The Signs of Death
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THE NEUROLOGIST'S VIEW ON THE DETERMINATION OF BRAIN DEATH*

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It is a great honour to be invited again to a Study Workshop of the Pontifical Academy of Sciences in the beautiful Casina Pio IV in the Vatican gardens. The first time I was here was in October 1988, participating in the Study Week on the 'Principles of Design and Operation of the Brain', organized by the late Sir John Eccles, Nobel laureate (cf. Eccles & Creutzfeldt (eds.), *Scripta Varia* No. 78). We were dealing with the miracles of the living human brain in particular regarding movement, action and will (Deecke & Lang, 1990), while the topic is now the dying and dead human brain with all the consequences. Above all: is brain death the death of the whole person.

What is the most common clinical situation that leads to brain death? It is circulatory arrest. This has a very wide range extending from syncope to brain death.

From Syncope to Brain Death

Transient circulatory arrest may lead to global cerebral ischemia and thus to syncope. Sometimes syncope is preceded by non-specific premonitory symptoms such as:

- paraesthesiae
- light-headedness
- palpitations, and
- greying-out of vision.

Syncope is associated with pallor and loss of muscle tone, but with prolonged ischemia, *tonic posturing* occurs (see Fig. 1), sometimes accompanied by irregular jerking movements that resemble seizures.

If postictal confusion occurs, it clears within 1 minute. In elderly patients, syncope may present simply as unexplained falls.

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.

Syncope may be related to:
– cardiac pathology,
– dysautonomia,
– postural hypotension,
– endocrinopathies, and
– metabolic disorders.

'Neurocardiogenic' (vasovagal) syncope is the most common variety. Depending on its duration, ventricular fibrillation or asystole may cause irreversible anoxic-ischemic brain damage.

The prognosis varies with
– the patient's *age*
– the *duration* of circulatory arrest, and
– the *interval* before cardiopulmonary resuscitation and defibrillating procedures were undertaken.

Circulatory arrest from ventricular fibrillation has a better prognosis than that from asystole.

The neurologic consequences of the arrest may relate to the accumulation of intracellular calcium, increased extracellular concentrations of glutamate and aspartate, and increased levels of free radicals.

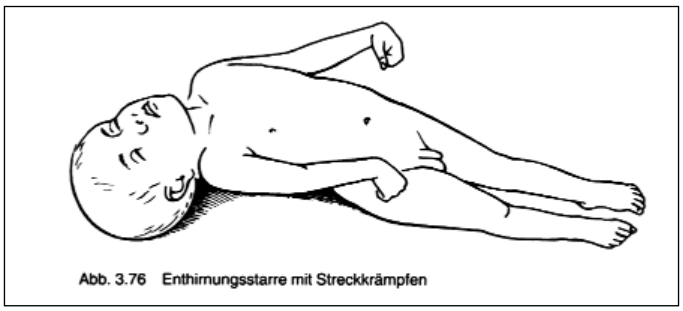

Figure 1. Decerebration with Extension Seizures. *Tonic posturing*.

In the mature nervous system, *grey matter* is generally *more* vulnerable to ischemia than white matter. The cerebral *cortex* is *more* sensitive than the brain stem. So-called *watershed areas* bordering the zones supplied by major arteries are especially vulnerable.

Circulatory Arrest Under *5 Minutes' Duration*

Circulation arrest shorter than 5 minutes leads to
- transient confusion or
- temporary loss of consciousness and
- impaired cognitive function.

Complete recovery is usual.

