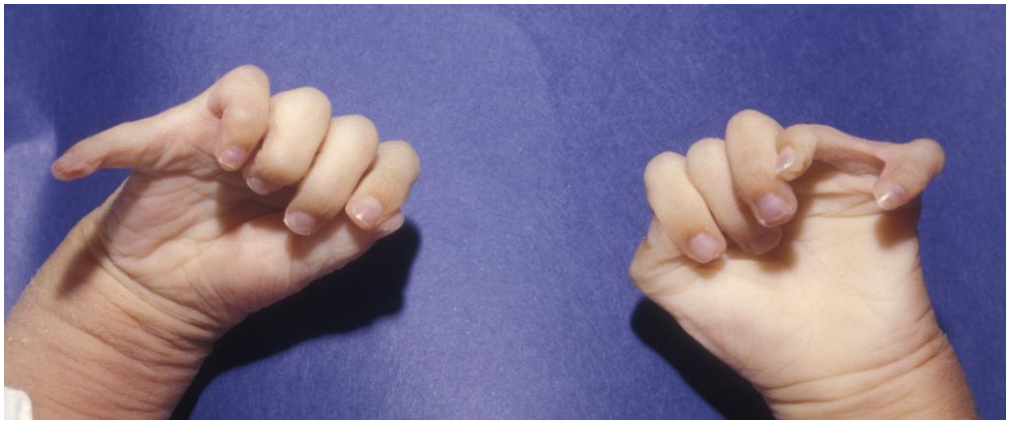


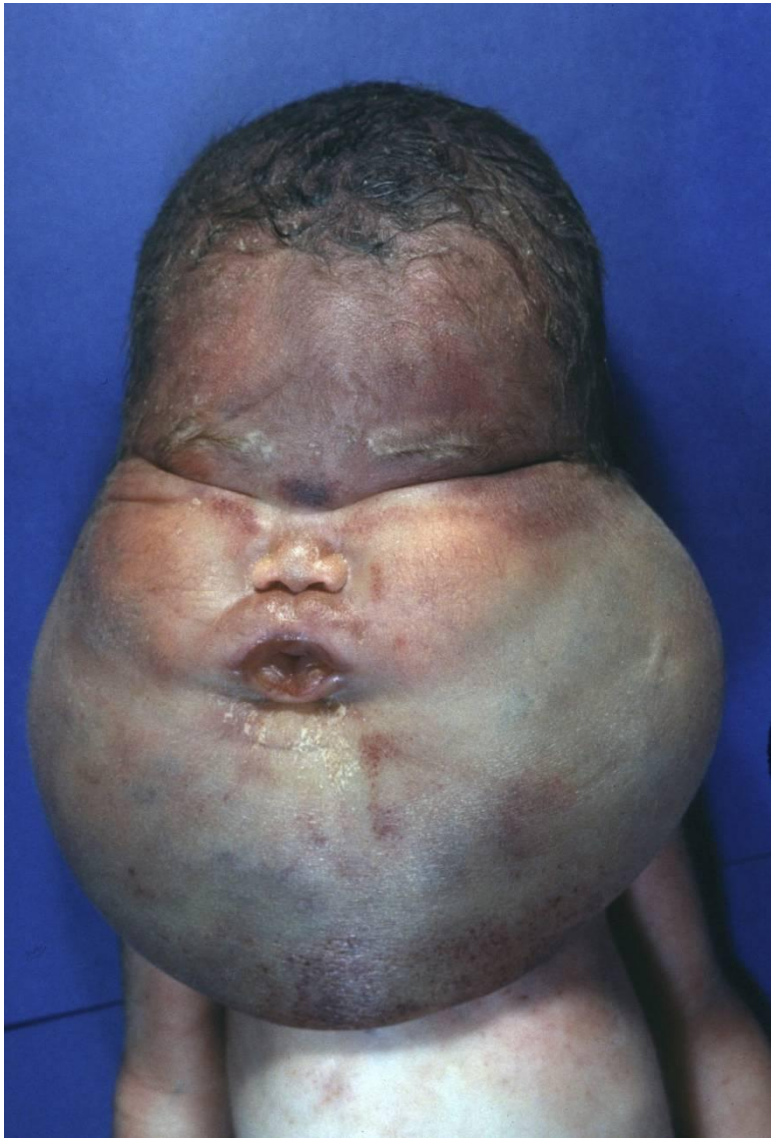
Congenital anomalies.
Left: **epignathus** (mature nasal teratoma)
Right: **thoracopagus** (conjoined twins)



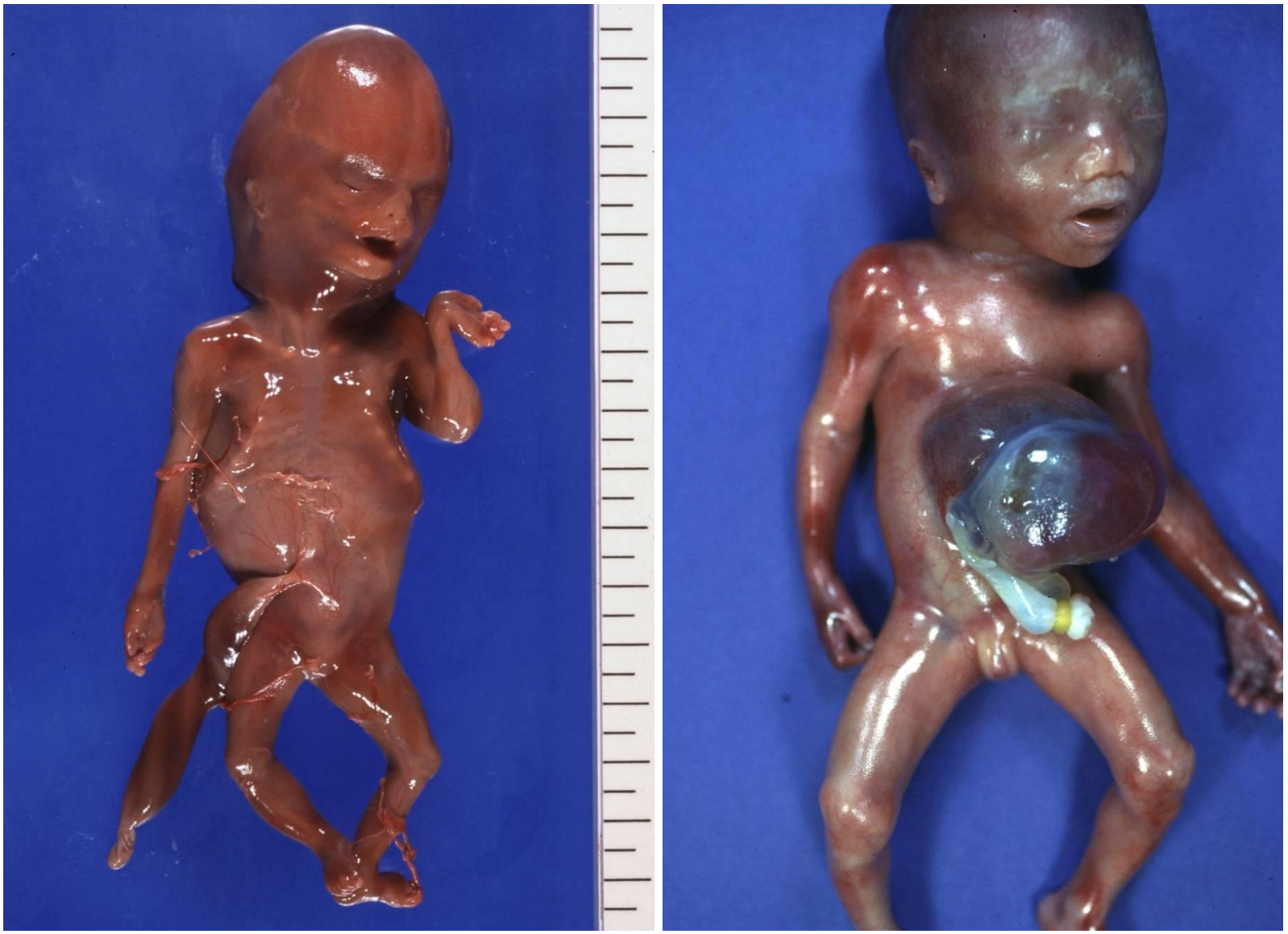
Neural tube defect caused by folate deficiency.
Left: spina bifida with meningocele
Right: anencephaly and spina bifida



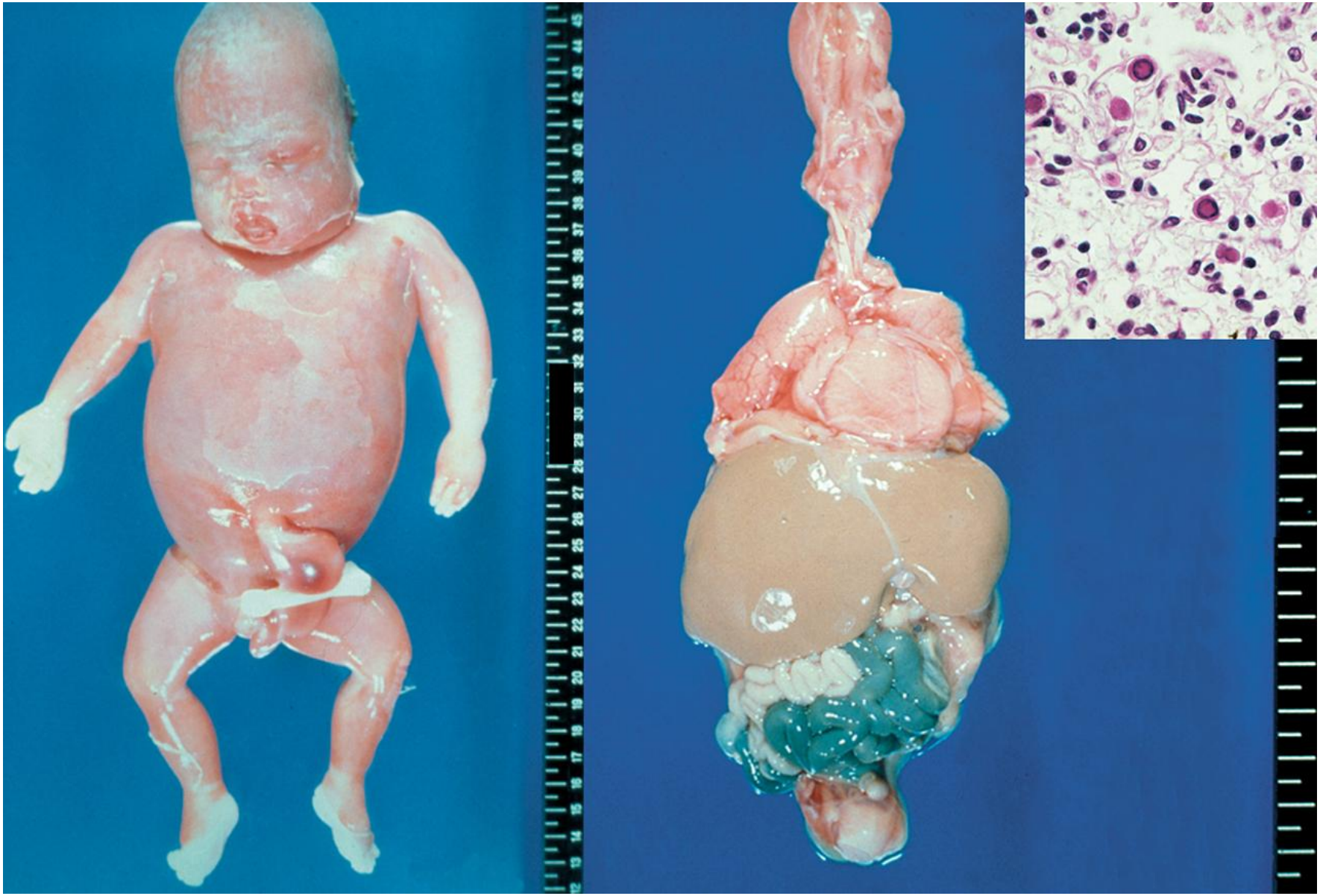




Congenital anomalies. left top: congenital hydrocephalus, left bottom: polydactyly, right: cystic hygroma of the neck



Congenital anomalies.
Left: stenosis of the umbilical cord, right: omphalocele



Hydrops fetalis caused by parvovirus B19 infection (erythema infectiosum)
As indicated in the inset (H&E), the virus infects the nucleus of erythroblasts, resulting in severe anemia. Note markedly anemic color of the liver.

