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Historical study of coma: looking back through medical and neurological texts

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In the 1960s, two major works on coma by Fisher, Plum and Poser were published and ushered in the beginning of a comprehensive clinical examination in coma. How these ideas matured has been rarely investigated. In this article, we describe observations and experiments that led to a better understanding of consciousness and coma in medical texts prior to that episode. We consulted medical texts published between 1640 and 1960. Subject indexes and tables of contents of textbooks were reviewed for the words coma, (loss of) consciousness, stupor and somnolence. Chapters on apoplexy were reviewed for descriptions of impaired consciousness. We found information on terminology, classification, causes, observation and examination, pathophysiology, treatment and experimental coma. Up to the middle of the 19th century, disorders of sense, motion and breathing, and also changes in the patient's pulse, were recognized as clinical cues. The distinction between a structural and toxic (endogenous and exogenous) cause was recognized early. Observed phenomena were explained from the perspective of humoral medicine and treated likewise. After the middle of the 19th century, specialization in medicine and experimental research of intracranial pressure resulted in important insights and more accurate clinical examination. Cranial surgery and the discovery of the brainstem reticular activating system in the first half of the 20th century contributed to further increases in knowledge. The understanding, clinical examination and treatment of coma has gone through a gradual evolution over many decades. The recapitulation of clinical signs in impaired consciousness into a teachable and reproducible module marks an abrupt change in clinical approach. This transition is very recent, based on close clinical observation and interpretation of experimental and pathology studies and less on modern neuroimaging.

Keywords: coma; history of medicine; history of neurology

Abbreviations: ARAS = ascending reticular activating system; CSF = cerebrospinal fluid; ICP = intracranial pressure.

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Introduction

There is an increased interest in coma. This renewed focus applies to acute conditions causing coma (e.g. survivors of cardiopulmonary resuscitation) and to chronic conditions (e.g. persistent vegetative state). Clinicians in emergency departments and intensive care units commonly assess patients with impaired consciousness and have used clinical tools that have withstood the test of time. Over the centuries, several terms were used to describe the phenomena that were observed and to grade the level of (un)consciousness. In 1977, a landmark paper on aspects of coma following severe head injury was published, presenting a new scale for grading the level of consciousness after head trauma (Jennett and Teasdale, 1977). Critical evaluation of the validity of some of these clinical signs has only recently surfaced. At the other end of the spectrum are the concerns with difficulties of physician interpretation of prolonged comatose states. True or false, the recent Schiavo case further catapulted these conditions into a sphere of clinical uncertainty. Moreover, a few case studies with functional MRI have claimed to be able to identify 'awareness' where none was expected. Most of our current teaching is based on two monographs published in the 1960s (Plum and Posner, 1966; Fisher, 1969). Little is known how this knowledge has evolved.

In this article, we present descriptions of coma from the past 300 years and document that clinical examination, causes and mechanisms of coma were poorly taught up to the 1960s.

Methods

We consulted medical and neurological textbooks from the 1640s to the 1960s. In order to secure a representative list of books from this period, we selected commonly known medical and neurological books in English, German, French and Latin language from two standard books, *Garrison's history of neurology* (McHenry, 1969) and the 'Diseases of the nervous system' section in *Morton's medical bibliography* (Norman, 1991, p. 701–15). We added three works by prominent Dutch physicians for comparison (Tulp, 1641; Bouman and Brouwer, 1922–30; Biemond, 1946). Boissier de Sauvages de la Croix (1763) was added, being the main nosographic work of the 18th century. Most of the books were published in the period after 1850 when specialization in medicine emerged. This dramatic increase of knowledge was a consequence of the introduction of the scientific method into medicine around the middle of the 19th century. Subject indexes and tables of contents were consulted for the words coma, (loss of) consciousness, stupor and somnolence (or the translation of the words in the mentioned languages). As this did not always result in the descriptions we were looking for, we also studied chapters of apoplexy. This term has been used since Hippocrates and although it gradually disappeared from the neurologists' vocabulary, haemorrhage, in particular cerebral, was its meaning until recently. The ancient word, however, originally meant 'being struck with violence' and might be compared with the English word 'stroke' or the German 'Schlaganfall'. In the Hippocratic writings, the term had two meanings. It was applied to syndromes in which the patients lost consciousness rapidly after which they often died or, if they survived, showed signs of focal brain damage. Sometimes it was also used to indicate paralysis of a part of the body. The meaning changed over the centuries but unconsciousness at the beginning, and sometimes lasting, was almost always present (Clarke, 1963). As the meaning of the term coma evolved over the centuries, we chose to put it between quotation marks when referring to its use by a particular author and without quotation marks when it was used it in a modern sense.