In rare instances, circulatory arrest is followed after 7-10 days by a demyelinating encephalopathy, with increasing cognitive dysfunction and pyramidal or extrapyramidal deficits that may have a fatal outcome. In such rare cases (under 5 min.), patients regain consciousness several hours after the circulatory arrest but then develop progressive neurologic deficits, such as:
- intellectual deterioration
- personality changes
- seizures
- cortical blindness
- amnestic syndromes or rarely
- locked-in syndrome (characterized by quadriplegia and mutism)
- extrapyramidal syndromes
- bibrachial paresis, or
- intention (action) myoclonus

Circulatory Arrest Over *5 Minutes' Duration*

Circulatory arrest that lasts longer than 5 minutes may cause widespread and irreversible brain damage, resulting in prolonged coma. Prognosis for survival or useful recovery is poor, especially when brain stem reflexes (most notably the pupillary responses to light) are lost. In particular, loss of pupillary reactivity for more than 24 hours or persistence of coma for more than 4 days indicates a poor prognosis.

In a study, comatose survivors of cardiac arrest who continued to have non-reactive pupils, failed to open their eyes in response to pain, or had absent or reflex motor responses 3 days after onset of coma, generally failed to survive or to regain useful independent function. In this study, the most accurate single predictor of poor outcome immediately after restoration of spontaneous circulation was the absence of pupillary responses, 73 had a poor outcome (i.e., death or persistent vegetative state). Even if consciousness is regained, focal or multifocal neurologic signs may lead to significant

disability from focal motor deficits, extrapyramidal disturbances (e.g. parkinsonism), sensory loss, seizures, myoclonus, and disturbances of higher cortical function from which recovery is usually delayed and incomplete.

TABLE 1. Clinical Evaluation of Prognosis in Comatose Survivors of Cardiac Arrest.

Sign	*Patients with poor outcome %*		
	Immediate	*Day 3*	*Day 7*
Lack of response to pain:			
No opening of the eyes	*69*	*100*	*100*
No motor response	*75*	*100*	*100*
Lack of response to verbal stimuli	*67*	*94*	*100*
Lack of pupillary response	*83*	*100*	*100*

Intention (action) myoclonus is particularly characteristic in such circumstances; it is often activated by startle or various sensory stimuli and is responsive only occasionally to clonazepam, valproate, piracetam, or 5-hydroxytryptophan.

Some patients never fully regain consciousness after circulatory arrest, remaining in a persistent vegetative state or showing evidence of brain death. The persistent vegetative state is characterized by the return of sleep-wake cycles and of various reflex activities, but wakefulness is without awareness.

Brain Death

In the conditions discussed above the brain may be severely injured, but these patients are not all in the state of brain death. Brain death is defined as loss of *all* cerebral activity, including activity of the cerebral cortex, cerebellum and brainstem, for at least 6 hours, if confirmed by electroencephalographic evidence of electrocerebral inactivity or for 24 hours without a confirmatory (isoelectric) EEG.

Apnea Test

In patients with suspected brain death the apnea test may be employed (*and is safe because oxygen is supplied*). This test involves evaluation of the respiratory response of the brain stem by allowing the carbon dioxide tension

(P_{CO2}) to rise to 60 mmHg *while 100% oxygen is given through the endotracheal tube*. Brain dead patients have no ventilatory response to the apnea test.

Simulation of Brain Death

Brain death may be simulated clinically by
- deep *hypothermia*
- *sedative overdose*, and
- *neuromuscular* blockade.

Such conditions must always be excluded, especially when no clear history of circulatory arrest can be obtained. Besides hypothermia (for example if drowned in winter under the ice) also children can look like being brain dead and are not. A list of some of the drugs that have to be excluded is given in Table II.

TABLE II. Drugs that may confound neurological examination in brain death.

Lorazepam	*Primidone*
Clonazepam	*Morphine*
Midazolam	*Fentanyl*
Flurazepam	*Ketamine*
Diazepam	*Amitryptiline*
Phenytoin	*Pancuronium*
Chlordiazepoxide	*Vecuronium*
Carbamazepine	*Pipecuronium*
Valproic acid	*Alcohol*
Phenobarbital	*Cocaine*
Thiopental	*Codeine*
Pentobarbital	

Cardiac Procedures

In present day medicine, diagnostic and therapeutic procedures on the heart are very advanced, but embolism into the brain remains a certain risk. Cardiac catheterisation or percutaneous transluminal coronary angioplasty sometimes causes cerebral emboli that may lead to focal neurologic deficits or an encephalopathy manifested by a behavioural disturbance. Encephalopathy, seizures, and cerebral infarction after cardiac surgery usually result from hypoxia or emboli.