Representative anomalies of the digestive tract

Cleft lip/palate

Bochdalek-type diaphragmatic hernia

Atresia of the digestive tract

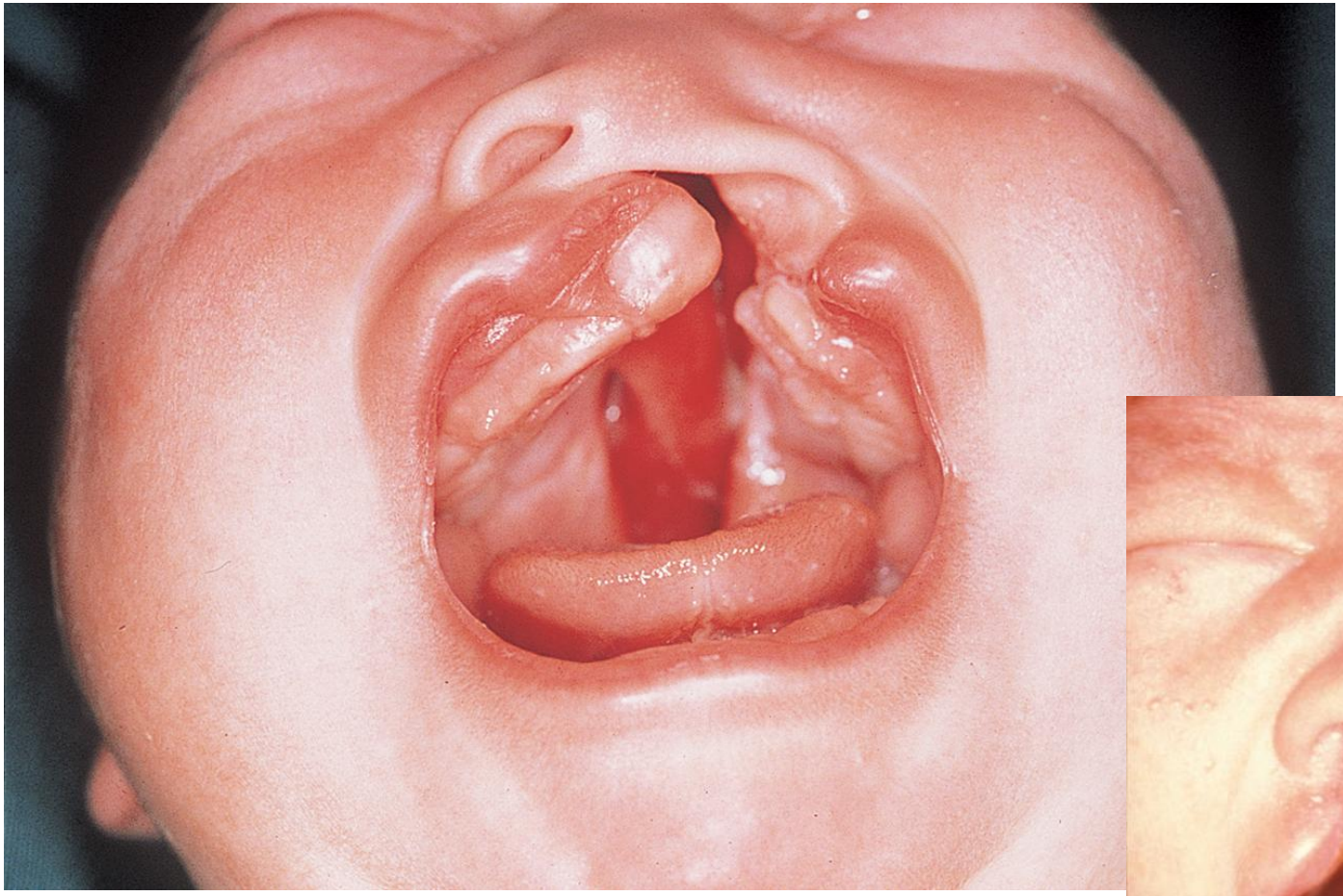
(esophageal atresia, duodenal atresia)

