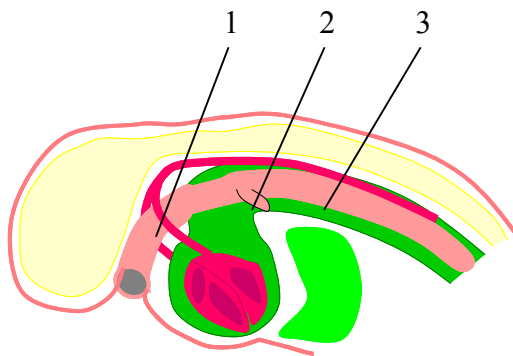# Development of the Respiratory System and Diaphragm

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The foregut can be divided into three parts:

1. The **first part** lies ventral to the developing brain, and forms the primitive pharynx, which has the branchial arches associated with it.
2. The **second part** lies dorsal to the heart, and forms the lung bud and the oesophagus.
3. The **third part** lies dorsal to the septum transversum and forms the stomach and other related gastro-intestinal structures.

The respiratory system is a derivative of the second part of the foregut.

laryngo-tracheal groove

respratory diverticulum

oesophagus

day 22

day 24
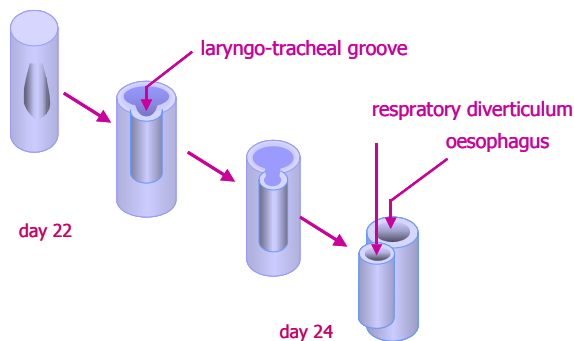
a. It begins to develop in the beginning of the fourth week (day 22)
b. It begins as a laryngo- tracheal groove on the ventral aspect of the foregut, which deepens and forms a repiratory diverticulum.
c. Separates from the oesophagus

The respiratory diverticulum bifurcates into right and left bronchial buds on day 26-28.

day 24

day 26-28
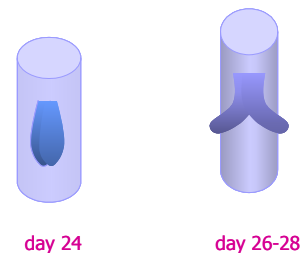
Asymmetric branching occurs during the following 2 weeks to form secondary bronchi: 3 on the right and 2 on the left forming the main divisions of the bronchial tree.

Week 4

Week 5

Week 6

Secondary bronchi
3 on the right
2 on the left

Main divisions of the bronchial tree are formed
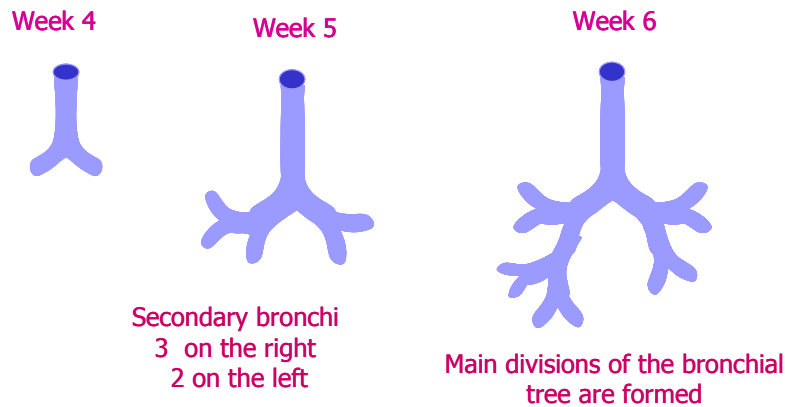
The lung bud and its subsequent branches are of **endodermal** origin.
They give rise to the **epithelium** lining all the respiratory passages, the alveoli and the associated glands.
The surrounding mesoderm, the **splanchnopleure**, gives rise to all the supporting structures: the connective tissue, cartilage, muscle and blood vessels.

The pattern of branching is regulated by the surrounding mesoderm.

