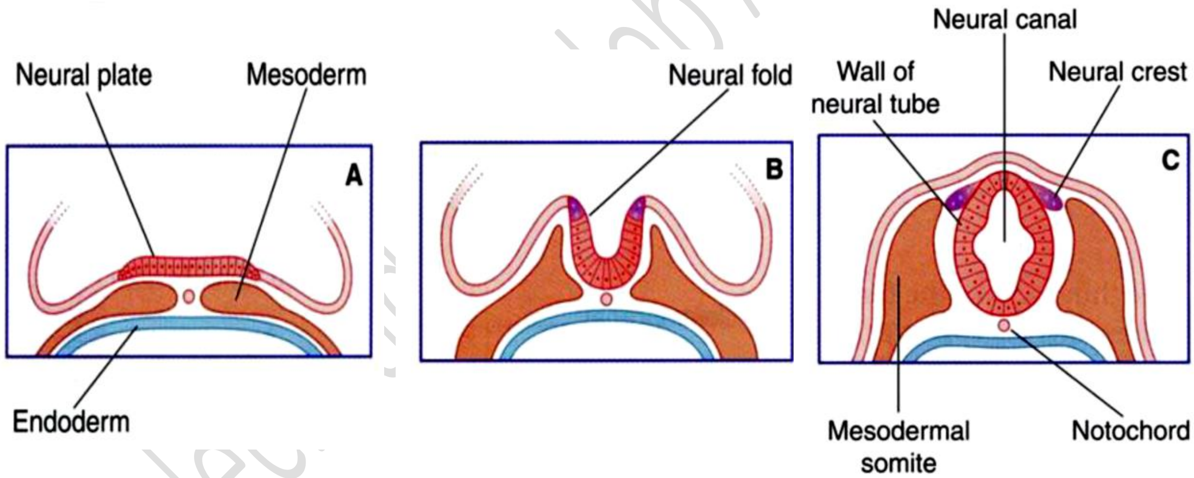
Development of the Nervous System

It is important to know about the development of the nervous system so we can understand the mature CNS better. Also, some neurological disorders have a developmental origin, and knowledge of some of these mechanisms may be useful in treatment.

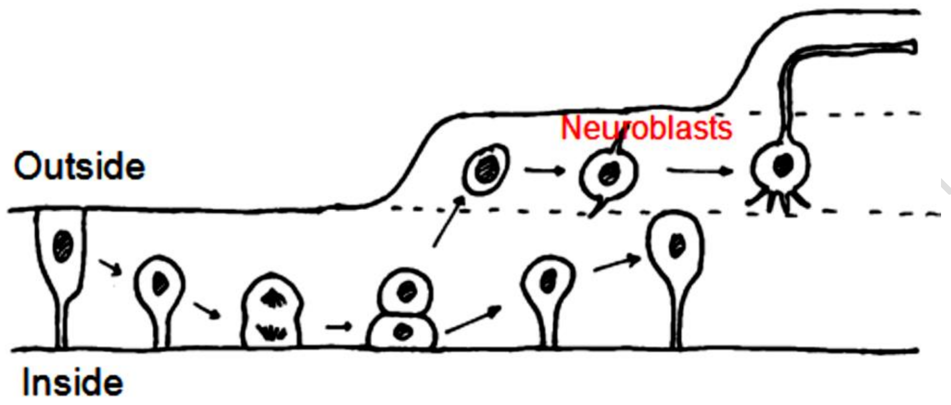
The early development of the nervous system is shown in the diagram below, as the formation of the neural tube. A strip in the ectoderm of the trilaminar disc differentiates and proliferates to form the neural plate. This then folds to form the neural groove, and these folds to form the neural tube. The wall of the neural tube (neuroepithelium) becomes the CNS, and the neural crest cells become the PNS.



Differentiation

The neuroepithelium differentiates into several types of principal cells. Neuroblasts are all neurons with cell bodies in the CNS. Glioblasts include astrocytes and oligodendrocytes, and also microglia from the mesoderm, which are modified macrophages that migrate into the nervous system. Ependymal cells are the cells that line the ventricles and the central canal. The diagram below shows the formation of ependymal, grey and white matter layers.

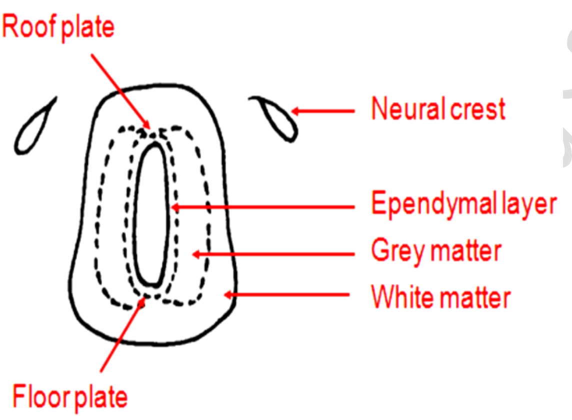
The neural crest cells also differentiate into several types of principal cells to contribute to the peripheral nervous system. For example, sensory neurons of the dorsal root ganglia and cranial ganglia, postganglionic autonomic neurons, Schwann cells of the PNS, and non-neuronal derivatives such as melanocytes.