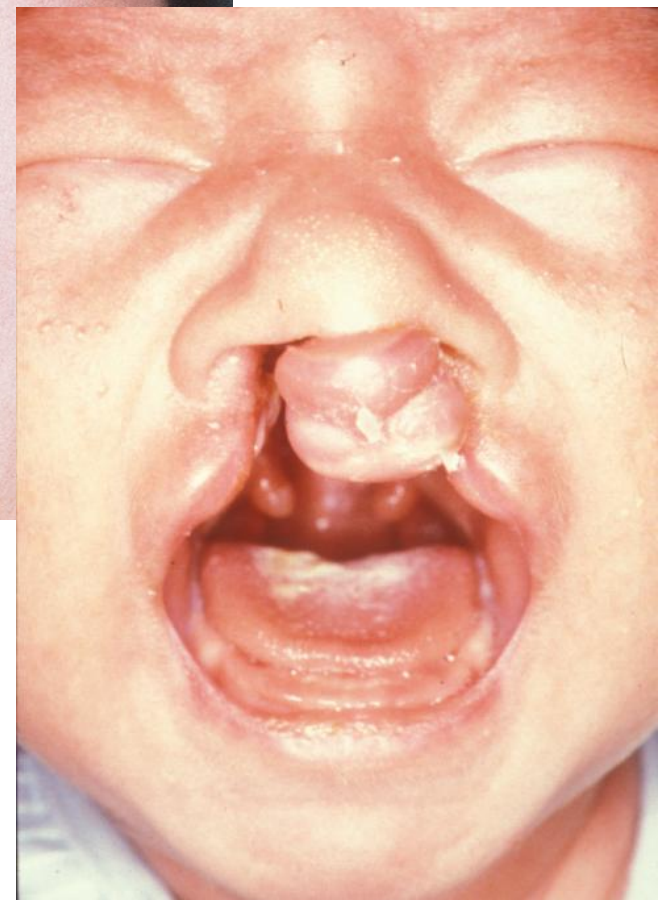
Meckel's diverticulum

Hirschsprung's disease

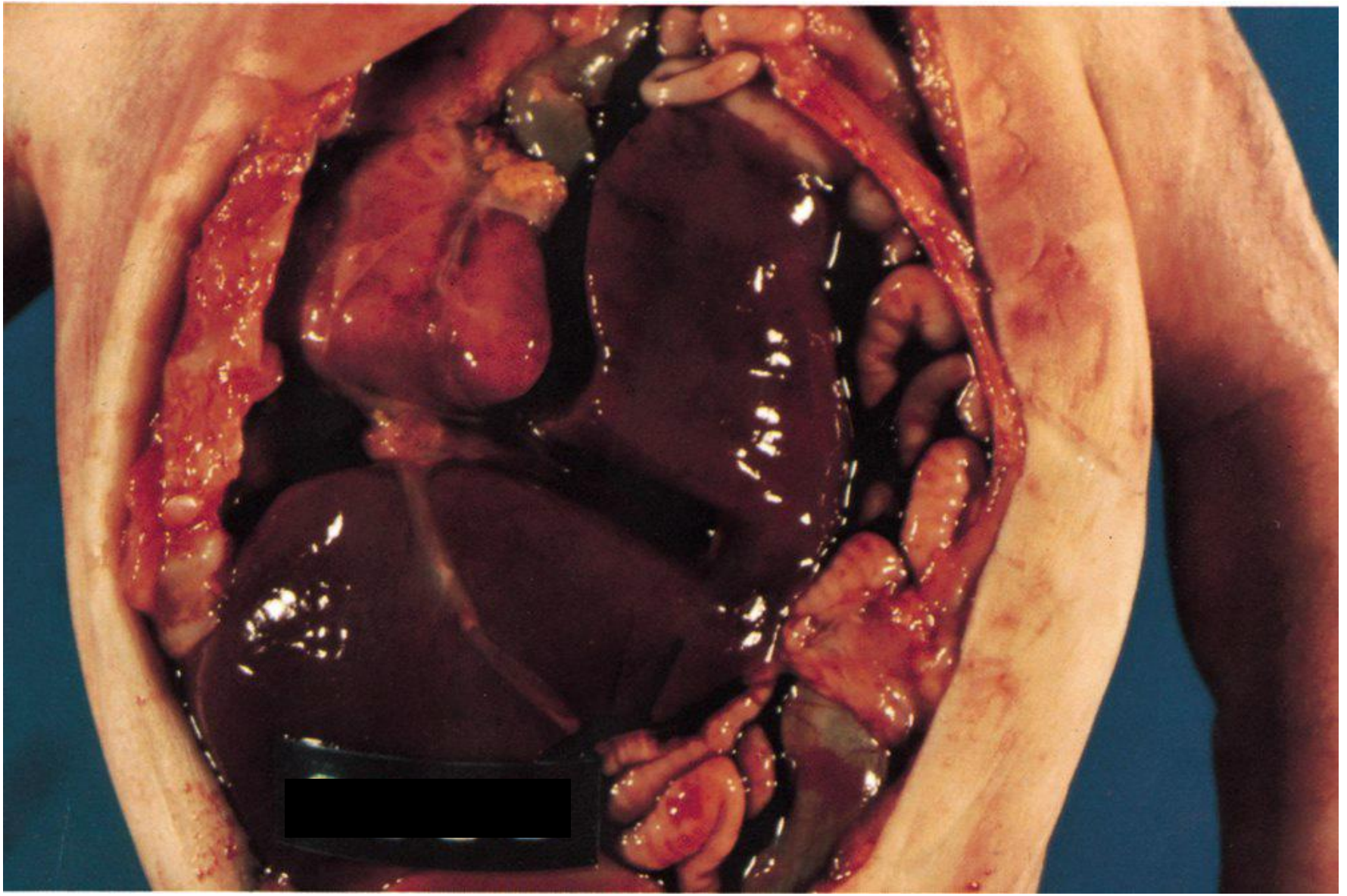
Anal atresia

Extrahepatic biliary atresia

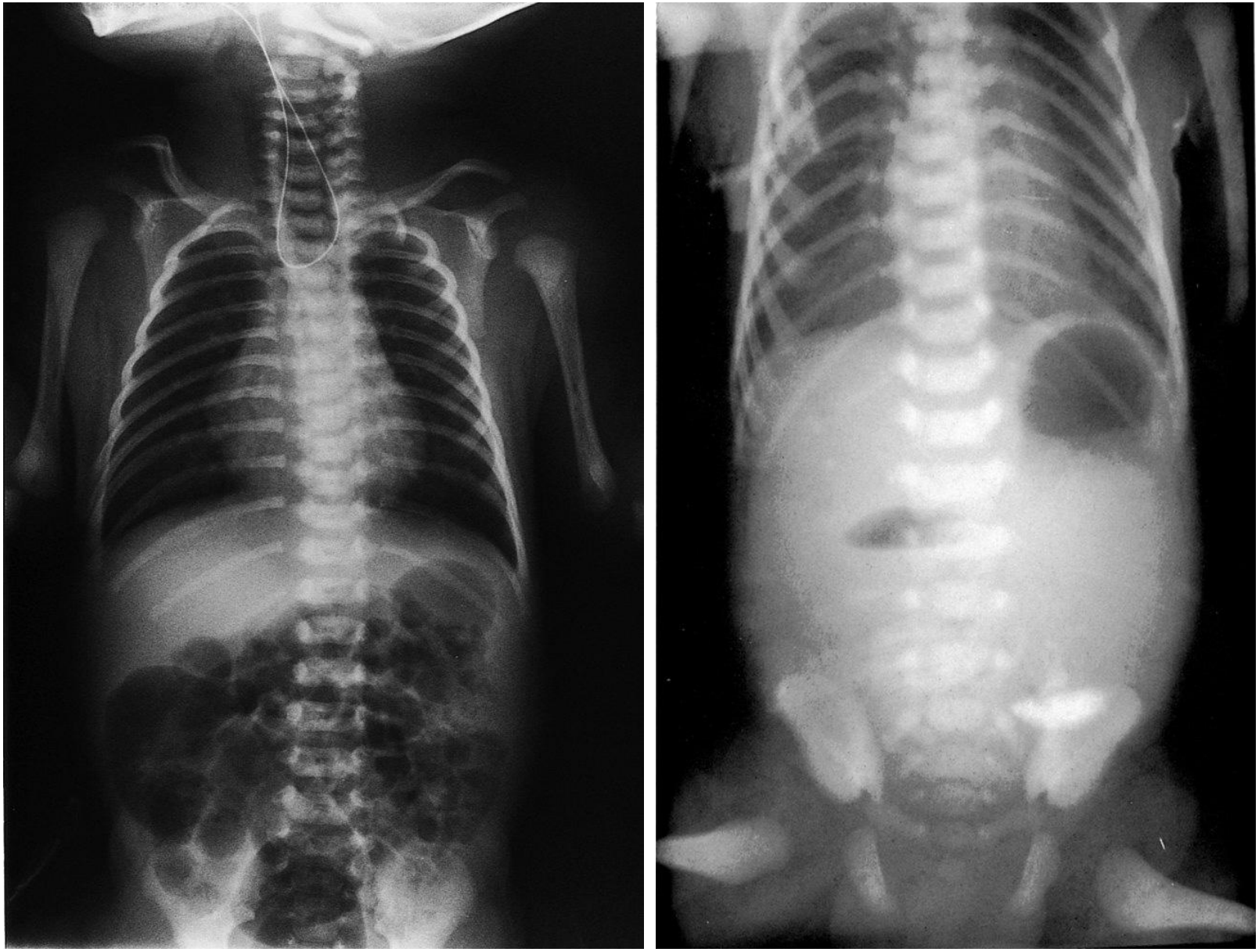




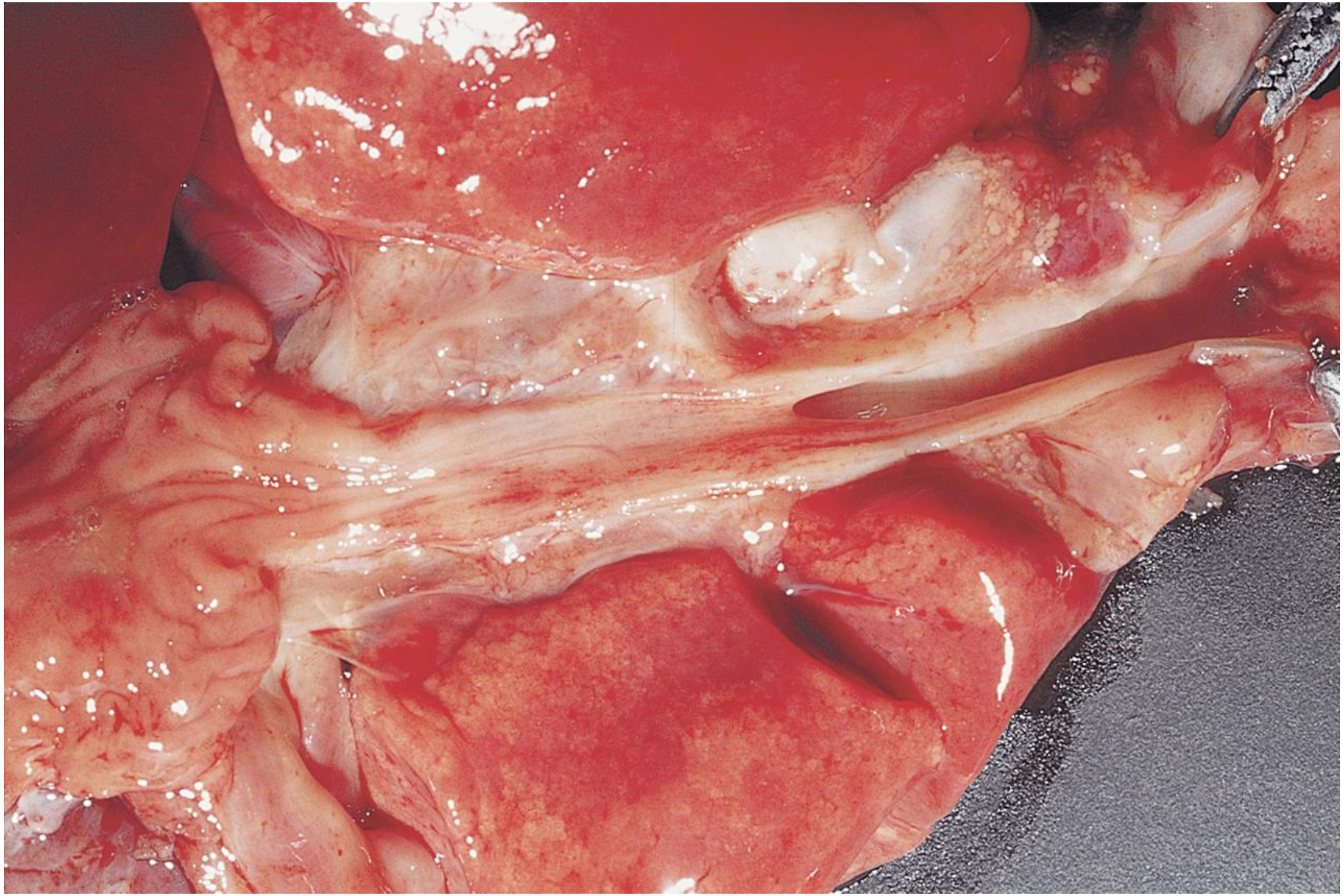
Gross appearance of
cleft lip and palate



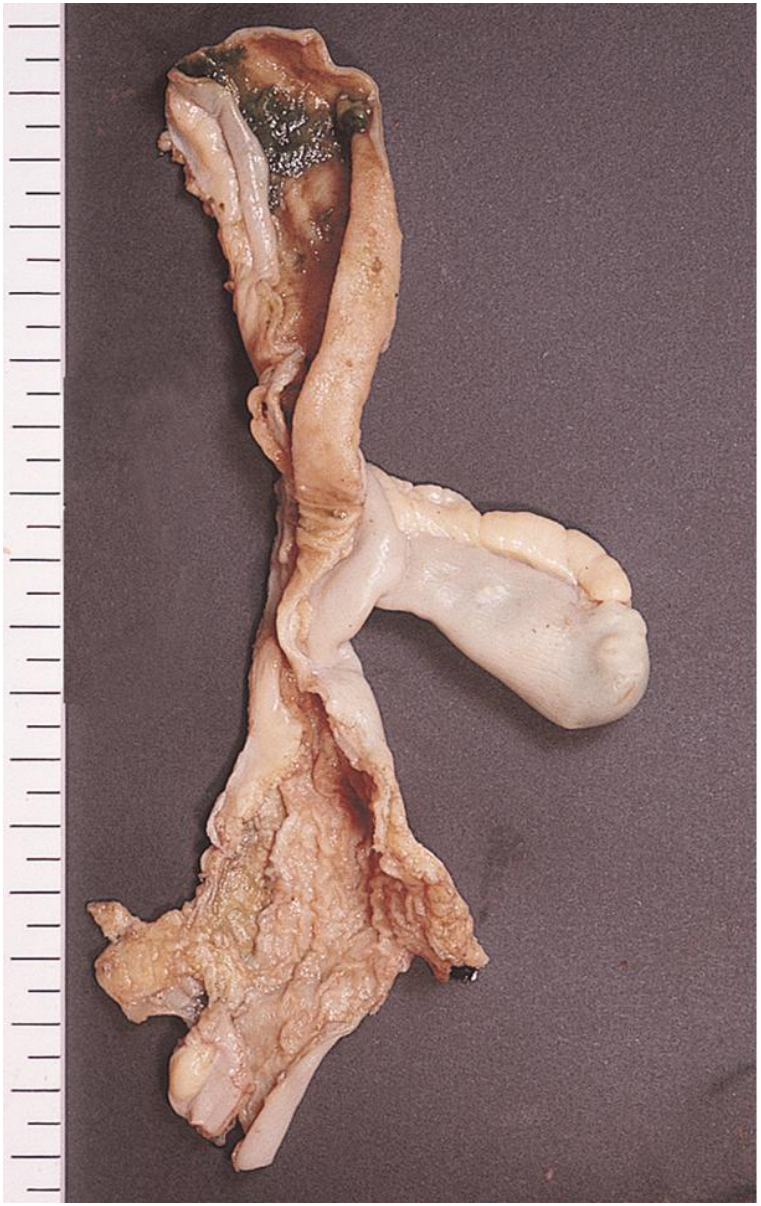
Bochdalek-type diaphragmatic hernia (autopsy case).
Massive herniation of the liver and intestine into the left thoracic cavity

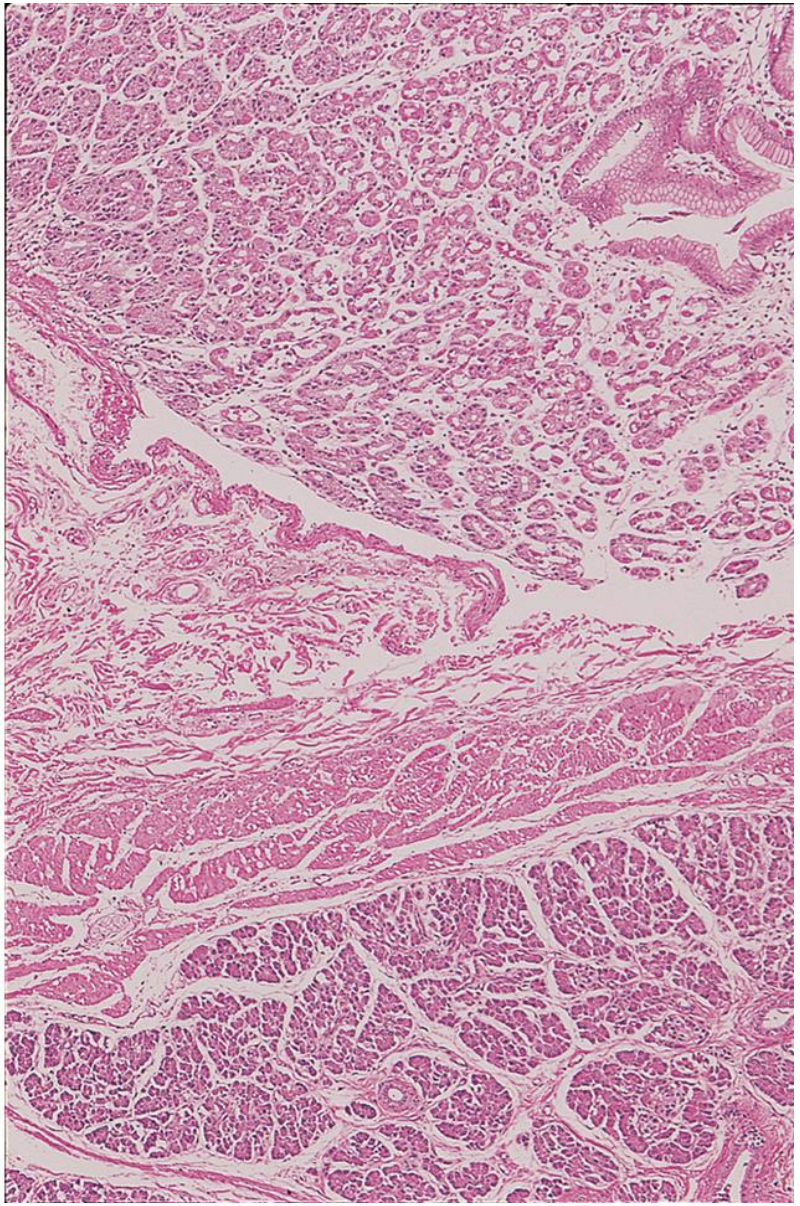


X-ray appearance of atresia of the digestive tract.
Left: esophageal atresia, type C, right: duodenal atresia with double bubble sign

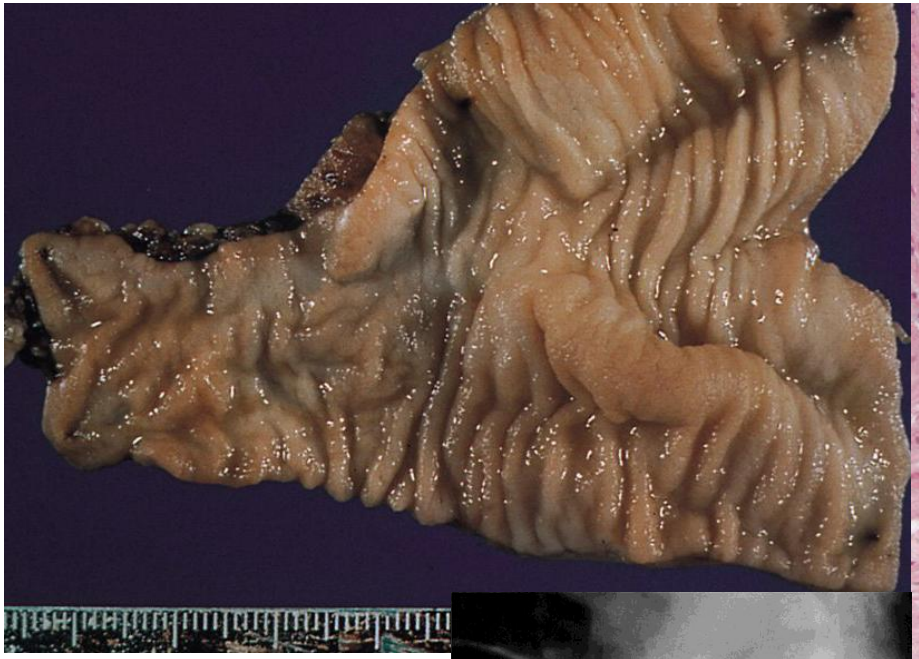


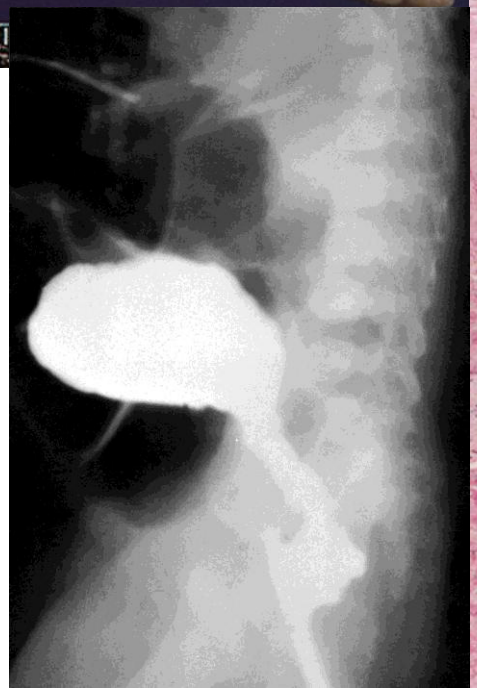
Esophageal atresia, type C, with tracheo-esophageal fistula