The mesoderm surrounding the trachea inhibits branching whereas the mesoderm surrounding the bronchi stimulates branching. Transplantation of part of the bronchial mesoderm to replace part of the tracheal mesoderm forms an ectopic lobe of the lung arising directly from the trachea. Transplantation of part of the tracheal mesoderm to replace part of the bronchial mesoderm suppresses the formation of a lobe.

Mesoderm surrounding the trachea inhibits branching

Mesoderm surrounding the bronchi stimulates branching

Reciprocal transplantation of tracheal and bronchial mesoderm

Ectopic lobe - brochial mesoderm

Suppressed lobe - tracheal mesoderm
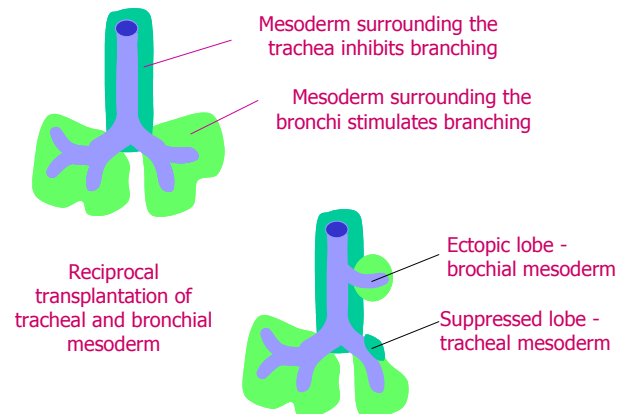
Formation of the respiratory system is regulated by a cascade of molecules.
  1. **Fibroblast growth factor 10** (**FGF-10**)
      a. produced by the mesoderm;
      b. stimulates the initial outgrowth of the lung buds
  2. The **Hox genes:**
      a. Hox-3, Hox-4, Hox-5 and Hox-6 are expressed in early development of the lung buds
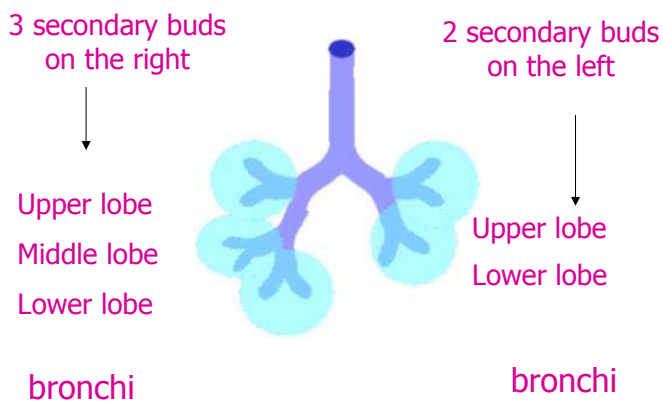   b. Combinations of Hox genes specify different regions of the respiratory system.

3. **Sonic hedgehog**
     a. Is produced by the endoderm.
     b. It stimulates **Bone Morphogenetic protein-4 (BMP-4)**, which is produced by the mesoderm
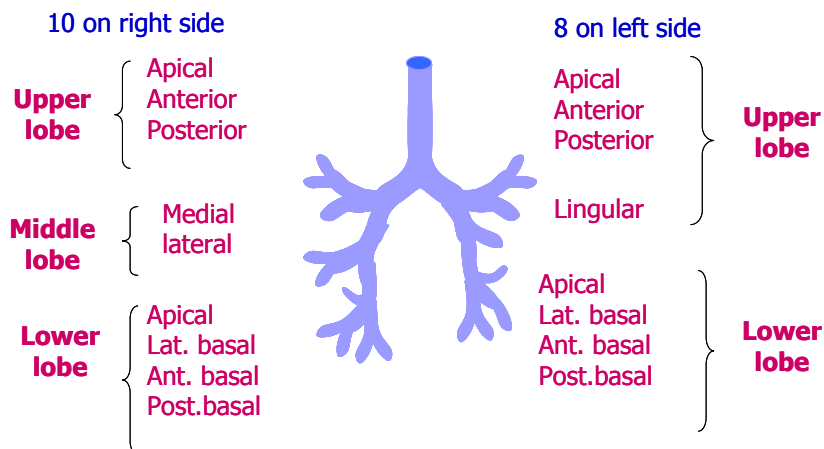   c. It inhibits FGF-10

Other molecules in the mesoderm regulate branching and differentiation of epithelia of lung buds. The main regulatory molecules are:
1. **N-Myc** (a proto-oncogene) – stimulates branching
2. **Fibronectin** and **Collagen types I and III** stabilize branching sites
3. **Syndecan** (a proteoglycan) and **Tenascin** (a matrix protein) stabilize the epithelia
4. **Epimorphin** (a matrix protein) organizes the epithelium, including the polarity of the cells and their arrangement in the epithelium.