Results and discussion

Seventeenth century

The term 'coma', from the Greek koma, meaning deep sleep, had already been used in the Hippocratic corpus (*Epidemica*) and later by Galen (second century AD). Subsequently, it was hardly used in the known literature up to the middle of the 17th century. The term is found again in Thomas Willis' (1621–75) influential *De anima brutorum* (1672), where lethargy (pathological sleep, which he localized in the outer cortex), 'coma' (heavy sleeping), *carus* (deprivation of the senses) and apoplexy (into which *carus* could turn and which he localized in the white matter) are mentioned, the sequence indicating increasingly deeper forms of unresponsiveness. The term *carus* is also derived from Greek, where it can be found in the roots of several words meaning soporific or sleepy. It can still be found in the root of the term 'carotid'. Thomas Sydenham (1624–89) mentioned the term 'coma' in several cases of fever (Sydenham, 1685).

Partly due to the methodology we applied, apoplexy and stroke are causes often encountered. Trauma has always been known as a cause and an example is found in Tulp's *Observationes Medicae* (Tulp, 1641). Before the 19th century, physical examination, next to observation, was largely confined to palpating the pulse and to inspection of urine, faeces, sputum and pus (Bynum and Porter, 1994). In this period, observations on arousal to sensory stimuli (shouting, pinching, applying stimuli to the nostrils), movements and breathing were described. Johann Jakob Wepfer (1620–95) mentioned a full and strong pulse that became weak, small and frequent (Wepfer, 1932).

Obviously, treatment was determined by the pathophysiological models of the period. In the older texts mainly dealing with apoplexy, bloodletting was a therapy often mentioned. Tulp described the case of an obese young man who suffered from a stroke caused by too much blood in the head, distinguishing it from strokes caused by too much cold phlegm or black bile (Tulp, 1641). Tulp's views of (humoral) pathophysiology were still influenced by Hippocratic and Galenic teaching. The man was treated by bloodletting from both arms, resulting in diminished rattling within minutes. Breathing improved and the patient was cured. The patient was advised to 'give air to the blood every spring' (bloodletting to prevent accumulation of blood in the head), but as he did not follow up this advise, he died within 2 years. Tulp compared the situation with that of one of The Netherlands' main threats of the period. 'Similar to the breaking through of banks or dams, causing inundation of the land, the brain may easily be threatened by the blood' (Tulp, 1641, Koehler, 1996). Wepfer mentioned 'anti-apoplectic water' (Wepfer, 1932) and Willis (1672) advised to evacuate the morbific matter, which, again, should be understood from the perspective of humoral medicine: an excess of humours needed to be removed by bloodletting or emptying the stomach.

Eighteenth century

The term 'coma' may be found in Boerhaave's Lectures from the first half of the 18th century (Boerhaave, 1730–5). His teaching was very influential in 18th century European medicine until the centre of medical teaching moved from Leyden, The Netherlands, to Edinburgh, Scotland, in the second half of the century. Disorders of consciousness were compared with an increased tendency to sleep, which had already been recognized by Galen. 'It is the perfect image of a very profound sleep, like in healthy persons, due to exercise or fuddle. Therefore, there is little distinction,