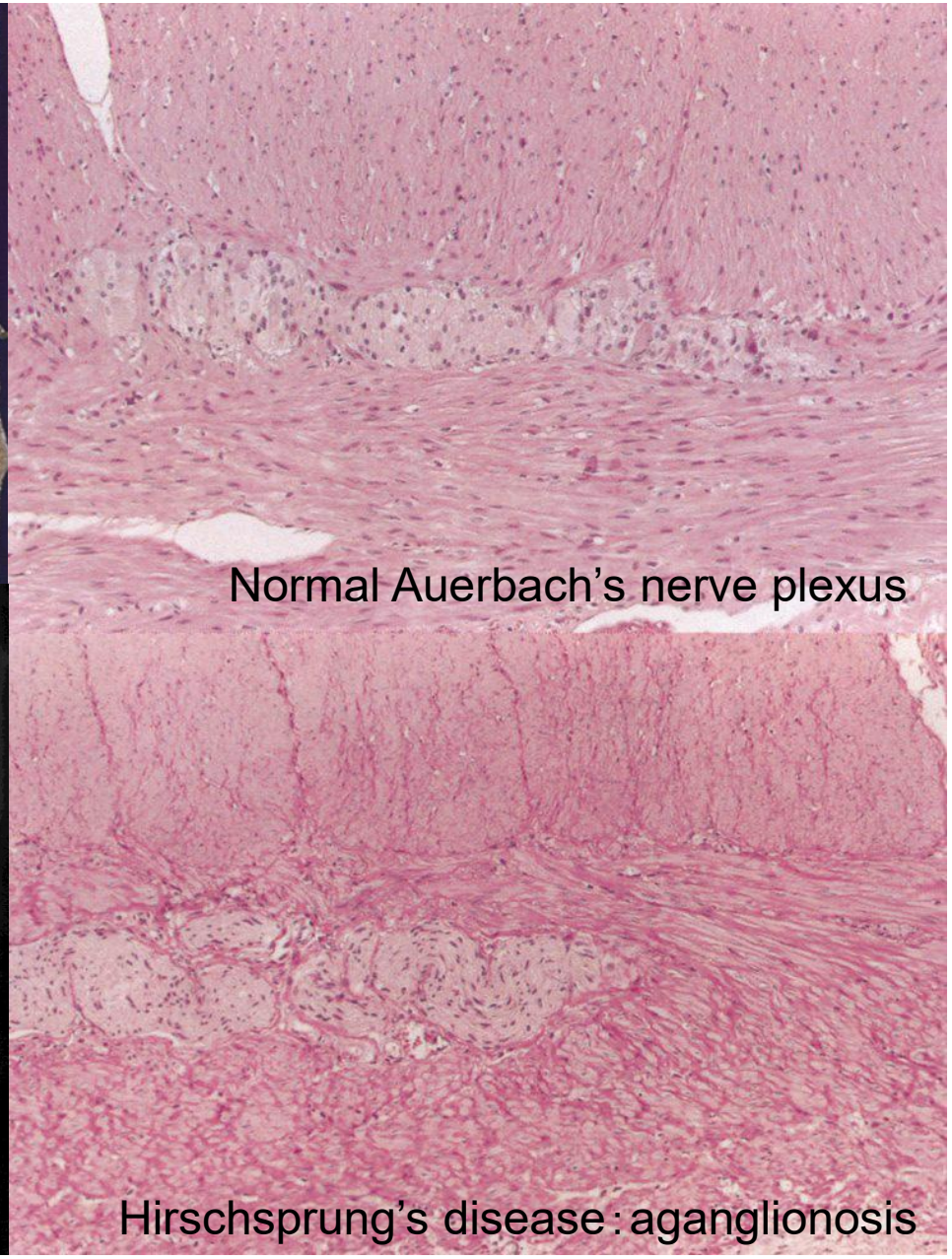
Meckel's diverticulum (left: gross appearance after formalin fixation, right: ectopic gastric and pancreatic tissues, H&E)

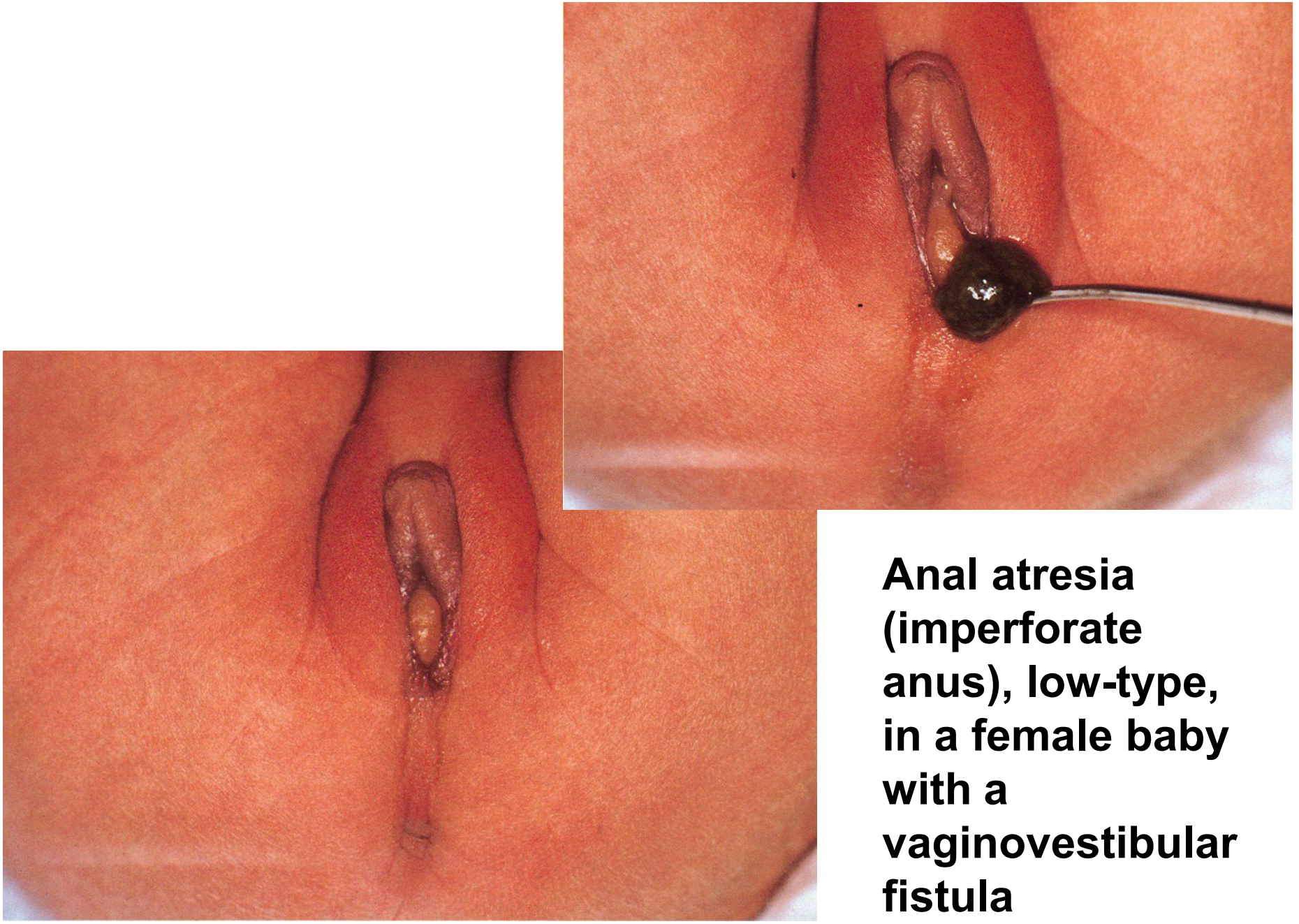




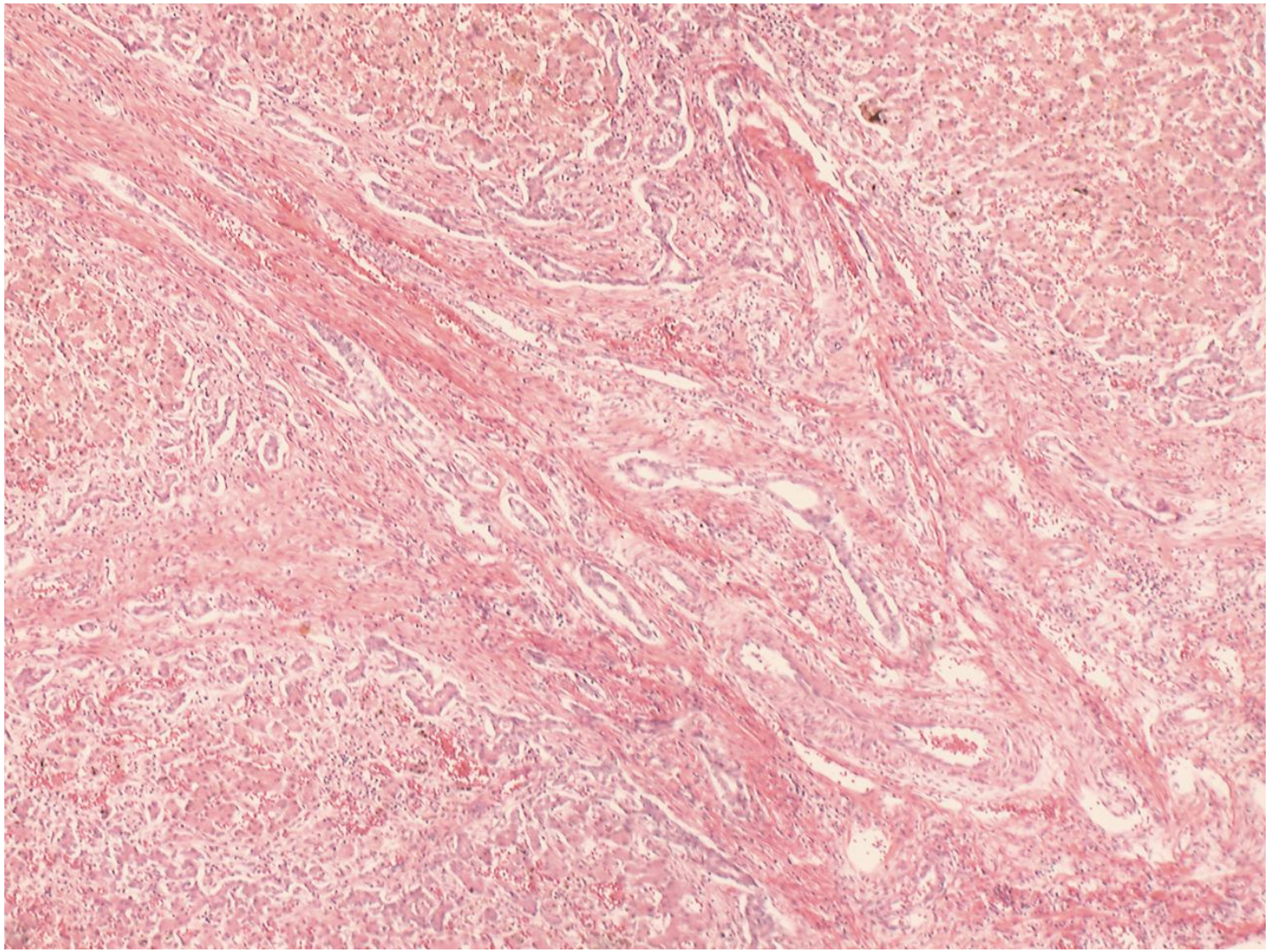
Hirschsprung's disease

Left top: surgical specimen
Left bottom: opaque enema with caliber change
Right: Auerbach's nerve plexus (H&E)





Anal atresia (imperforate anus), low-type, in a female baby with a vaginovestibular fistula



Extrahepatic biliary atresia (H&E). The hepatohilar tissue of a 5-month-old boy was obtained by Kasai's operation. The atresia occurs after birth, and the disease is not strictly congenital.