## Asymmetric branching in week 5 forms the lobes of the lungs:

3 secondary buds
on the right

2 secondary buds
on the left

Upper lobe

Middle lobe

Lower lobe

Upper lobe

Lower lobe

bronchi

bronchi

In week 6 the 4th set of branching forms tertiary bronchi and the

10 on right side

8 on left side

Upper lobe
Apical
Anterior
Posterior

Apical
Anterior
Posterior

Upper lobe

Lingular

Middle lobe
Medial
lateral

Lower lobe
Apical
Lat. basal
Ant. basal
Post.basal

Apical
Lat. basal
Ant. basal
Post.basal

Lower lobe

broncho-pulmonary segments

During weeks 7 to 16 branching occurs about 14 times to the level of terminal bronchioles. At this stage there are no alveoli. The foetal lung during this period is described as the **glandular stage** because the terminal bronchioles resemble glandular acini. The bronchi, containing cartilage in their walls, identify the sections as foetal lung.

Bronchus & cartilage   Bronchioles
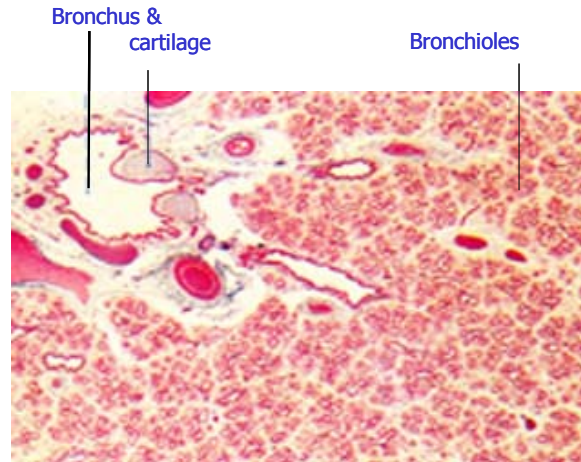
Development of the lungs passes through three stages:
1. The **glandular stage** – weeks 7 to 16 – there is repeated branching(about 14 times) to the level of the terminal bronchioles.
2. The **canalicular stage** – weeks 16 to 28 – the respiratory bronchioles develop
3. The **saccular stage** – weeks 28 to 36 – the primary alveoli develop.
4. The **alveolar stage** – weeks 36 to 40 – the alveoli mature:
   a. Pneumocytes type I are differentiated and the epithelium becomes thinned out.
   b. Pneumocytes type II differentiate and secrete surfactant

Postnatally new alveoli continue to be formed during childhood to the age of about 8 years.

Clinical Implications

Babies born before 28 weeks have very small chances of survival because they lack pulmonary alveoli. A few manage to survive following intensive respiratory assistance.

Babies born between 32 and 36 weeks usually suffer from the **respiratory distress syndrome** due to lack of surfactant secreted by pneumocytes type II. The respiratory distress syndrome is treated by:
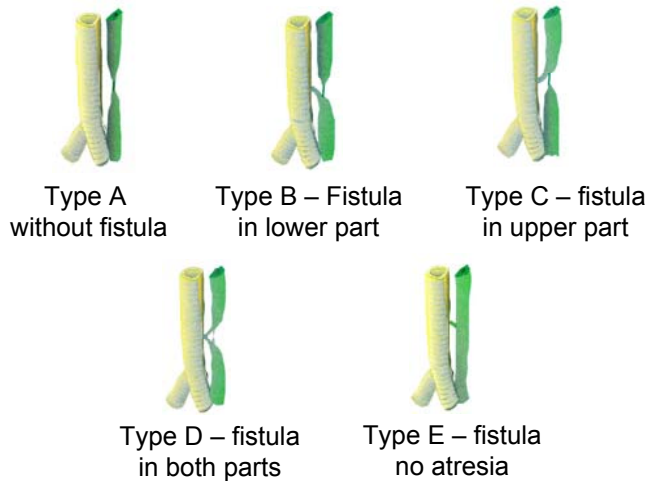   a. Intensive respiratory assistance
   b. Surfactant therapy including surfactant lipoprotein and surfactant associated proteins A,B and C.