Above is a cross section through the neural tube. In the neural tube there is symmetrical cell division. Eventually, there is asymmetrical cell division and differentiation of the daughter cells. The first thing that happens is that a cell contracts down towards the inner membrane and it then undergoes mitosis into two daughter cells. One of these cells remains attached to the inner membrane, and eventually goes back into the cell cycle, but the other daughter cell actually migrates away and begins to differentiate. If it is a neuroblast, as in the above diagram, it grows processes (axons) and these are directed away from the cell. These are the very early stages of differentiation between grey (neuronal cell bodies) and white (axons) matter. If this was a glioblast, there wouldn't be axons forming, and they wouldn't necessarily be restricted to the developing grey area. If it was an ependymal cell, it would stay very close to the inner membrane and eventually spread out to line the neural tube.

A cross section through the whole neural tube . The space in the middle is the neural canal, and there are three layers. Control of differentiation is down to signalling molecule. These molecules affect that target differentiating cells by affecting their phenotype and sending them in certain directions of differentiation. It is an extremely complex process. Timing is important because the target cells have to have reached a certain stage of development in order to respond to the signalling molecules.

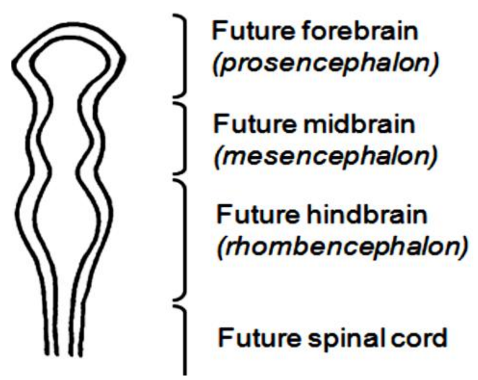
The signalling molecules are important for influencing cell migration and axonal growth guided by attraction or repulsion.



Development of the brain

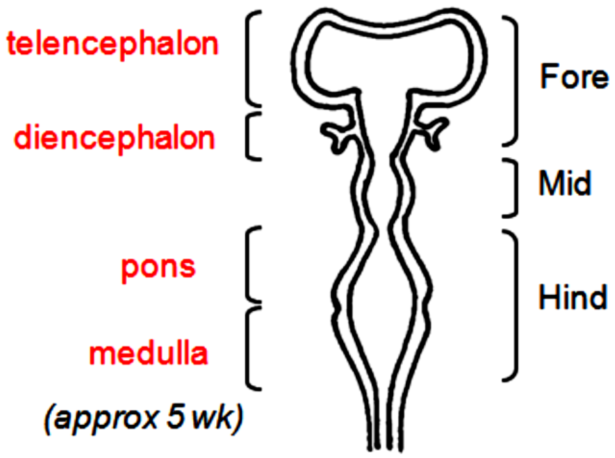
The brain develops from the most anterior tip of the neural tube. The first thing is that there is differential growth of that part of the tube to form three bulges - the primary vesicles. The most anterior vesicle develops into the forebrain, the middle one into the midbrain, and the third one into the hindbrain. This differentiation is at approximately 4 weeks of gestation. The remaining part of the neural tube will develop into the spinal cord.

During the next few days, the first vesicle and the third one divide into two, so there are five secondary vesicles.



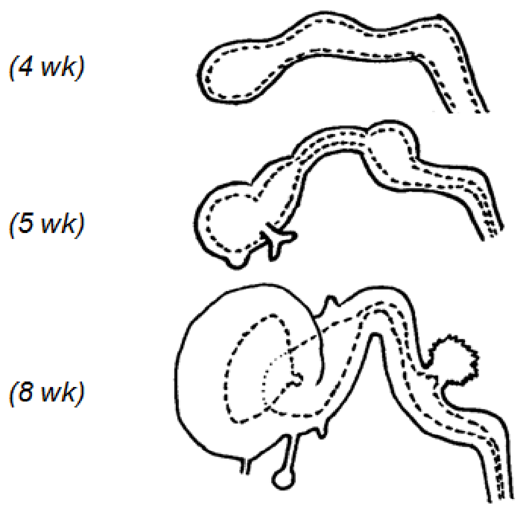
In the forebrain there is an expanded area, and behind it a less expanded area. The midbrain stays the same. The hindbrain divides into two.