Reprentative cardiovascular anomalies

Ventricular septal defect

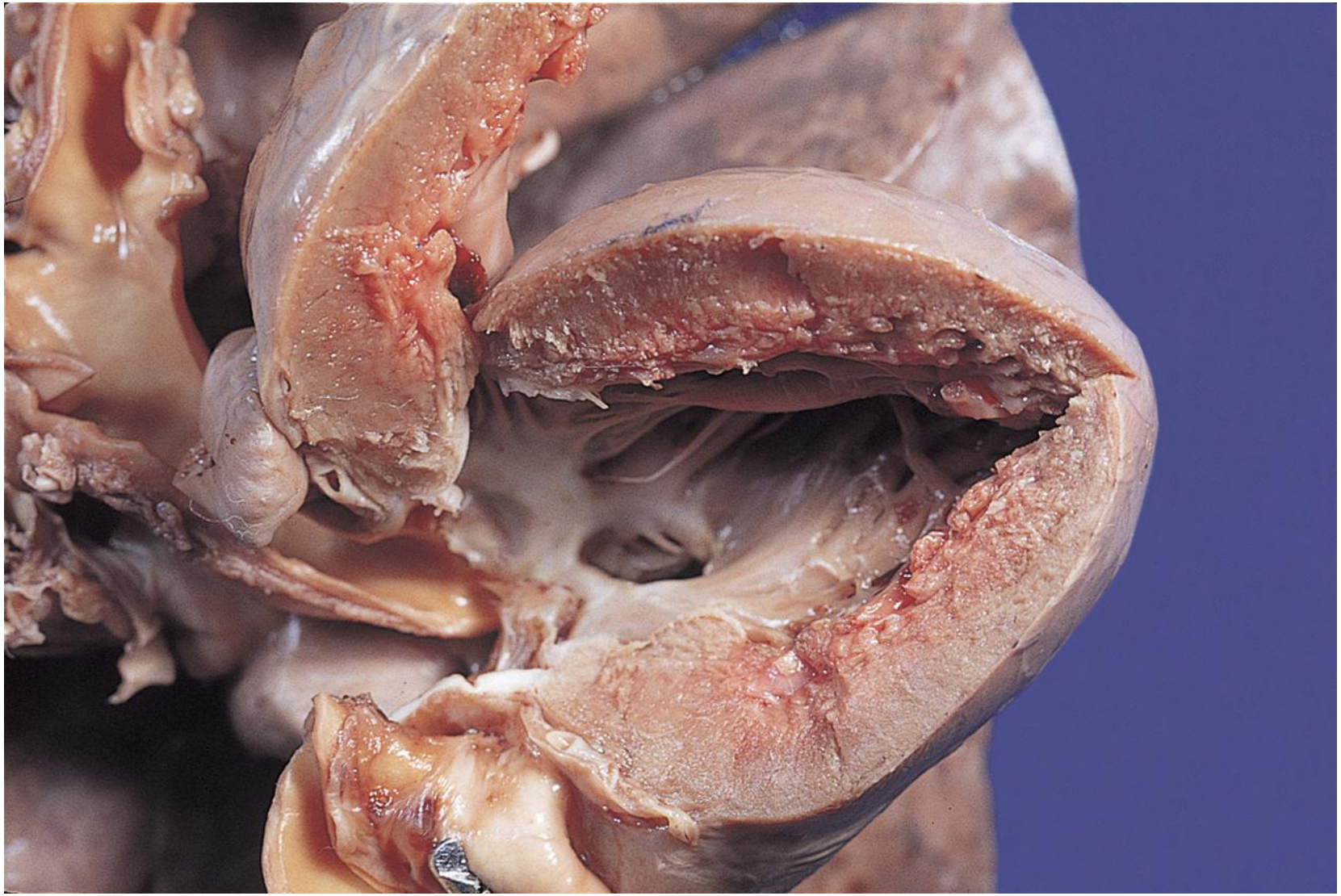
Tetralogy of Fallot

Aortic coarctation

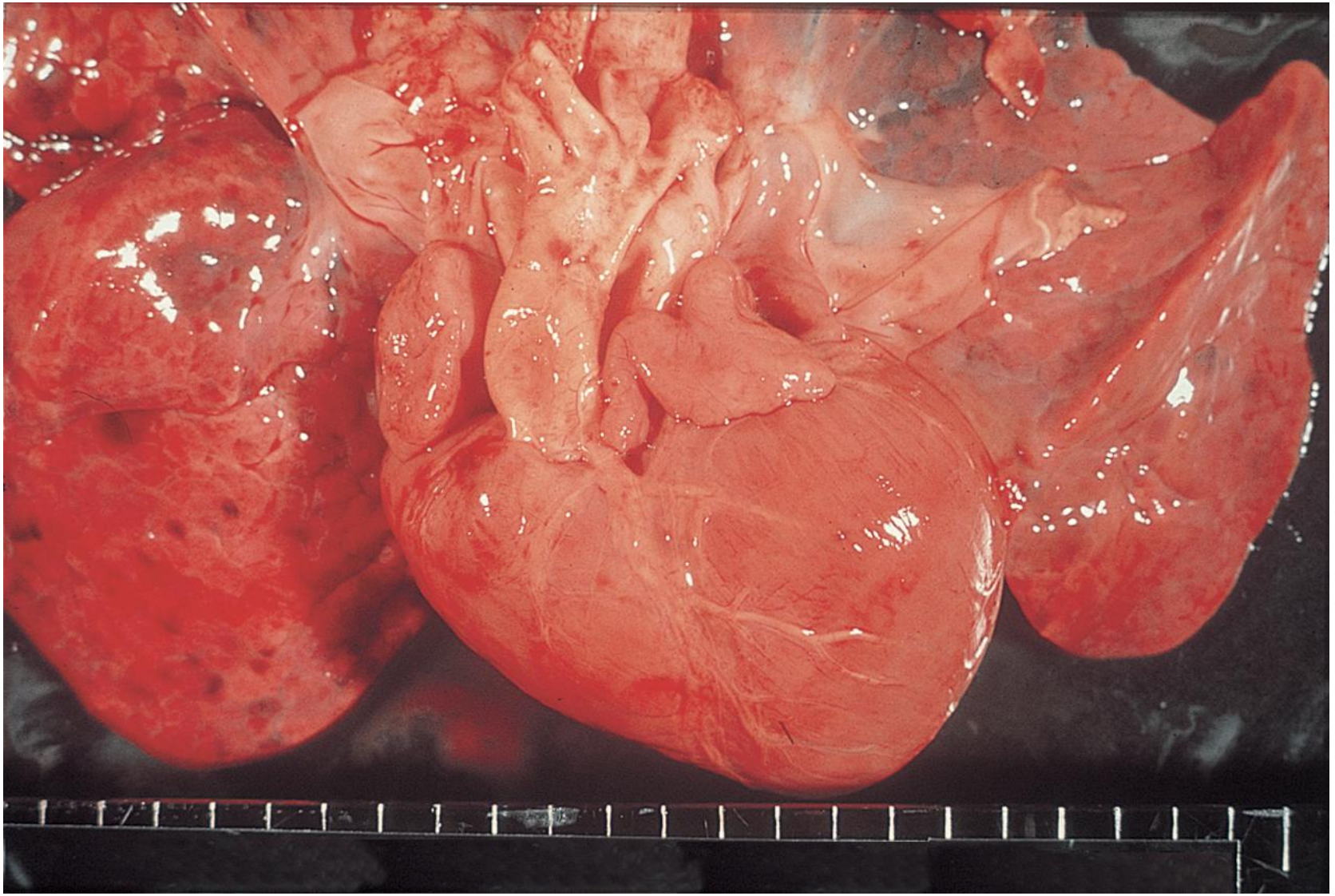
Asplenia syndrome

Kartagener’s syndrome

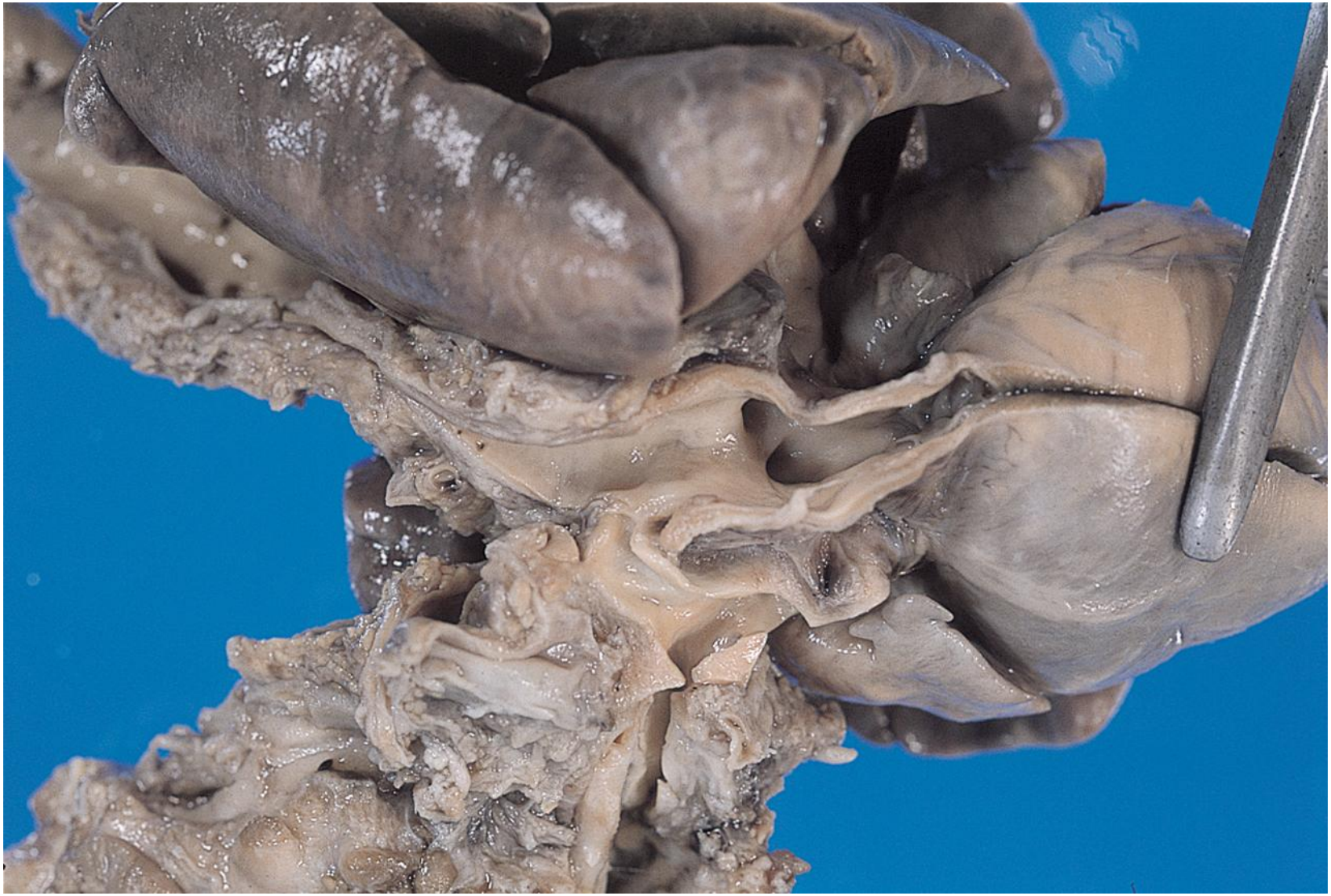
Single umbilical artery



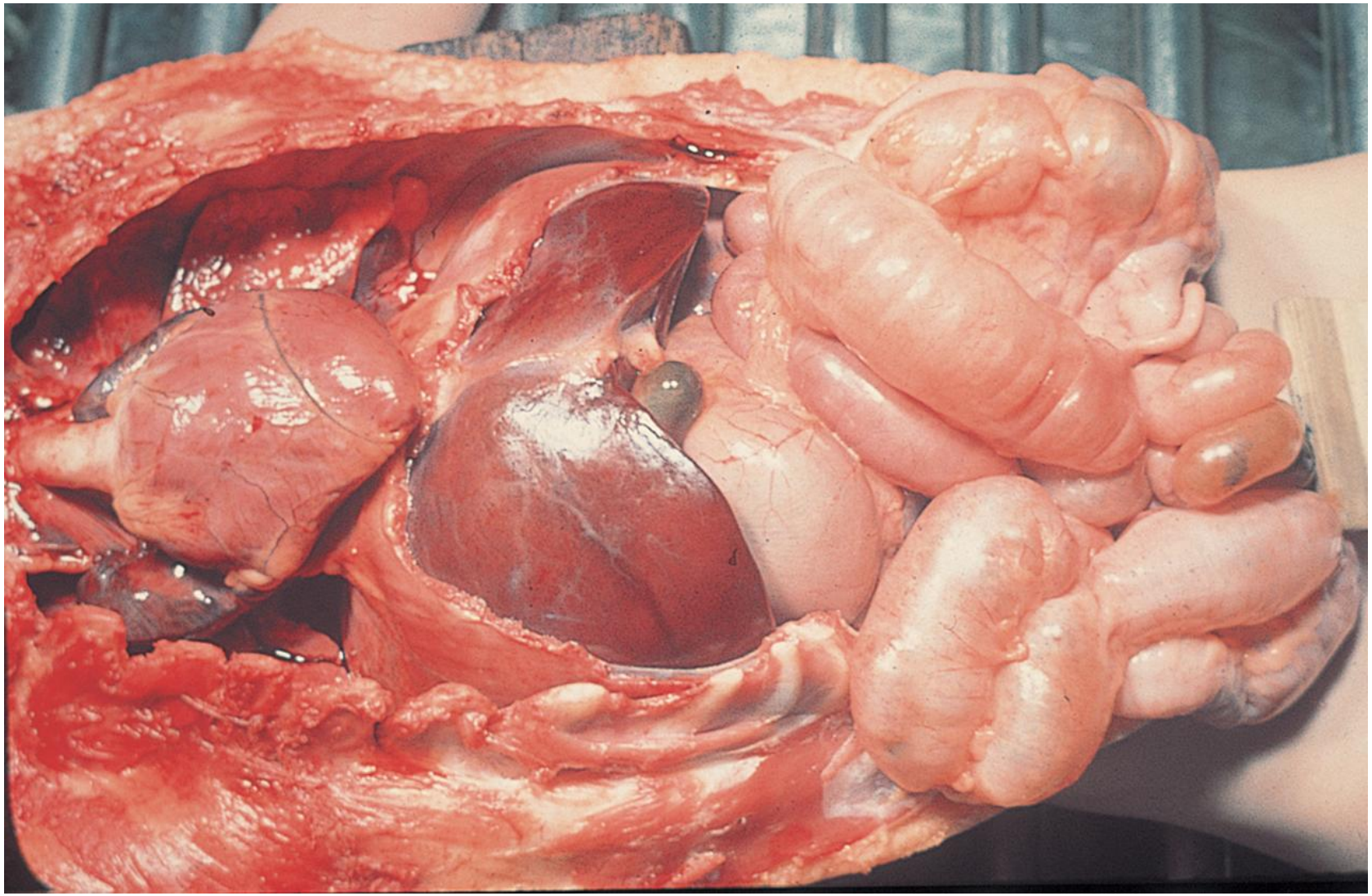
Ventricular septal defect
(gross appearance after formalin fixation)