Table I Authors, terminology, cause, examination and treatment of coma

	Author	Year	Terminology	Cause	Observation & examination	Treatment	Breathing	Movements	Comments
17th century	Tulp	1641	Did not speak, eyes closed, ears deaf	Stroke, trauma	Loss of speech, tremble, rattle, eyes closed, ears deaf	Bloodletting (apoplexy)	Rattling	Trembling	Humoral pathophysiology
	Wepfer	1658	Insensible to shouting and pinching	Stroke	Insensible to shouting, shaking, pinching, deprived of animate motion, pulse full & strong — weak, small and frequent	Anti-apoplectic water	Sputum from mouth, laborious	Deprived of animate motion	Humoral pathophysiology
	Willis	1672	Lethargus, coma, carus, apoplexy (increasing severity)	Stroke	Deep sleep, can hardly be awakened	Evacuate the morbific matter, stimulate the senses	Laboured		Humoral pathophysiology
18th century	Boerhaave	1730–5	Profound sleep, coma, etc (see table 2)	Stroke, intoxication	Loss of voluntary motion or sense, swallowing (sometimes), vomiting and bowel movements remain; (profound) sleep	Bloodletting, cooling, emptying stomach	Normal or snoring, rattling,	Loss of motion or sense	Humoral and iatro-physical (compression)
	Haller	1747		Blood loss, cooling medicines, opium, fevers	Sleepiness				Humoral and iatro-physical: compression of nerves, brain, congestion
	Boissier de Sauvages	1763	Taxonomy of comata, apoplexy indicating level of coma	Apoplexy, trauma	Loss of voluntary motion & perception, somnolence. Look for external bleeding or bone crepitation, snoring				
	Cullen	1789	Coma, carus, cataphora, lethargy	Trauma, tumor, intoxication, cerebral hemorrhage	Loss of sense & voluntary motion, sometimes more on one side with convulsions on the other	Bloodletting, blistering, purging Prevention by diet, exercise; purging, laxatives	Often stertorous	Loss of motion and sense (sometimes partly)	Humoral and iatro-physical: compression of the origin of nerves or medullary part of the brain
19th century	Cheyne	1812	Apoplexy & lethargy, apoplexy indicating level of coma	Stroke, intoxication	Shouting, applying eau-de-luce to nostrils, shaking, pinching, face red, pupils narrow — wide. Preceded by loss of ideas, voluntary motion, speech		Often irregular, slow & laboring	May be preceded by loss of motion or speech	Pupils may dilate
	Rostan	1823	Somnolence, coma, carus	Stroke (softening)	Intelligence and sense disappears, extremities immobile, succumbs 4th or 5th day. Eyes closed, pupils moderately dilated, irregular and immobile; normal pulse; no pain on abdominal compression		Like in deep sleep	Immobile	Loss of intelligence and sense preceeds it; dilated pupil grave sign
	Romberg	1840–6	Coma		–				Only mentioned preceding death
	Trousseau	1882	Stupor	Trauma	Theoretical discussion				Experimental coma

(continued)

Table 1 Continued

	Author	Year	Terminology	Cause	Observation & examination	Treatment	Breathing	Movements	Comments
	Hammond	1872	Coma, stupor	Apoplexy, softening, meningitis,	Insensibility		Loud, slow, rarely stertorous		
	Charcot	1890	Coma, carus, lethargy	Hemorrhage and CO intoxication	Profound coma, absolute insensibility		Slow & loud		Hardly mentioned coma
	Hughlings Jackson	1876	Coma	After-effects of epileptic discharges	–				Physical and psychic states distinguished; evolution-dissolution theory
	Gowers	1888	Coma and stupor (partial loss of consciousness)	Often by hemorrhage; or toxaemia (without local symptoms; endogenous or exogenous)	No spontaneous or elicited mental action, loss of tone, 'conjuntivae may be touched' with blink reflex, state of pupils. No local symptoms, less profound Nb. Smell of opium, alcohol, albuminuria		Lessened, shallow or vary in rhythm; Cheyne–Stokes, rattle	Swallowing impossible in coma (possible in stupor); loss of tone if severe	One of the best descriptions; pupils small or wide; blink reflex mentioned; experimental coma
	Osler	1892	Coma	Many causes: diabetic, epileptic, heat-stroke, abscess, alcohol apoplexy, etc	Differentiates coma from apoplexy from that of other brain diseases: tonus of muscles different on two sides, facial paralysis, eye deviation. Similar to Gowers				Much in common with Gower's description
	Dana (in Dercum)	1895	Coma (transient)	Hemorrhage	Pupils contracted and immobile, anisocoria (more contracted on the sound side), eyes partly closed, slow heart beat, pulse hard and full. Pricking/pinching: some manifestation of consciousness		Slow, stertorous		
	Oppenheim	1898	Several levels: Benommenheit, Somnolenz, Sopor and Coma	Several causes, hemorrhage, but also embolism	Abolished reflexes and tendon phenomena, does not awake on strong stimuli				
20th century	Starr	1903	Coma	Alcohol, apoplexy, opium, uremia, diabetes, encephalitis	Less deep than apoplexy, preserved corneal and pupil reflexes. Slow respiration, slow rapid pulse, blue skin, extreme contracted pupils. Tibial and facial oedema, bloody or albumin in urine; may begin with headache, vomiting, convulsions. Acetone smell Pulse full, slow, irregular, stertorous respiration, no arousal, eye deviation Bad prognosis if: Cheyne–Stokes, > 1 day, rise/fall of temperature, signs of intracranial pressure		Slow in opium poisoning, stertorous or Cheyne–Stokes in apoplexy		