Postoperative encephalopathies may also relate to metabolic disturbances, medication, infection (especially in immunosuppressed patients), or multiple organ dysfunction syndrome (MODS).

Postoperative seizures may result from focal or generalized cerebral ischemia, electrolyte or metabolic disturbances, or MODS (multi organ failure). Recognition of the precise cause of encephalopathy in such cases can be difficult. After cardiopulmonary bypass is performed, intracranial haemorrhage may result because of diminished platelet adhesiveness and reduced levels of coagulation factors. Coronary angioplasty leads to cerebral emboli in app. 1% of cases. But when undertaken after acute myocardial infarction, it is associated with a higher risk of stroke and anoxic encephalopathy.

An encephalopathy may occur soon after cardiac transplantation as a side effect of an immunosuppressive agent or as the result of an infection, for example: meningitis, meningoencephalitis, or cerebral abscess related to immunosuppressive therapy. Infecting organisms include Aspergillus, Toxoplasma, Cryptococcus, Candida, Nocardia, and viruses (Fig. 2, page 429).

After *coronary bypass surgery* the occurrence of an encephalopathy may be caused by stroke, which develops in about 5% of bypass patients and is either embolic or, less commonly, the result of watershed infarction from hypoperfusion. A carotid bruit or radiologic evidence of atherosclerosis of the carotid artery does not clearly increase the risk of stroke, and carotid endarterectomy before cardiac surgery is of questionable utility. In rare cases, patients do not recover consciousness after surgery, and no specific metabolic cause can be identified. This encephalopathy is probably the result of diffuse cerebral ischemia of hypoxia. Hemispheric or multifocal infarction is sometimes responsible.

In Fig. 2, the possibilities of cardiogenic embolism in general are depicted.

Brain Death in Other Settings

The cerebrovascular / post cardiac arrest scenarium has been given more space here, because it is cause No. 1 for brain death. However, cerebral death may also result from severe *head trauma* (cause No. 2) and its complications in the form of delayed haematomas. Space-occupying lesions (brain tumours) in their final states may end in brain death (cause No. 3). Finally, inflammation has to be mentioned as cause No. 4 but is not to be discussed in the context of transplantation.

The Lethal Final Pathomechanism: Brain Swelling and Herniation

The fatal pathomechanism in all 4 causes is the same: it is *brain swelling*, which is the sum of brain oedema and hyperaemia. The problem arises when brain swelling gets out of control, i.e. when all possible therapies have failed. These consist of sedation (with morphine), muscular relaxation, ventricular drainage if necessary, mannitol, hyperventilation and – *ultima ratio* – 'barbiturate coma' (Pentobarbital narcosis). If all these therapeutic measures fail, the brain gets under pressure, i.e. the intra cranial pressure rises. It continues rising, and when the intracranial pressure overrules the systolic blood pressure, the heart is no longer capable of pumping blood into the skull / through the brain. In other words, the brain compresses itself within its hard shell – the absolutely rigid skull. The incarcerated brain herniates through openings. Upper herniation (upper red arrows in Fig. 3) occurs through the *tentorium* slit causing decortication clinically. Further in the process a lower herniation develops as well (lower red arrows in Fig. 3), in which portions of cerebellum and brain stem herniate through the *foramen magnum*. Clinically, this leads to a loss of all brain stem reflexes and finally to the cessation of breathing (Fig. 3, page 430).

If a four vessel Angiography is employed, it shows exactly the complete stasis of blood circulation: on the pictures the contrast medium suddenly breaks off exactly where the arteries enter the skull, i.e. the two internal carotid arteries at the upper siphon, and the two vertebral arteries at the *foramen magnum*. The four vessel angiography is a proof of brain death, however critics argue that the relatively large amounts of contrast medium could have negative effects on the brain, which is already pre-injured and compromised anyhow.