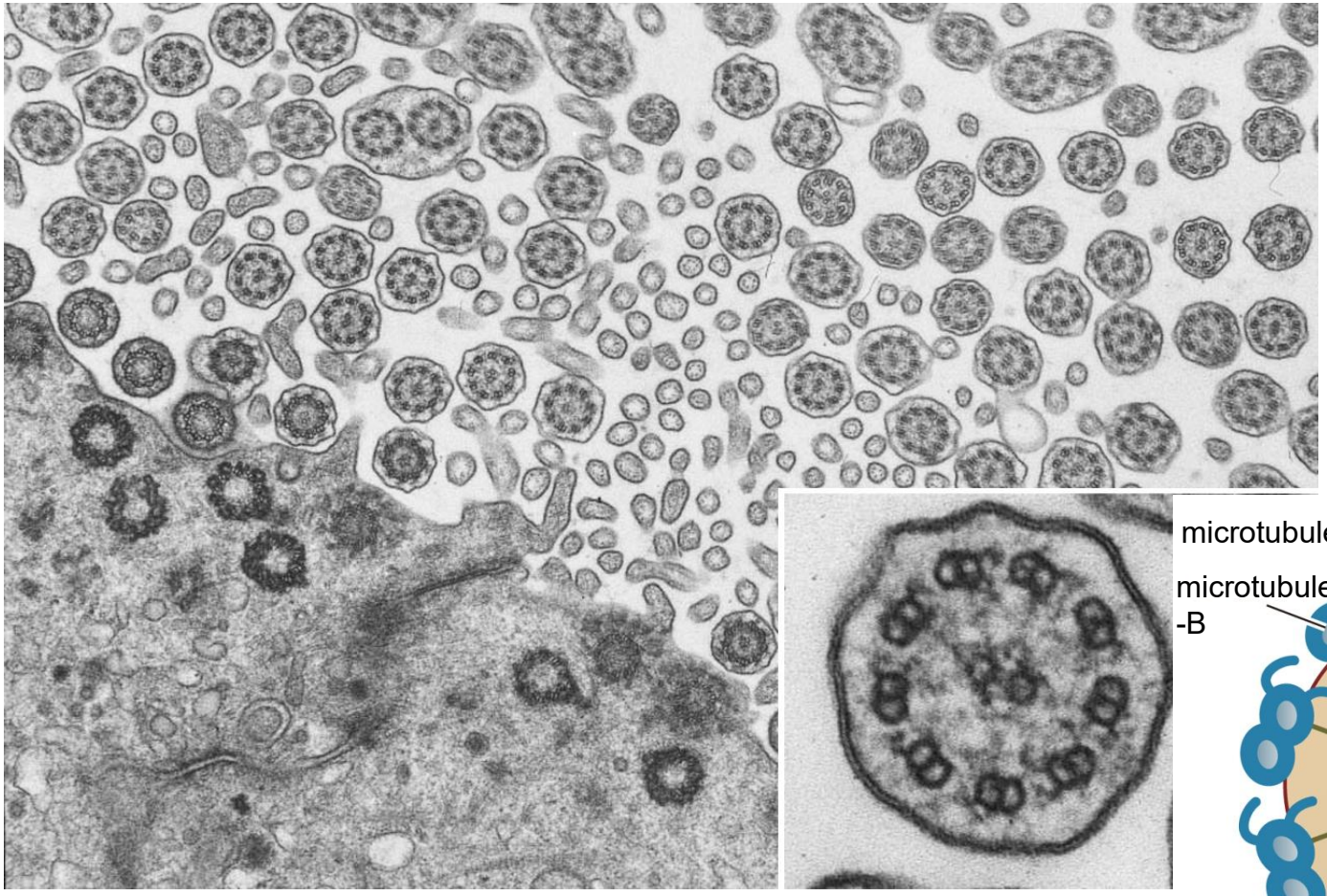
Tetralogy of Fallot (gross appearance).
with over-riding of the aorta and right ventricular hypertrophy



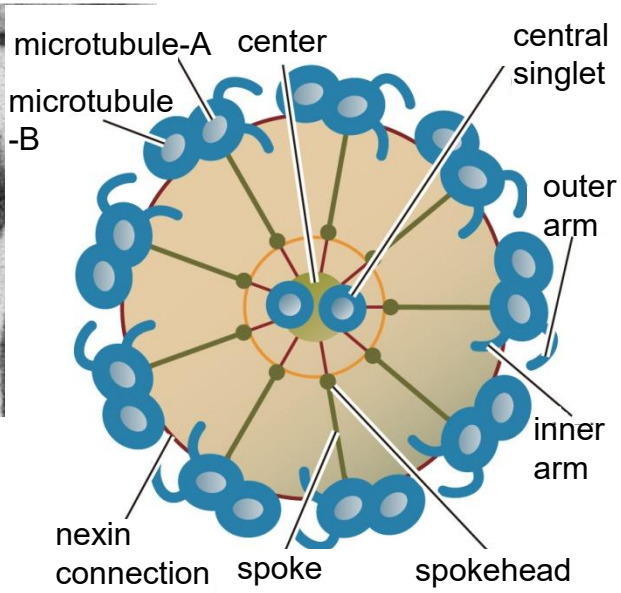
Coarctation of aorta, preductal type
(gross appearance after formalin fixation)



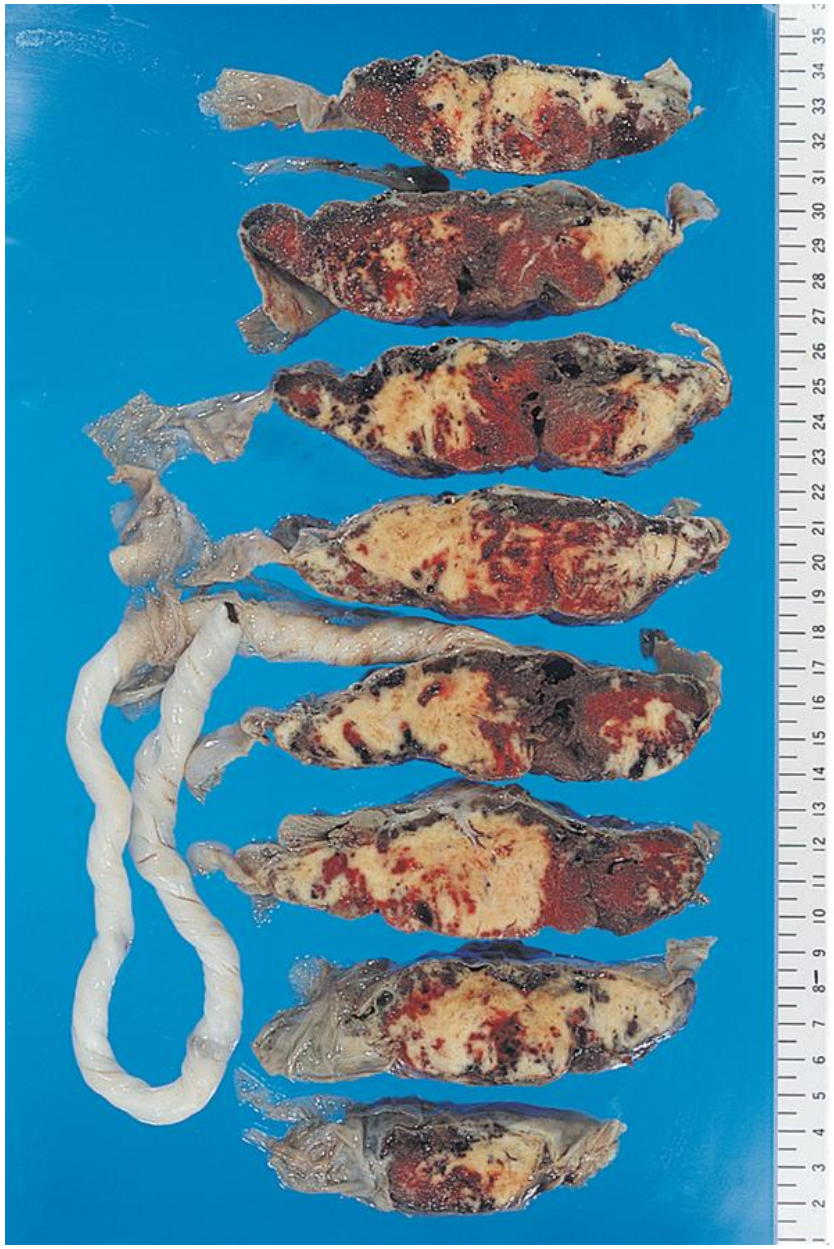
Asplenia syndrome (gross appearance).
Severe cardiac anomalies (single ventricle/single atrium) and left-right symmetry of organs (heterotaxy)



Immotile cilia syndrome with dextrocardia（**Kartagener's syndrome**). The lack of inner dynein arms is observed in the cilia on the respiratory mucosa



Schema of the cut surface of the cilium



Left: multiple infarcts of the placenta
Right: single umbilical artery (cut surfaces of the umbilical cord)