Marie	1911	Deep coma/carus, stupor	Stroke, trauma, infection, intoxication (endogenous or exogenous)	Loss of consciousness, motion, sensibility, suppression of reflexes. Smell of breath, signs of trauma? Plantar reflex				Mentioned *coma vigile*. Accurate examination to find cause
Dejerine	1914	Coma, distinguished 3 degrees: 'léger', profound and carus	Long list of causes	Loss of intelligence, sensibility, and movement; reflex movements. Breathing: slow, deep, sometimes fast. Deep coma: loss of reflexes, often hyperthermia.		Often profoundly influenced: slow, deep and sometimes fast		Ref. to reflex action and theories of Duret. Mention of *coma vigil*
Lewandowsky	1910–2	Degrees from drowsiness to coma	Mechanic, toxic, metabolic, 'shock' or 'diaschisis'	Muscle tone remains. Muscle and pupillary reflexes often present. Corneal and skin reflexes lost if deep. Prognosis on pulse, blood pressure and breathing (medulla oblongata signs). Slowing pulse and increasing blood pressure		Regular or Cheyne–Stokes		Provides theoretical overview; interest in sudden coma after moderate hemorrhages. Ref. to Kocher and Duret
Jelliffe & White	1919	Coma	Apoplexy, alcohol, diabetes, uremia	Slow, full& regular pulse, relaxed limbs, irregular dilated and light-inactive pupils, loss of corneal reflexes, no reaction to painful stimuli, loss of reflexes in general, occasional involuntary urination & defecation Hyperthermia in profound c. Reflexes often preserved		Stertorous — irregular	No reaction to painful stimuli	In apoplexy: Dilated pupils, irregular pulse and hyperthermia
Bouman & Brouwer	1923	Various degrees somnolence — cataphora, carus, coma (lethargus)	Apoplexy, trauma, cardiac, encephalitis, etc.	Bradycardia, swallowing impossible, dilated non-reactive pupils, and areflexia. Hemiplegia if survival. Four stages of rising pressure: Ist stage: headache, slight drowsiness; 2nd dizzy, restless, blood pressure may rise, pulse slow; 3rd stage medulla oblongata: blood pressure further rises, pulse slows, breathing irregular, e.g. Cheyne–Stokes type, reflexes disappear & face may become cyanotic; 4th stage regulation of vasomotor centre fails, pulse & breathing become irregular, coma deepens, pupils become wide, blood pressure falls & breathing stops. Mentions free interval. Papiledema in chronic compression	Trepanation, lumbar punction	Snoring, Cheyne–Stokes	Restlessness in the 2nd phase	Bradycardia, dilated pupils; ref. to pressure theories of Bergmann & Kocher — symptoms in four phases.
Bumke & Foerster	1936	Coma	Trauma, and several other causes, infections (TBC)	Acute coma, duration depending on severity, lucid interval may occur, pressure symptoms	For low RR: atropine, strychnine, ergotin, ephedrine, and coffein; osmotherapy, trepanation for high intracranial pressure;	Cheyne–Stokes,	Depending on level	Summarizes four pathophys. theories on commotion

(continued)