Examination and Documentation of Brain Death

Examining patients with regard to brain death should be done by neurologists, i.e. a conservative non-operative field of medicine with no interest in transplantation medicine. This is the ethical reason why operative disciplines including neurosurgery should not be involved in brain death diagnosis, nor should anaesthesiology. At our hospital two specialists in Neurology independently establish the diagnosis of brain death. The diagnosis of brain death has the following prerequisites:

1. Deep coma (3 points only in GCS [Glasgow Coma Scale])
2. Loss of all brain stem reflexes – 'brain stem areflexia'
3. Apnea (documented by the 'Apnea Test')

The brain stem reflexes are as follows:

Pupillary reaction	→ dilated pupils, no reaction to light
Oculocephalic reflex	→ doll head phenomenon, no counterrolling of the eyes
Corneal reflex	→ no twinkling upon tactile stimuli to cornea
Trigeminal pain reaction in the face	→ no reaction to painful stimuli e.g. to the nose
Gag reflex	→ no reaction to manipulating the tracheal tube

(No vestibulo-ocular reflex [VOR] or nystagmus upon the caloric test with ice water irrigation of the ear canal as an option).

Examination and Documentation of Brain Death Through 'Supplementary' Means

The EEG (isoelectric EEG, zero line EEG, electrocerebral inactivity) is now in Austria a supplementary means only. We regret this. We still use it. It is a functional test. We are looking at *neuronal* function, at cortical function (EEG picks up activity from the cerebral coertex only, not from the brain stem). The EEG speeds up the process of brain death diagnostics: the waiting period is only 6 hours with confirmatory EEG, and as long as 24 hours without.

In case an EEG cannot be recorded e.g. in patients with head trauma and open wounds on the head, transcranial Doppler sonography (TCD) and colour-coded Doppler sonography can be used.

The classical angiography (digital subtraction angiography, DSA) should be performed only *after* brain death has been assessed. In the setting of transplantation it might still be useful, since 'on retreat', so to say, with the catheter other organs may be examined radiologically.

The 'All or Nothing-Situation' of Brain Death

It is important to realize that we have this all or nothing situation in the setting of brain death. Either our therapies against brain oedema (see above) are successful and brain death can be avoided or they are not successful. Then brain death is the inevitable result. If the galloping brain oedema cannot be stopped we have this mechanistic outcome that the brain compresses itself and in the end is totally destroyed. The galloping brain oedema is the result of a vicious circle: the normal brain has a blood flow of 55 ml/100g tissue/min. If blood flow goes down to 40 ml/100g tis-

sue/min, functional metabolism already begins to suffer, if it goes below 15 ml/100g tissue/min, structural brain metabolism is jeopardized. Poor blood flow results in lack of oxygen (O_2) and a rise in carbon dioxide (CO_2) that leads to acidosis of the brain. Brain acidosis leads to brain oedema, which leads to an increase in intracranial pressure and this leads to further lowering of cerebral blood flow. This is the vicious circle. Vicious circles are feedback cycles with *positive* feedback, i.e. they build up. Thus, the system is bound to take this disastrous course.

I think it can now be understood why neurologists are so certain about brain death, if this diagnosis is *lege artis* established. It is the inevitable end point of an inevitable cascade of fatal mechanisms resulting in the total destruction of the brain. The PET (positron emission tomography) is a functional method for measuring brain metabolism. Laureys S. *et al*. of the Cyclotron Research Centre, University of Liège, Belgium have investigated different states of consciousness in the PET looking at the glucose metabolism (see Fig. 4). They were recording the regional cerebral metabolic rates for glucose (rCMRGlu) using 18F fluorodeoxyglucose (t2 ± 2 hours), neural activity of ± 30 min in the awake state (upper left image in Fig. 4), in deep sleep during anaesthesia in the unconscious state (permanent vegetative state, apallic syndrome) and in the state of brain death. In the latter the rCMRGlu was zero (lower right image in Fig. 4, see page 430).