Representative anomalies of the urogenital tract

Horseshoe kidney and double ureters

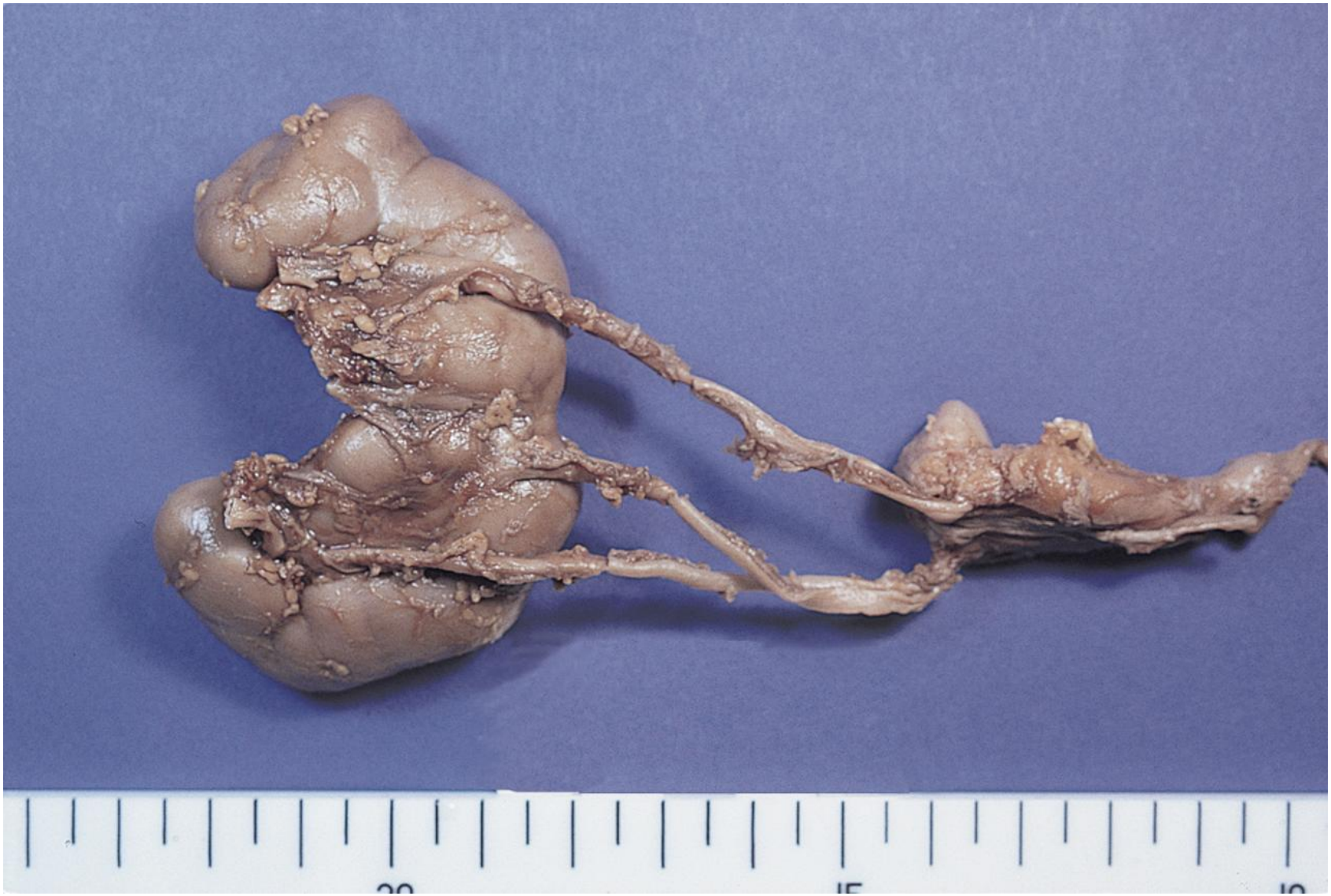
Vesicoureteral reflux

Hypospadias

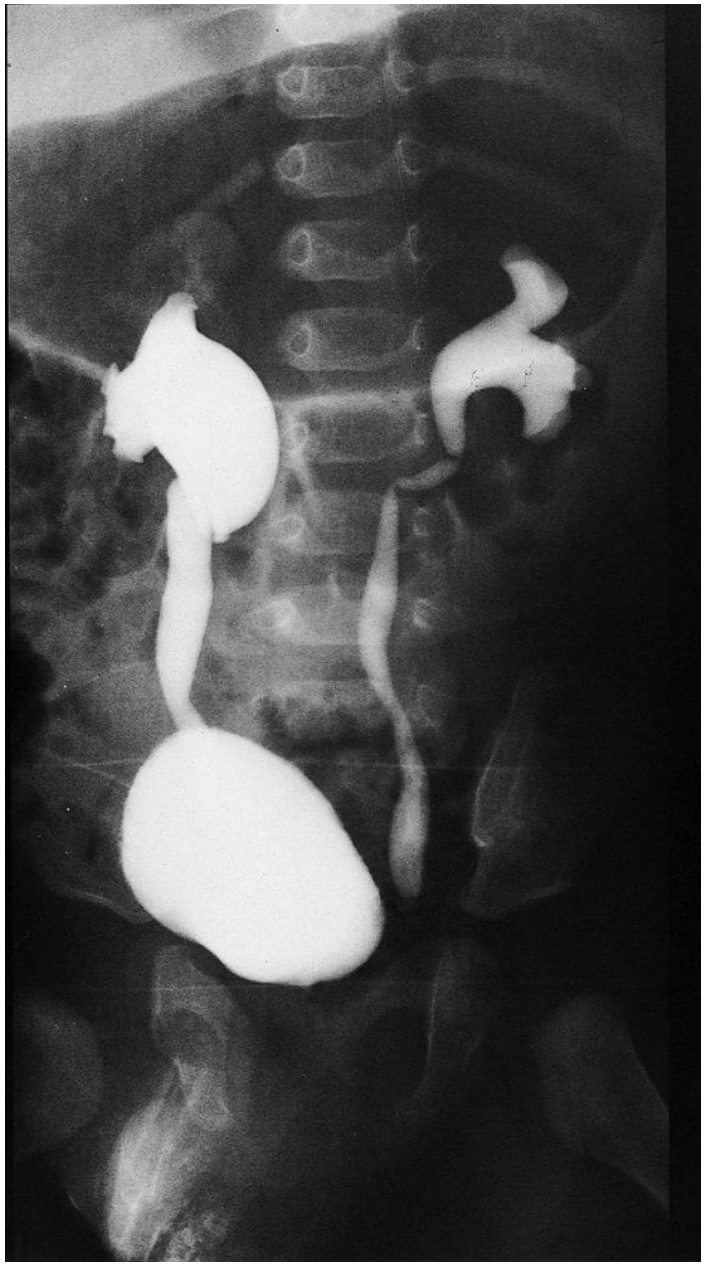
Patent urachus

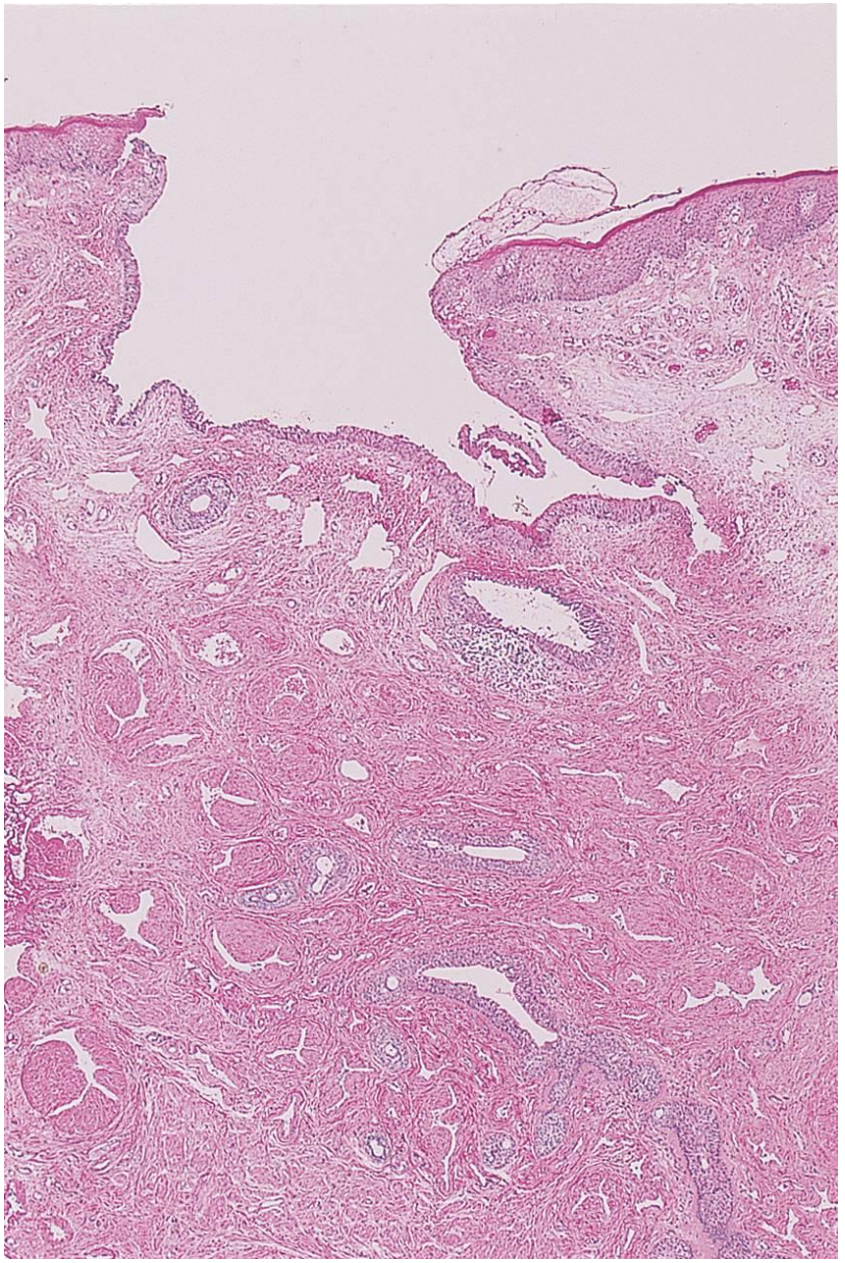
Ovotestis (true hermaphrodism)

Retentio testis (cryptorchism)

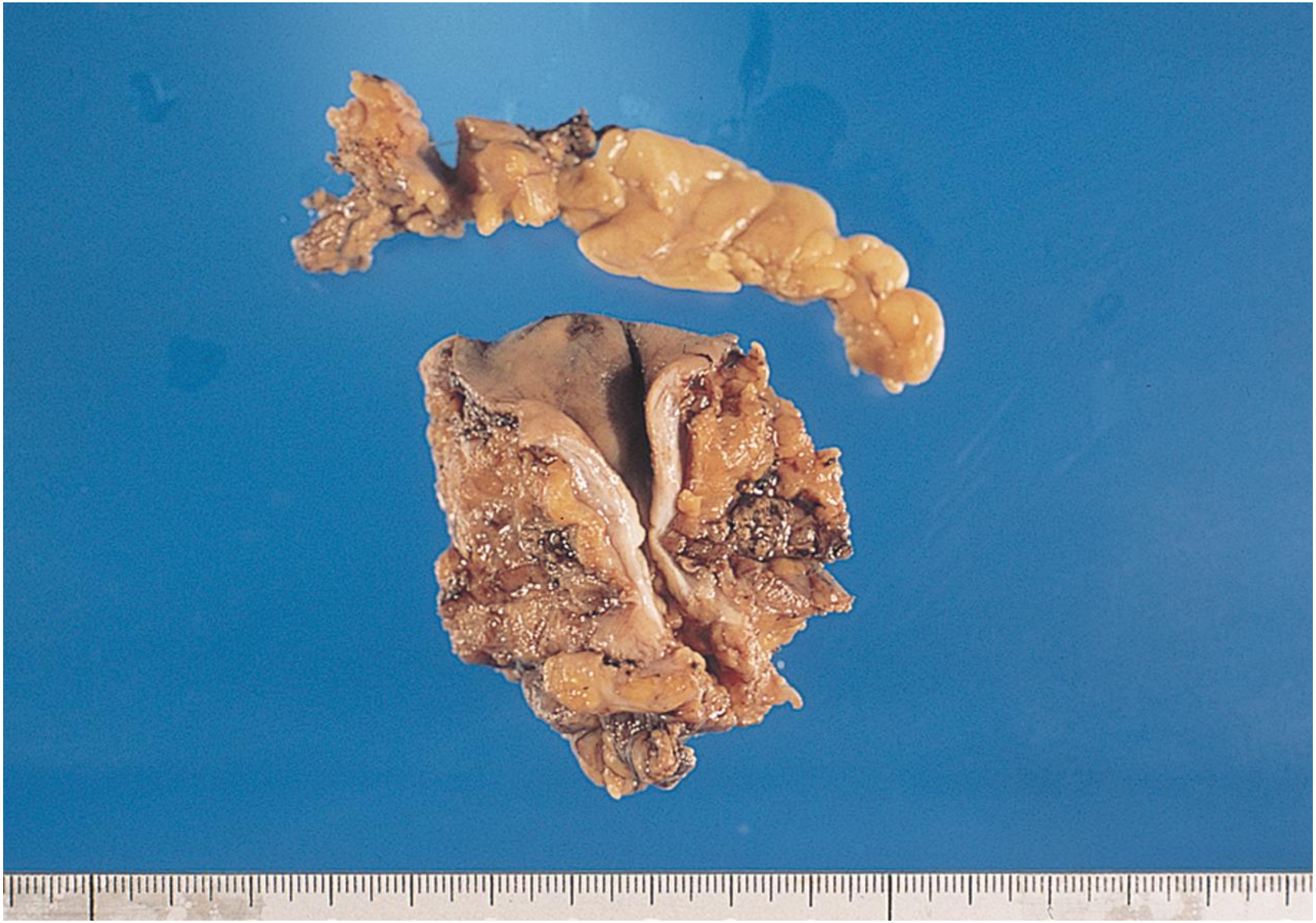


Horseshoe kidney and double ureter
(gross appearance after formalin fixation)

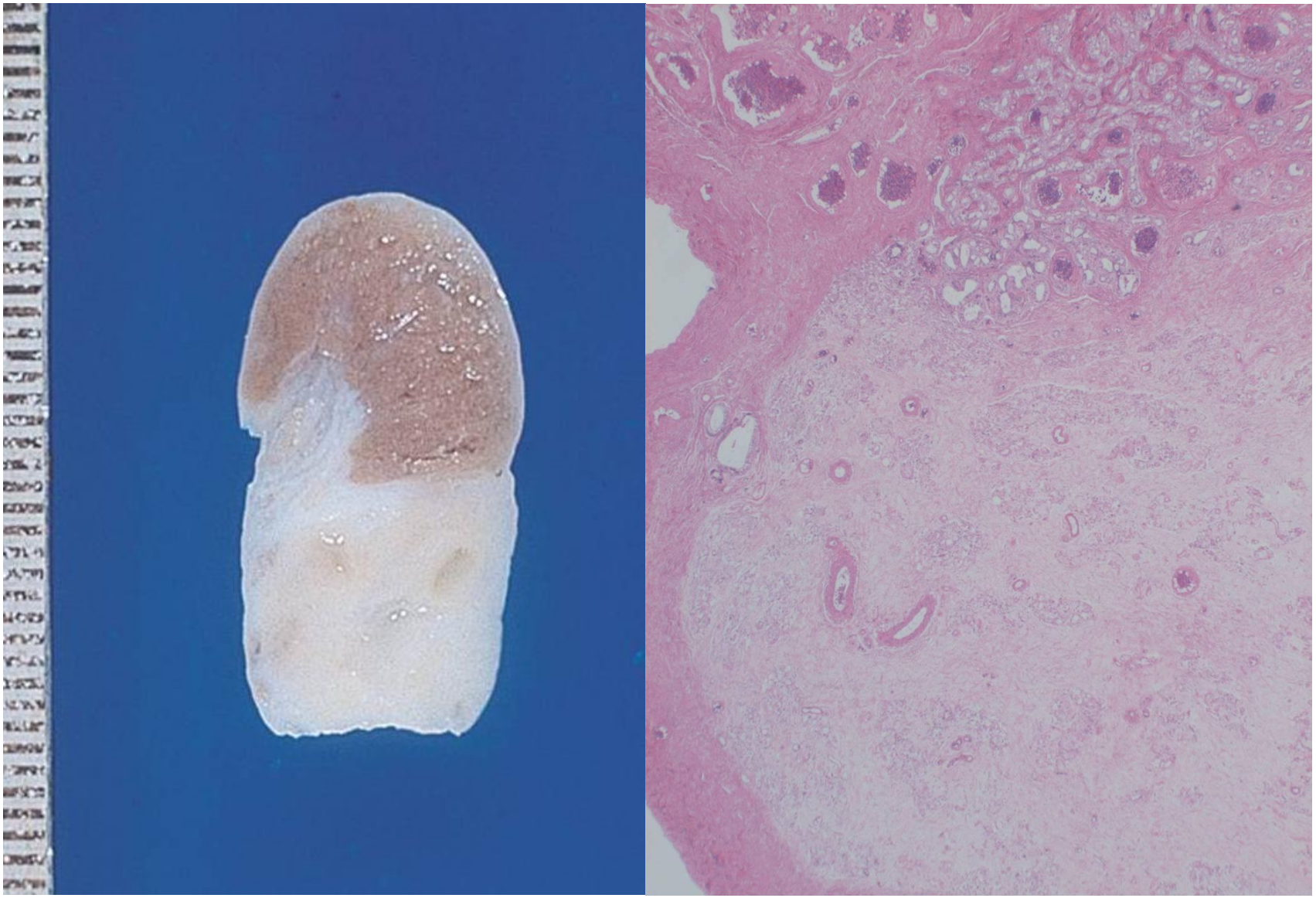




Left: vesicoureteral reflux (cystography)
Right: hypospadias (H&E). The urethra is open to the skin



Remnant urachus (gross appearance after formalin fixation)
The urachus is continuous to the navel.