Table 1 Continued

Author	Year	Terminology	Cause	Observation & examination	Treatment	Breathing	Movements	Comments
Kinnier Wilson	1940	Coma	TBC meningitis, malaria, cerebral hemorrhage	Slow, pulse, puffing cheeks, sweating skin, flaccid limbs, incontinence, loss of reflexes	Bedrest, venesection, lumbar punction, hypertonic fluids	Stertorous	Flaccid	No separate chapter on coma; mentions coma vigil; bad prognosis of ventricular bleeding;% of coma in various types of hemorrhage
Biemond	1946	Subcoma, coma, carus	Vascular, meningeal, endogenous, exogenous intoxication, encephalitis, trauma	As above, pupils, no nystagmus, funduscopy, lateralisation, brainstem reflexes, decerebration	Treat cyanosis, shock, blood loss, temperature, preventive measures	Slow, deep, Cheyne–Stokes	Sometimes decerebration hypertonia	Mentions Magoun's recent discoveries (ARAS)

unless by duration' (Boerhaave, 1730–5, p. 303). Next to 'coma', Boerhaave used several other terms for disturbances of consciousness, providing information on the pathophysiology and prognosis (Table 2). They were classified within the category of apoplexies, including lethargy and cataphora (both with fever), *carus* and 'coma' (Boerhaave, 1730–5, p. 394). With respect to lethargy, Boerhaave taught: 'Lethargy . . . is a brain disease accompanied by loss of motion and sense, with an irrepressible need to sleep, caused by cold, humid phlegm that moistens the brain, finally leading to putrefaction, slow fever and lassitude' (Boerhaave, 1730–5, p. 311; Koehler, 2007).

With respect to causes of 'coma', Boerhaave, as well as Haller (Koehler, 2007), added intoxications. Boerhaave mentioned that in contrast to voluntary movements, vomiting and bowel movements remain. Many pathophysiological mechanisms were mentioned including the compression of the cortex by any swelling substance, impression of the skull, increase of movement by 'full-bloodedness', bad condition of the humours and 'melancholy', obstructions in the descending aorta, etc. (Boerhaave, 1730–5, p. 307). The essential problem in apoplexy, according to Boerhaave, irrespective of the cause (e.g. cerebral haemorrhage), was the failing of the animal spirits. Therefore, it is easy to understand why he treated it with stimulating agents, almost literally resuscitating the life spirits. He also advised cooling and bloodletting, which similar to apoplexy, was a logic treatment considering the pathophysiological ideas (i.e. accumulating blood resulting into too much warmth) (Koehler, 2007).

In his well-known nosological work *Nosologia methodica sistens morborum classes*, *genera et species* (Boissier de Sauvages de la Croix, 1763) Boissier de Sauvages de la Croix classified the *Comata*, *assoupissemens* (slumber), *lethargies*, *affections soporeuses* as the fifth order of the sixth class called *Debilitates*, *seu morbid paralytodaei*. 'Comata' was defined as diminution or total loss of the powers of voluntary motion, and of perception, with somnolence. He further distinguished seven genera, including catalepsies, extasis, typhomania (or 'coma vigil'), lethargus, cataphora, *carus* and apoplexia. In catalepsy, volition and consciousness are interrupted while the limbs remain in the same position. Among the genus of lethargus, again six species were distinguished, including *Lethargus à narcoticis*. The patient can be easily awoken, responds to questions and may move. In cataphora, the patient may respond and open his eyes but falls asleep again. For each species, Boissier de Sauvages de la Croix also provided previous synonyms (e.g. within the genus of cataphora there are eight species), including *cataphora somnolentia*, which Willis called *somnolentia continua*. Another example is *cataphora coma*, which Avicenna called *subeth asarim*. In *carus*, the patient can hardly be aroused and respiration is quiet. They will only open their eyes at strong stimuli but they do not respond or move. One of the species within this genus is *carus traumaticus*, in which there may be

Table 2 Terms and characteristics used by Boerhaave (1730–5)

Boerhaave	Unconsciousness	Fever	Pathophysiology	Breathing	Prognosis
Lethargy		+	Cold, humid phlegm		
Cataphora	Deep	+			
Carus	Sudden, deep	–	Intoxication	Undisturbed	Good
Coma	Deep stupor	–			

contusion and fracture. These patients should be carefully examined for ecchymosis and crepitation of the bone. *Carus à narcoticis* is also mentioned in this genus. In apoplexy, respiration is accompanied by snoring and the patient sleeps very deeply, can hardly be aroused, and all limbs are flaccid. Eleven species were mentioned within this genus, the second of which is called *apoplexia traumatica*, in which the patient may vomit and blood may come from the nose (Boissier de Sauvages de la Croix, 1763, p. 410–58). Several physicians, including Boissier de Sauvages de la Croix, advised to search for signs of a traumatic origin.