Anomalies in the formation of the tracheal outgrowth result in oesophageal atresia and tracheo-oesophageal fistula.

The tracheal bud is the site of rapid cell proliferation of the tracheal outgrowth from the second (oesophageal part of the fore gut. This is followed by apoptosis to convert the outgrowth into a tubular structure. At the same time, the second (oesophageal) part of the foregut also proliferates rapidly, causing obliteration of the lumen and subsequent re-canalization by apoptosis. A defect in programming of foregut differentiation results in

oesophageal atresia or **tracheo-oesophageal atresia** or both. These are therefore considered to be one defect with different manifestations as shown in the diagrams below. Note that atresia is commonly present. The oesophagus often communicates with the trachea either above or below the atresia.

Oesophageal atresia and Tracheo-oesophageal fistula

| Type A without fistula | Type B – Fistula in lower part | Type C – fistula in upper part |

| Type D – fistula in both parts | Type E – fistula no atresia |

The **clinical features of oesophageal atresia** are:
   a. Inability to swallow and choking on attempts at feeding.
   b. Inability to introduce a naso-gastric tube
   c. X-rays often shows absence of a stomach bubble, but this may be present depending on the site of the atresia.

Oeosophageal atresia is usually accompanied by **polyhydramnios** during pregnancy. This is due to inability of the foetus to swallow amniotic fluid while it continues to be formed by the kidneys.
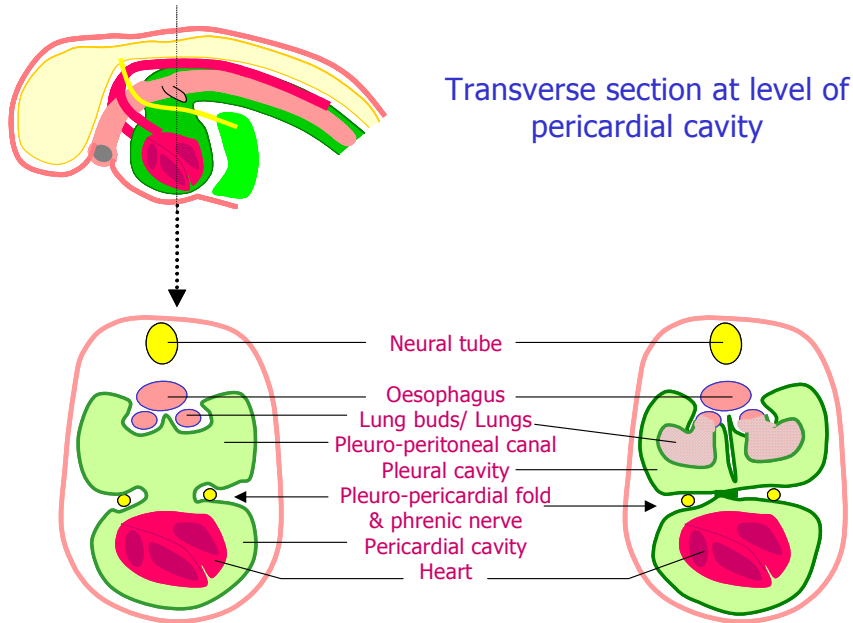