The hypophysis (pituitary gland, some call it 'neurohypophysis') has a special status. If we look at Fig. 5 (see page 431), we see the hypophysis under the brain in the *sella turcica* and see that it may be somewhat protected from elevated intracranial pressures, a protection made efficient by the *diaphragma sellae* separating the pituitary gland from the intracranial space. Furthermore, the pituitary has its own blood supply directly from the carotid artery. Thus, a remaining basic hormonal secretion may be maintained after brain death has occurred. The posterior lobe even produces antidiuretic hormone, ADH or vasopressin, a lack of which causes *diabetes insipidus*, which is common in the brain dead state. Lack of *diabetes insipidus*, though, cannot be taken as evidence against the concept of brain death (Renner, 1995).

A basic hormonal secretion of the anterior lobe of the neurohypophysis is also of interest, in particular in the case of brain dead mothers. This was an issue at the study workshop, and in the pre-conference correspondence, H.E. Msgr. Prof. Marcelo Sánchez Sorondo had asked: 'Do the children of brain dead mothers have a standard of normality in line with children not so born or do they have mental and physical impairments derived from the

condition of death of their mothers? And are children born to brain dead mothers the same as children born to alive mothers, and this in a society that has laid increasing stress on the particular importance of the intrauterine relationship between mother and child?'

L. Deecke had replied: to mothers in coma, yes. (i.e. they can have normal children). To mothers in the permanent vegetative state, also yes. Regarding brain dead mothers: whether the child has a damage or not depends on the circumstances that led to the state of the mother (accidents? other conditions?). The really brain-dead mother is an extreme situation. There is not really an intrauterine interaction between mother and child. These conditions are, in a sense, emergency conditions. For a long time obstetricians have had this emergency situation in which the mother is dying (cardiac death) and they are trying to rescue the child. This is called: '*Sectio in mortua*'. If it is not cardiac death but brain death it should be analogous: '*Sectio in mortua cerebralis*'.

Prof. DDr. Johannes Huber Vienna (theology and gynaecology & obstetrics) declared in the workshop that pregnancy seems to be stable even in the absence of brain function. Prof. Huber asked the question: 'Shall the delivery of the child by caesarean section be the only removal? Or do we allow at the same time that the brain dead mother also gives her organs?'

L. Deecke replied: '*Sectio in mortua cerebralis in pietate!*' No other organs. Only the child!

Prof. Posner was of a different opinion.

So this point remains open and subject to individual taste and own decision.