Another important book from this period is William Cullen's (1710–90) *First Lines of the Practice of Physics* (Cullen, 1808, p. 65–104), which contains a chapter entitled 'Of comata, or, of the loss of voluntary motion'. The diseases within this category, Cullen reasoned, 'are most properly distinguished by their consisting in some interruption or suppression of the powers of sense and voluntary motion, or of what are called the animal functions'. Cullen, who coined the term 'neurosis' (in the old sense of the word, not to be confused with the 20th century 'psychoneurosis'; see López Piñero, 1983), considered apoplexy and palsy two 'genera' within this category of his nosographic system. He defined apoplexy as an affection of the whole of the powers of sense and of voluntary motion, while the action of respiration and of the heart continues. As there was only a difference in degree, *carus*, cataphora, 'coma' and lethargus, were also comprehended. The two most frequent causes, distension of cerebral arteries and effusion, were discussed more extensively. Delayed venous return from the head to the heart was considered most important. Haemorrhage from the arteries or veins was possible. Trauma and tumours were only mentioned, but not further discussed. If the patient survived, palsy could occur (Cullen, 1808, p. 65–104). Treatment consisted of the removing of harmful humours. Moreover, preventive measures were provided.

Nineteenth century

Throughout the 19th century, older terms gradually disappeared, leaving the term 'coma' and sometimes stupor. Levels are indicated by other terms, for example, in Oppenheim, who distinguished dazedness, somnolence, sopor and 'coma' (Oppenheim, 1898). *Carus* is found back again in one of Charcot's books (Charcot, 1890). Charcot applied the term 'coma stertoreux' in a patient dying within 4 h after onset (Charcot, 1890, p. 27).

In the second half of the 19th century, with improving medical knowledge, many causes are mentioned, including endogenous and external intoxications (Gowers, 1888; Osler, 1892). Haemorrhage is found more often to cause 'coma' and softening is rarely the cause (Hammond, 1872). In his well-known book, Rostan stated that 'coma' is not a frequent symptom in softening. 'Somnolence, coma, or *carus*, hardly ever appears but to the final episode of the disease' (Rostan, 1823, p. 245). If this occurred, the patient's 'intelligence and functions of sense disappeared entirely, falling in a complete coma, the extremities become immobile, and he succumbs after some days, usually the fourth or fifth day . . .' (transl. PK) (Rostan, 1823, p. 18). Infections were also associated with 'coma' (Hammond, 1872; Osler, 1892), although fevers were already mentioned by Sydenham (1685) and Haller (Koehler, 2007), at a time when 'fever' was considered a diagnosis rather than a symptom.

Physical examination of the patient as practised today was gradually introduced in the course of the 19th century and beginning of the 20th century. Several observations in 'comatose' patients followed the experimental findings described below. Observations on the pupils were noted by Cheyne (1812), who observed narrow pupils. His name became associated with Cheyne–Stokes breathing pattern (Koehler and Lyons, 2000). He described the symptoms of approaching death in patients suffering from apoplexy. '. . . the organs of sense entirely lose their faculty of receiving impressions: the pharynx is insensible, the pupil becomes dilated, the eye opake, the jaw falls'. There were several levels of unconsciousness and it was possible to make a prognosis 'from the quantity of sensorial power which still exists in the body. Thus, we do not despair until the pupil ceases to contract. With any return of sensibility our hopes rise . . .' (Cheyne, 1812, p. 13). Among the most accurate descriptions was that by Gowers, who mentioned no spontaneous or elicited mental action, loss of tone, 'conjuntivae may be touched' without a blink reflex, respiration lessened, shallow, various rhythm, Cheyne–Stokes breathing, rattling and state of pupils. He emphasized the lack of local symptoms and less profound 'coma' in toxic causes and added the importance of the search for the smell of opium, alcohol and examine for albuminuria

(Gowers, 1888). Eye deviation in stroke was mentioned by Osler, probably having read Prévost's description (Prévost, 1868).