Development of the Pleural Cavities and Diaphragm.
Initially the intra-embryonic coelom is shaped like a U-tube. Following the formation of the head fold the pericardial cavity is shifted ventrally.
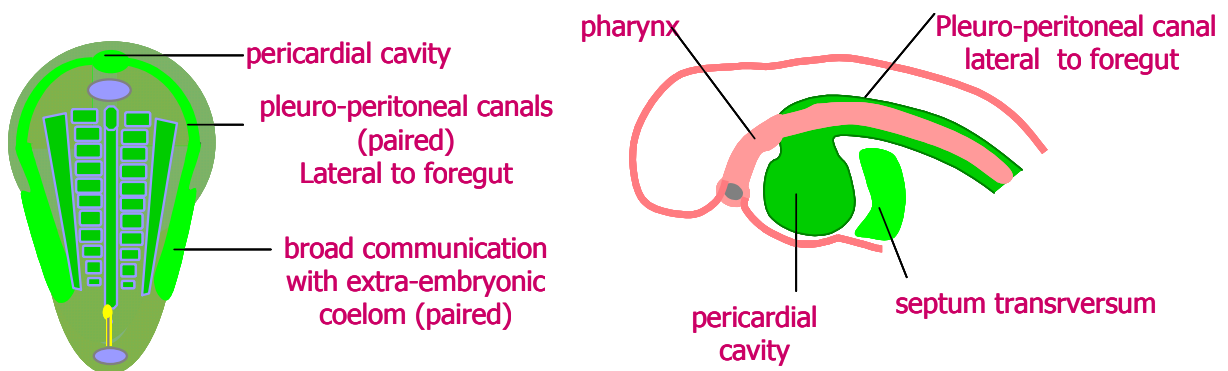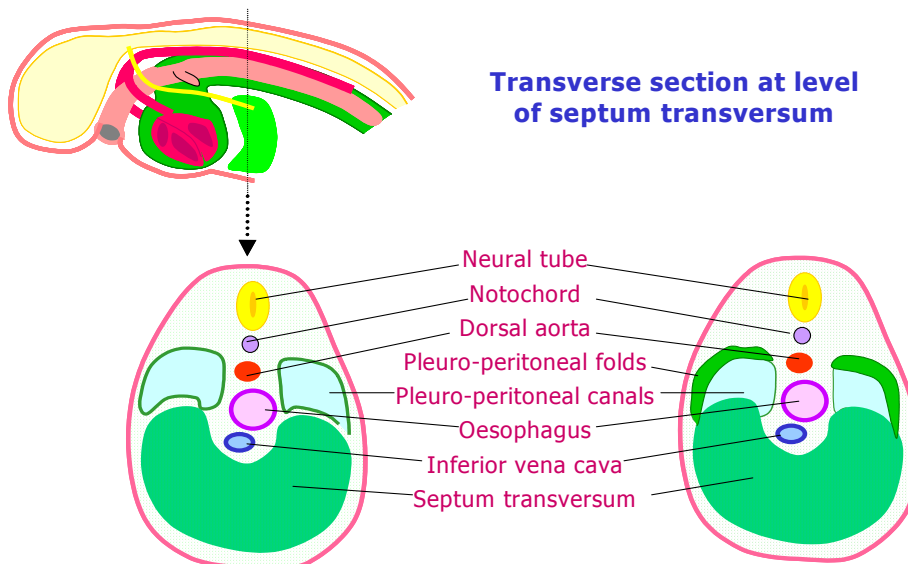
From the developing heart arise paired dorsal aortae, which lie by the sides of the primitive pharynx.

The **phrenic nerve** arises from the cervical segments 3,4,5, and innervates the septum transversum. As it extends ventrally, it passes lateral to the pericardio-peritoneal canals near their origins, raising a pair of folds, termed the **pleuropericardial folds**. These folds grow medially and separate the pericardial cavity from the pleuroperitoneal canals. The phrenic nerve lies within the fold. Note that this explains the definitve relation of the phrenic nerve lying between the pericardium and pleura.

Transverse section at level of pericardial cavity

Neural tube
Oesophagus
Lung buds/ Lungs
Pleuro-peritoneal canal
Pleural cavity
Pleuro-pericardial fold & phrenic nerve
Pericardial cavity
Heart

The pleuro-peritoneal canals pass dorso-lateral to the septum transversum. Separation of the pleural and peritoneal cavities occurs by growth of paired **pleuro-peritoneal folds** (or **membranes**) at the level of the septum transversum. The pleuroperitoneal folds arise from the posterolateral part of the pleuro-peritoneal canals and grow towards the septum transversum between the 5th and 7th weeks. The left pleuro-peritoneal canal is larger than the right, and closure occurs slightly later.