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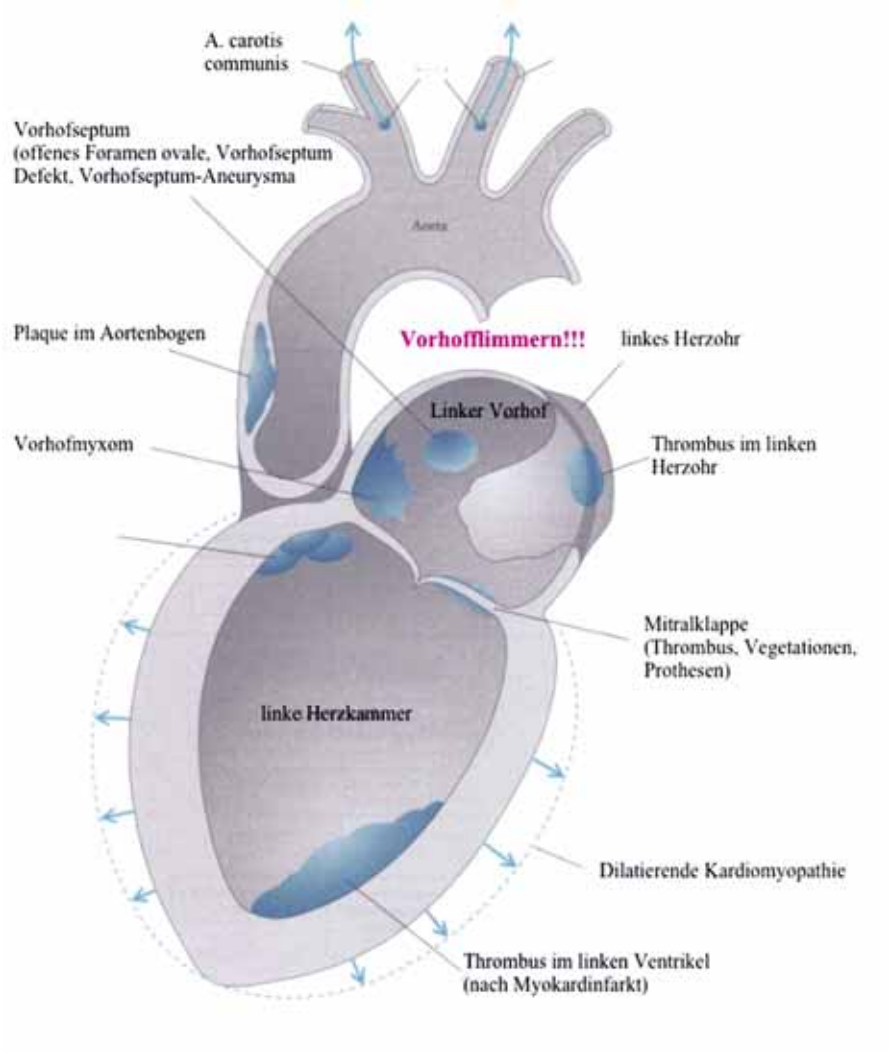

Figure 2. Possibilities of cardiogenic embolism.

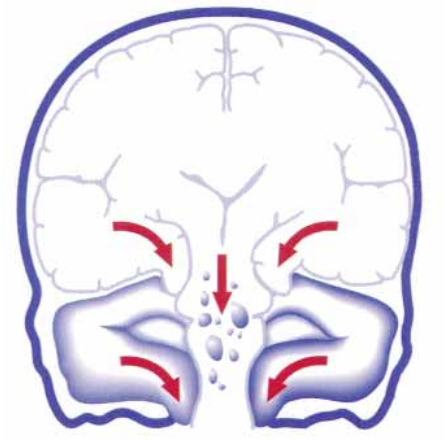

Figure 3.