Dana was among the first to mention a slow heart beat in clinical examination, whereas the pulse was hard and full (Dana, 1895). Not surprisingly, Oppenheim mentioned the disappearance in deep 'coma' of reflexes and tendon phenomena (following the latter's description in 1875 by his teacher Westphal and compatriot Erb) (Oppenheim, 1898).

Respiratory disorders were observed and mentioned by all authors we studied. In classical texts, rattling has always been considered a bad prognostic sign. Stertorousness (in apoplexy), irregularity (e.g. Cheyne-Stokes), slowness, shallowness and loudness were terms often used. Slowness of breath was mentioned in opium intoxication.

Some authors whose books we studied scarcely referred to 'coma' or disorders of consciousness. For instance, in the index and table of contents of Romberg's *Lehrbuch der Nervenkrankheiten des Menschen* (1840–6), we do not find the terms 'coma', consciousness, apoplexy or unconsciousness. The terms are found in some of the cases presented in the chapter on cerebral paralyses. 'Coma' was mentioned in a few cases preceding death. Furthermore, in neither of Charcot's two volumes of *Leçons de Mardi* (1889 and 1892), we found a treatise on 'coma' or consciousness. This may be explained by the mere fact that these lectures concerned mainly out-patients (Charcot, 1892). An exception is the short mention of 'coma' in cases of carbon monoxide intoxication (Charcot, 1889). The Friday lessons were more formal and concentrated on certain subjects. These were published in the three volumes of *Leçons sur les maladies du système nerveux* (Charcot, 1872—87; Goetz *et al*., 1995). In these three volumes the subject was not discussed, nor in his *Leçons sur les localisations dans les maladies du cerveau, faites à la Faculté de médecine de Paris*, except in a chapter on secondary degenerations of the pyramidal tract, where he mentioned the term, but rather to indicate the symptoms that remain after 'the comatose phenomena and intellectual torpor of the apoplectic attack have already passed away...' (Charcot, 1883). Finally, in *Hémorrhagie et ramollisement du cerveau. Métallothérapie et hypnotisme. Électrothérapie* (vol. IX of the *Oeuvres Complètes*), a volume of collected papers, edited by his pupil Bourneville, some of the ancient terms occur (*carus*, lethargy) (Charcot, 1890). In general, more attention was paid to autopsy findings than to clinical observation.

Hughlings Jackson discussed the pathophysiology rather on a philosophical level. In line with his other writings on physico-psychological parallelism (or the concomitance of psychical and nervous states), he distinguished between physical and psychical aspects. With respect to the first, 'to be comatose is only a greater degree or greater depth of loss of consciousness, as this is only a greater degree of that slight defect permitting only slight confusion of thought (defect of consciousness)'. With respect to the physical states that correspond to this psychical loss, he argued that 'there must be negative states of nervous centres in these cases, as certainly as there are positive states during degrees of consciousness'. Whereas 'object consciousness is continually changing and varying; subject consciousness is comparatively persistent and unvarying'. He referred to the gradual scale from a slight defect of consciousness to 'coma'. In post-epileptic 'coma', 'not only the highest centres [will] be exhausted, but more or less of many lower centres through which the currents developed have passed'. In metaphysico-materialistic views, 'the centres for consciousness are not centres for receiving impressions, and giving out impulses for movements, but centres which play upon lower centres for movements autocratically'. In these thoughts, we recognize some of Hughlings Jackson's theories on evolution and dissolution of the nervous system, derived from Herbert Spencer. However, these views are not consistent with anatomy (Hughlings Jackson, 1931). Levels of defects of consciousness after epilepsy are explained in terms of this evolution–dissolution theory. In post-epileptic 'coma', three hypothetical layers are out of function (the third degree of dissolution) and the nervous system is functioning only at the fourth layer of evolution (Hughlings Jackson, 1931, p. 380–1).