Transverse section at level of septum transversum

Neural tube
Notochord
Dorsal aorta
Pleuro-peritoneal folds
Pleuro-peritoneal canals
Oesophagus
Inferior vena cava
Septum transversum

The diaphragm is a composite structure derived from four main sources:

1. Pleuro-peritoneal membranes

2. Septum transversum

3. Mesoderm of the body wall

4. Mesentery of the foregut
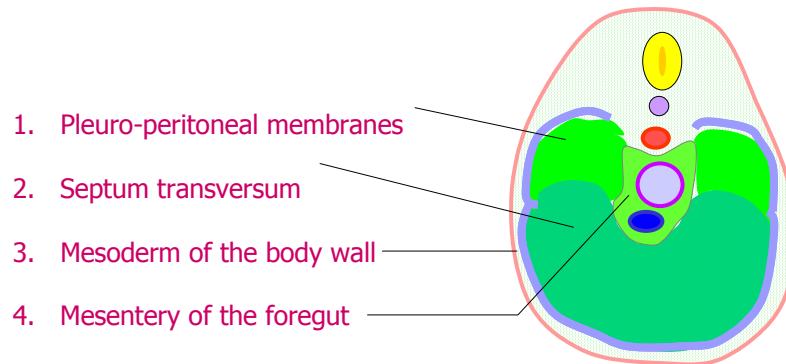
The **muscle of the diaphragm** is derived from myoblasts that migrate into the septum transversum from the cervical **myotomes C3,4,5**, innervated by the phrenic nerve.
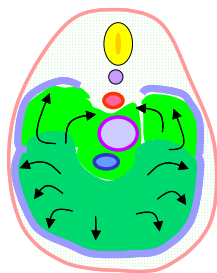
a. Migration of myoblasts into the diaphragm.
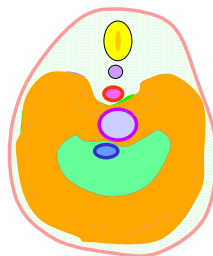
b. The central part devoid of myoblasts forms the central tendon enclosing the inferior vena cava

The myoblasts migrate distally into the diaphragm, and its component parts are no longer identifiable. The myoblasts do not settle in the central part of the diaphragm, which forms the central tendon, enclosing the inferior vena cava.

The **sensory innervation** of the diaphragm is from phrenic nerve, which supplies the domes and central tendon and from the local somatic nerves T7–12, which supply the peripheral rim and L1-3, which supply the crura of the diaphragm.

Congenital anomalies of the Respiratory system and diaphragm.

1. Congenital diaphragmatic hernia is a defect in the formation of the diaphragm. It is usually due to failure of closure of the pleuro-peritoneal canal (Foramen of Bochdalelek), and occurs more commonly on the left, where the pleuro-peritoneal canal is larger and closes later than on the right side.

In congenital diaphragmatic hernia the abdominal contents herniate into the thorax and compresses the lung, causing severe pulmonary hypoplasia, which is frequently the cause of death. The clinical features are:
   o Respiratory difficulty
   o Absent breath sounds on the affected side.
   o Impaired thoracic movements
   o Radiologically, coils of intestine are visible in the thorax and the mediastinum is shifted to the opposite side.

Surgical correction of the diaphragmatic defect is possible, but there is a high mortality depending mainly on the degree of pulmonary hypoplasia.

2. Eventration of the diaphragm is caused by defective development of the diaphragmatic musculature. The diaphragm is intact but very thin due to absence of muscle. The pressure of the abdominal contents cause the diaphragm to tbe pushed up into the thorax (eventration), producing pulmonary hypopasia and respiratory difficulty.

Note that diaphragmatic hernia and eventration of the diaphragm are not defects of the respiratory system, but defects of the somatic body wall mesoderm and are classifed with defects of the musculoskeletal system.

3. Pulmonary agenesis and **pulmonary aplasia** are defects in the development of the lung buds or of the surrounding mesoderm. They are both quite rare.

4. Pulmonary hypoplasia is usually secondary to pulmonary compression during development. This is usually secondary to
   a. congenital diaphragmatic hernia;
   b. eventration of the diaphragm;
   c. oligohydromnios
   d. The **Potter (foetal compression) sequence** in which there is a sequence of events involving renal agenesis, which results in oligohydramnios, pulmonary hypoplasia due to thoracic compression, and a characteristic facial dysmorhology due to facial compression.
   e. Other causes of foetal compression e.g. the amniotic band sequence, in which a large amniotic band happens to pass over and compress the thorax.

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