Over the next few weeks there is further development. The wall gets thicker, the space inside gets relatively smaller and you see the development of the ventricular system. There are two lateral ventricles in the developing hemispheres, the third ventricle in the middle of the diencephalon, the aqueduct going through the midbrain, and the fourth ventricle in the hindbrain.



Rather late on you get the development of the cerebellum, which is an outpouching from the wall of the pons.

These diagrams below show the same development of the neural tube, but from the side. So firstly during the early development with the three primary vesicles there is folding. There are three folds, and are known as flexures: the cephalic, pontine and cervical flexures. During the next few weeks there is an exaggeration of that folding. This is important in order to get the brain packed inside the developing cranium.



At five weeks there is more differentiation and folding, and at eight weeks the cerebral hemispheres spread backwards to partially hide the diencephalon.

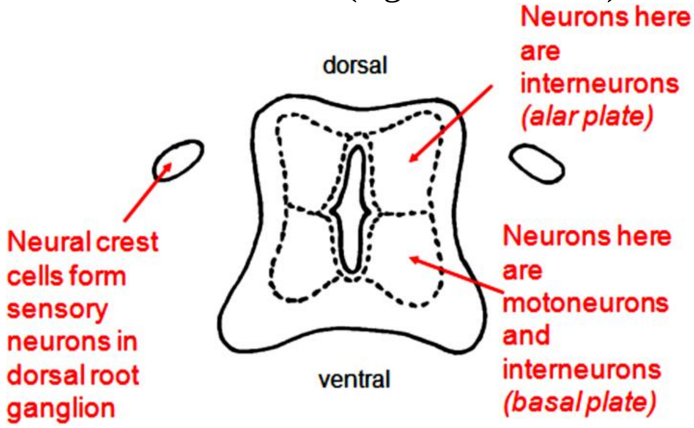
At term, there is a brain that is recognisable at a mature brain with a ventricular system inside it.

This is not the end of the development of the brain, however, as a lot happens post-natally. In fact, myelination doesn't finish until late teens.

Development of the spinal cord

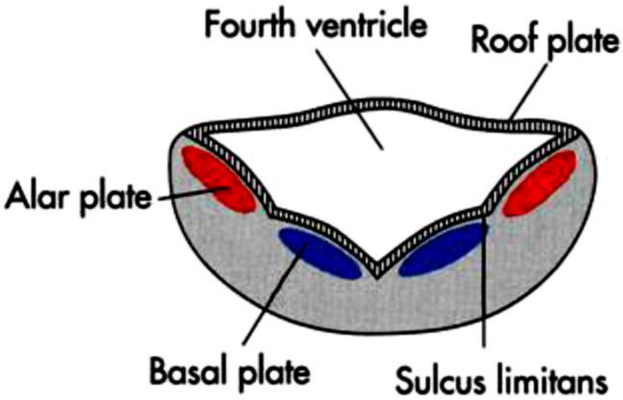
In the basic layout of the neural tube, there are three layers (ependymal, grey and white). As you get more towards the development of the spinal cord, there is increased proliferation. The space in the middle is smaller and there is division of the grey matter into plates. There are two alar plates dorsally, and two basal plates ventrally. In the alar plates, the neuroblasts develop into interneurons with sensory function. Some of the neurons in the basal plate will also develop into interneurons, but some will also develop into motor neurones and will send their axons out through the ventral roots to peripheral nerves. At the same time, the neural crest tissue on either side will develop into sensory neurons as the dorsal root ganglia. In the mature spinal cord, the alar plates are called the dorsal horns and the basal plates are the ventral horns.

Signalling molecules come into play when there is the division of function. This is called dorso-ventral patterning. There are several signalling molecules derived from the notochord (one of which is called Sonic Hedgehog) and these particular signalling molecules spread out and induce neuroblasts in the ventral part to differentiate as motor neurons. There is also a set of signalling molecules from the ectoderm which induce the dorsal neuroblasts to develop into sensory cells. There are also other molecules from the mesoderm (e.g. retinoic acid).



Development of the brainstem

The brainstem is a tubular structure like the spinal cord. There is one big difference - the fourth ventricle opens up in the brainstem. This space means that the structures in the grey matter alter their relationship with each other. In the bit of the neural tube that develops into the brainstem, there is a sudden proliferation in a part called the roof plate, where previously there hasn't yet been much proliferation. This proliferation rapidly occurs, and there is natural expansion of the roof plate. This pushes the alar plates more laterally, and so their relationship to the basal plates is that they are lateral to them rather than dorsal to them.
Cranial nerves are associated with various cranial nerve nuclei, which lie in the floor of the fourth ventricle in the brainstem. Some of them are motor, some have a sensory function. The sensory nuclei are more lateral, and the motor nuclei are more medial.



Development of the cortex

There is a layer of grey matter cortex over the whole cerebral hemispheres. To get the grey matter cells there, they have to undergo a large amount of migration from the germinal layer.