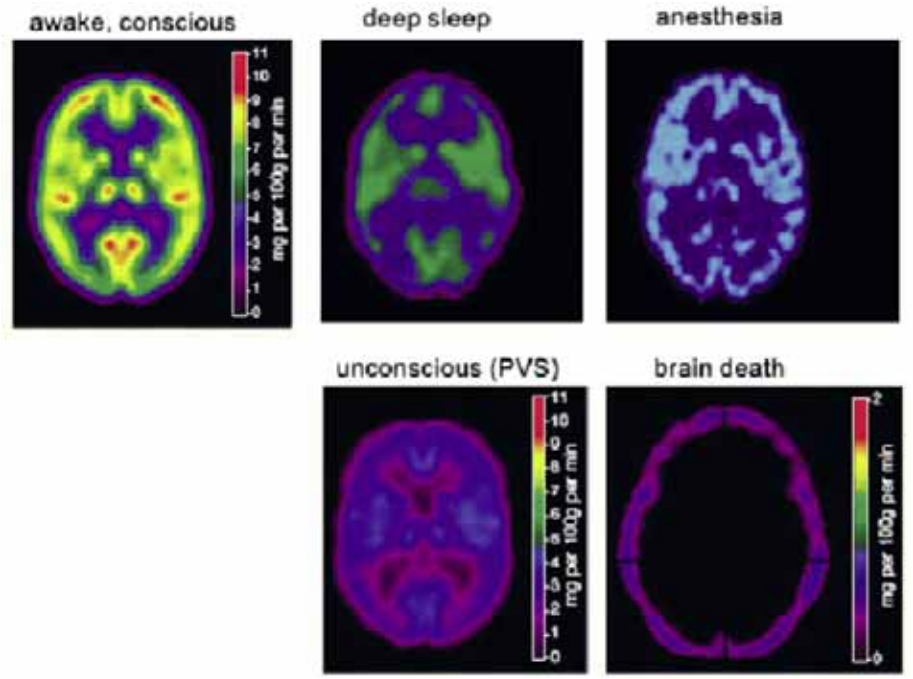

Figure 4. Regional cerebral metabolic rates of glucose (rCMRGlu) using positron emission tomography (PET). Lauryes S. *et al.*, *Nature Rev. Neurosci.* 2005; TICS 2005.

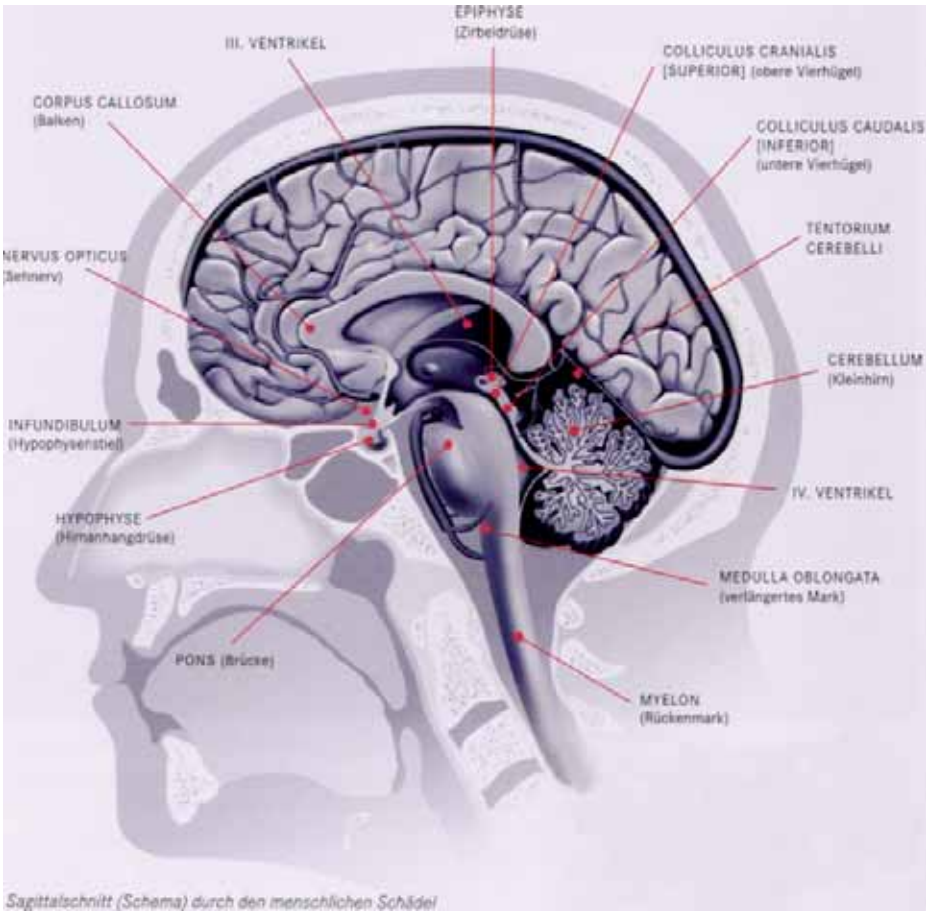

Figure 5. The Neurohypophysis (pituitary gland) separated from the brain, the *infundibulum* leads through the *diaphragma sellae* into the *sella turcica*.