Left: ovotestis (gross appearance after formalin fixation)
Right: retentio testis (cryptorchism, H&E:
marked atrophy of testicular tubules seen)

Representative anomalies of the skeletal system

Congenital dislocation of the hip

Torticollis

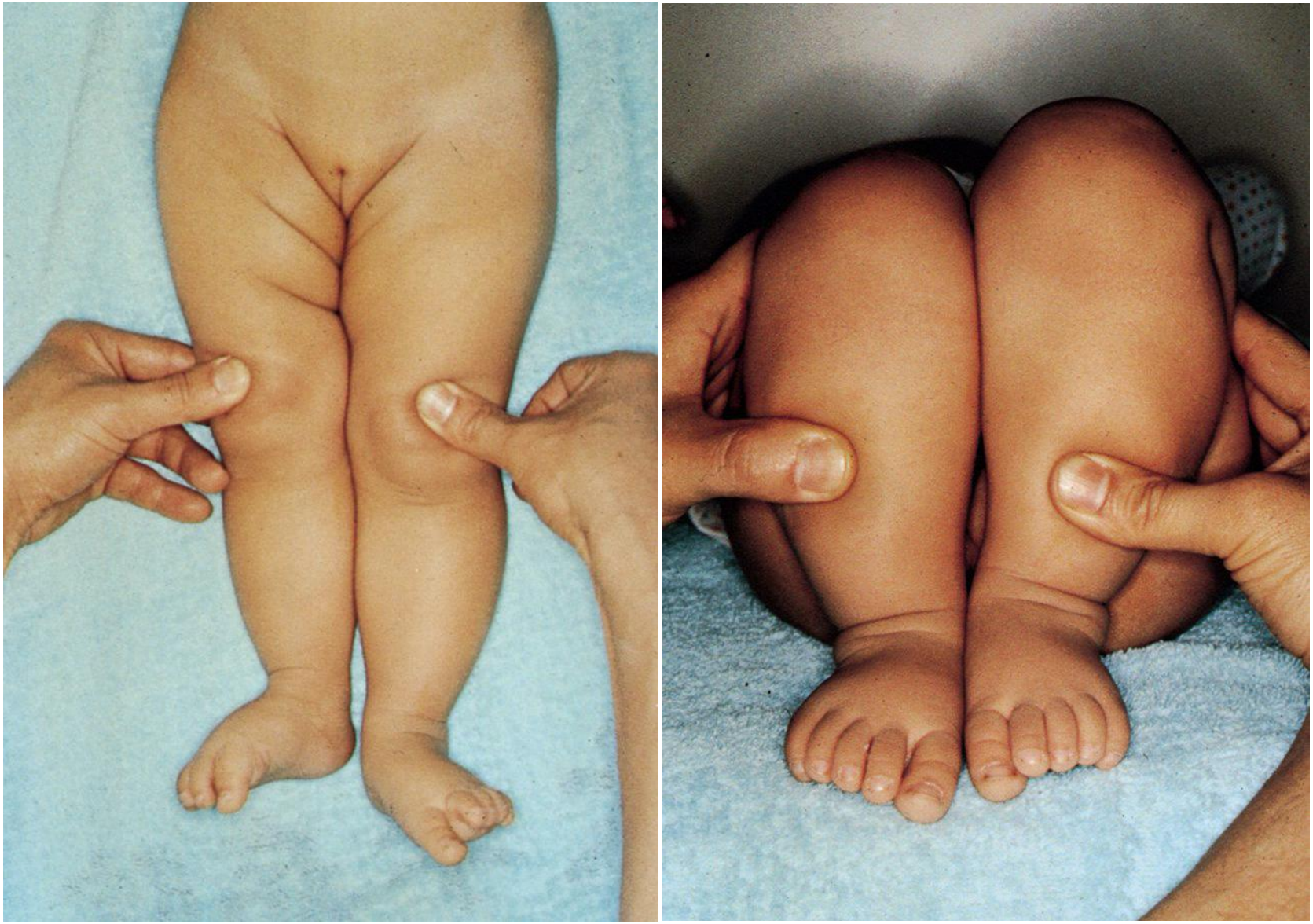
Pes adductus (clubfoot)

Skeletal abnormalities are often associated with genetic disorders.

a) Mucopolysaccharidosis(Hurler/Hunter's disease)

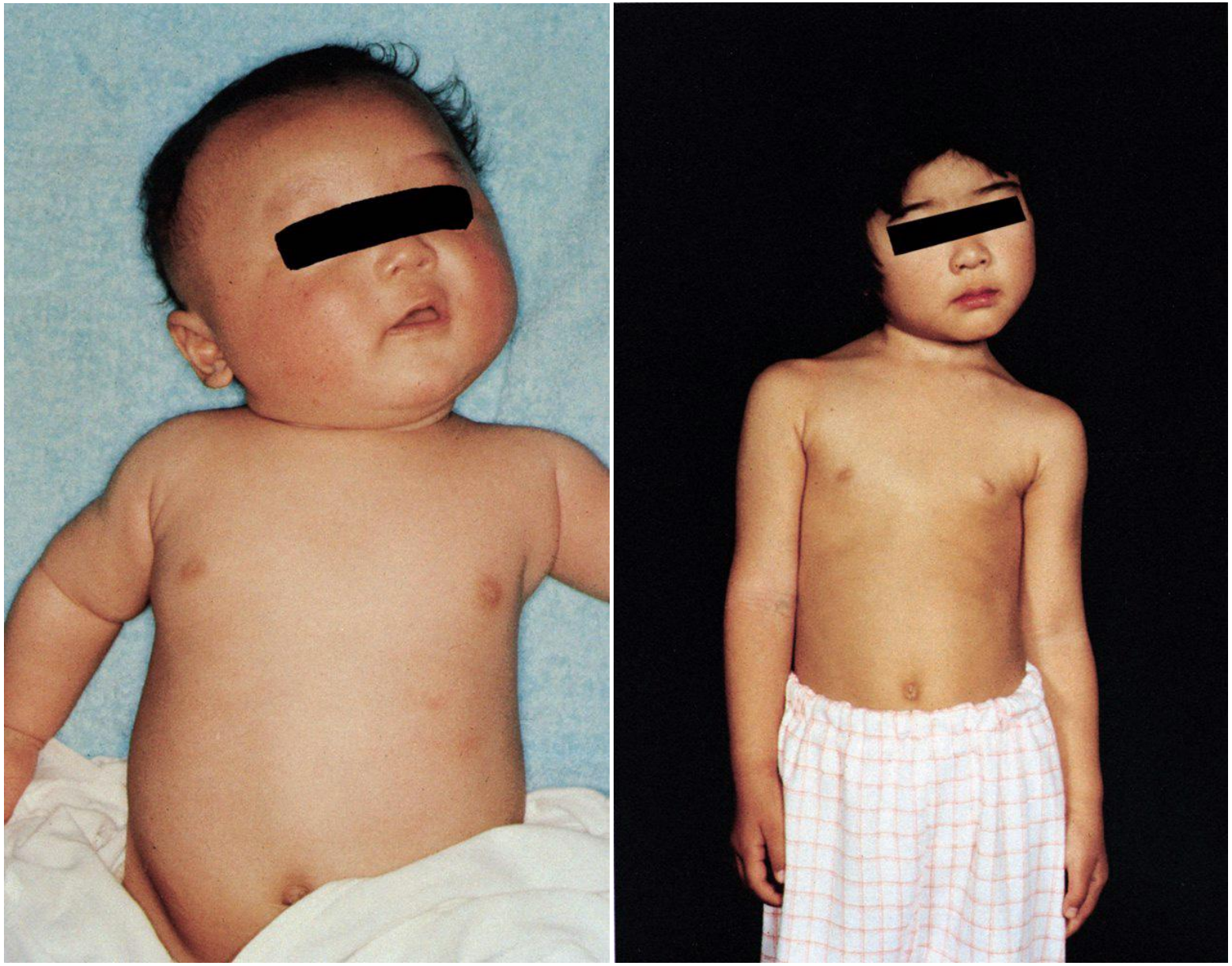
b) Osteogenesis imperfecta/achondroplasia

c) Marfan's syndrome

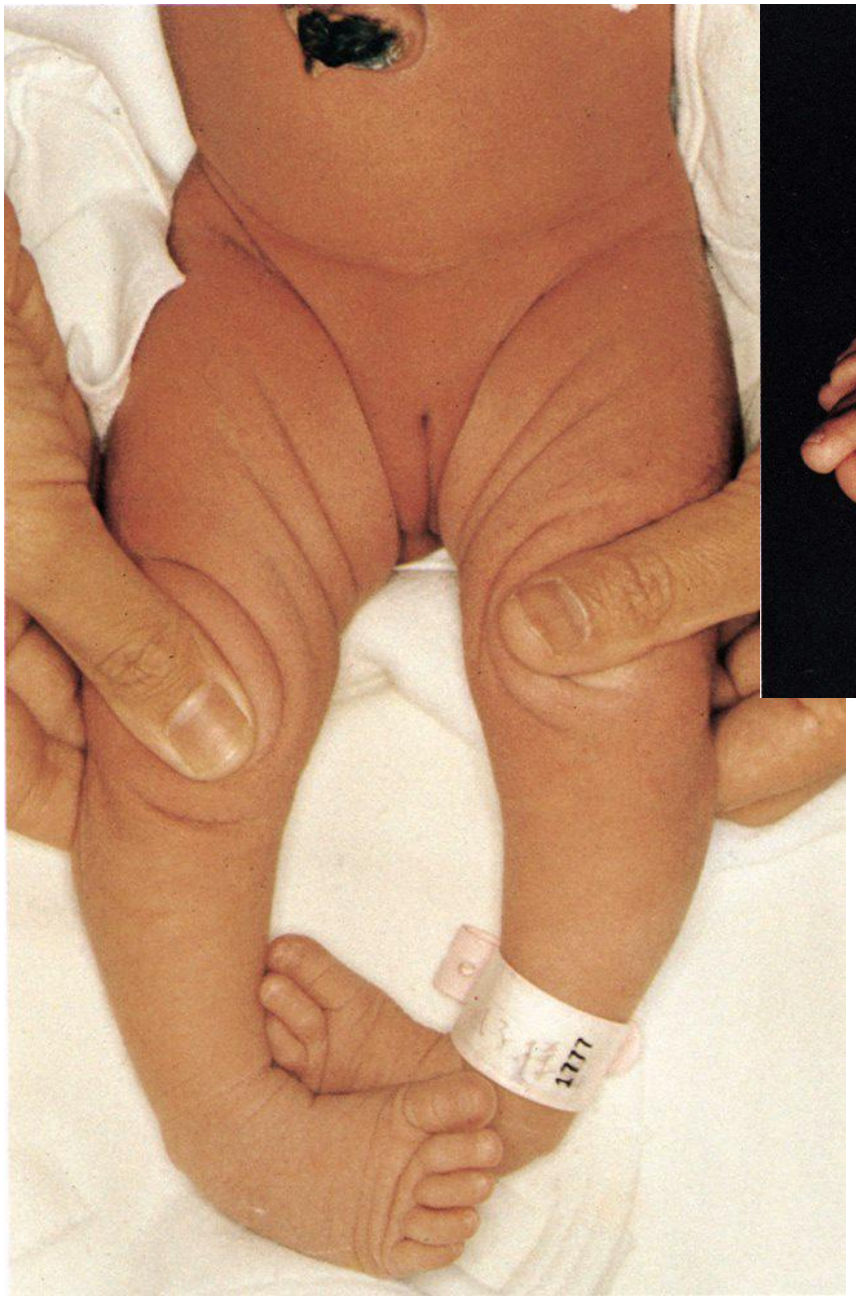


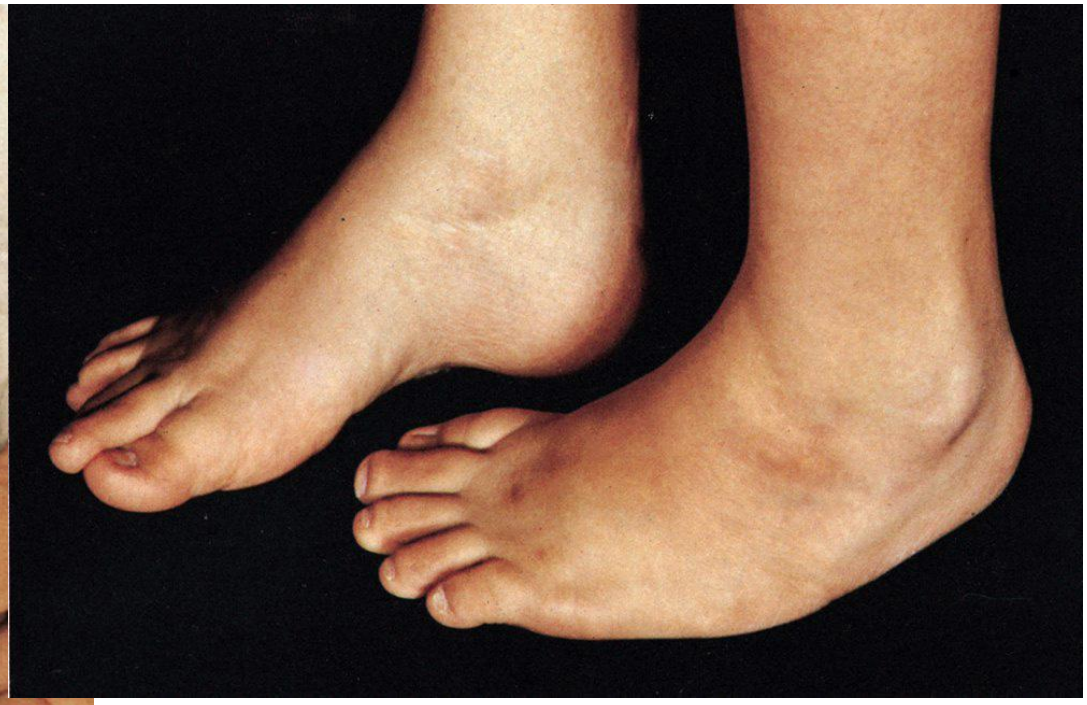
Congenital dislocation of the right hip (luxatio coxae congenita: LCC)

Left: the length of the legs is different, the left leg is longer than the right.
Right: Allis' sign with shortening of the thigh



Torticollis.
Left: A neonate with shortening of the sternocleidomastoid muscle
Right: A boy in the school period showing right convexed scoliosis





Pes adductus (clubfoot)

Left: A neonate with bilateral clubfeet

Right: An adult with unilateral clubfoot