The early 20th century

During the early 20th century, only a few additions were added with respect to terminology, classification, observation and examination. The term 'coma' is mentioned by nearly all authors. *Carus* is still found in some texts, including Marie's book (Moutier, 1911), Biemond's book (Biemond, 1946), and *carus*, cataphora and lethargus in Bouman and Brouwer's book (Wertheim-Salomonson, 1923). Starr emphasized the various signs of endogenous and exogenous toxic 'coma' (Starr, 1903). The list of findings on observation and examination gradually enlarged. Lewandowsky was among the first to mention the absence of skin and corneal reflexes (Lewandowsky, 1910). Next to the slowing of the pulse, he added the significance of increasing blood pressure, not surprising following the recent discoveries of Kocher and Cushing that were described in the same handbook (Braun and Lewandowsky, 1912). Hyperthermia may accompany deep 'coma', as was described by Starr (1903), Dejerine (1914) and by Jelliffe and White (1919). With respect to causes, we did not find many changes in comparison with the 19th century. Whereas meningitis had been mentioned previously (Hammond, 1872), encephalitis was now added to the list (Starr, 1903; Wertheim-Salomonson, 1923). New treatment options arose following the insights derived from experimental coma and will be described below.

Experimental coma

Experiments to explain observed phenomena in coma started in the second half of the 19th century, although

Magendie already experimented by compressing a child's spina-bifida sack (meningocele) leading to the rise of the fontanelle and somnolence (Kocher, 1901). Trousseau was one of the first to refer to experimental coma. In his well-known *Clinique médicale de l'hôtel-dieu de Paris*, he appears to have been fascinated by the sudden loss of consciousness in cerebral haemorrhages that may last for hours or days, ultimately rendering the patient with only a slight hemiparesis. Frequently, there was no relationship between the severity of these first phenomena and the residual symptoms of intelligence, sensibility and movement. It was often said this was due to the accompanying cerebral congestion, an old pathophysiogical concept. Trousseau, however, though assuming that congestion may have played a part, believed another factor should play a role to explain the stupor, similar to that following commotion and he called it 'étonnement cérébral' (cerebral surprise) (Trousseau, 1882). He went on to compare the situation to cerebral trauma (e.g. in bullet impact). He mentioned animal experiments in which, following trepanation, a small ball of lead was placed between the skull and the cerebral surface. He probably referred to the work of the surgeon Henri Duret (1849–1921), who had published *Etudes expérimentales et cliniques sur les traumatismes cérébraux* a few years previously (Duret, 1878). Although there was no cerebral commotion, the experiment resulted in short-lasting stupor followed by hemiparesis that was proportionate to the compression. The brain seemed to be 'surprised' by the accident, which was translated by a transient disturbance. He reasoned that this theory would also result in new treatments besides those applied to cerebral hyperaemia or congestion. The distinction between the sudden and residual symptoms by which Trousseau like many others was fascinated, was later extensively studied by Von Monakow, resulting in his theories on diaschisis (Monakow, 1914/1969, p. 28–9; Finger *et al*., 2004).

Ernst von Leyden (1832–1910) experimented on dogs, increasing the cerebrospinal pressure by 180–900 mmHg. The animals being anaesthetized with morphine, were injected with a protein solution in the cerebrospinal fluid (CSF) space and observed for the signs with increasing pressure up to 250 mmHg. Von Leyden demonstrated the dependency of the decreasing pulse rate on the vagal nerve by section. Respiration frequency first increased, became irregular, then in 'coma' profound and slow and with increasing pressure irregular, a sequence we recognize today. The heart continued beating for 2 min after respiratory arrest. The Berlin surgeon Bergmann repeated Magendie's experiments in human meningocele/spina bifida, observing the fontanelle following the emptying of the cele. Increasing the pressure resulted in 'coma', and if done too fast, in convulsions (Kocher, 1901).

Gowers also referred to experiments on 'coma'. He wrote about the mechanism of apoplexy, referring to experiments in dogs, in which pressure on the brain surface caused unconsciousness. This explained the symptoms in large haemorrhages, but not in small or cases of apoplexy caused by 'the sudden closure of a large vessel'. The common mechanism, he reasoned, should be arrest of function in the cortex, 'inhibition in current phraseology, by the irritation of the sudden lesion'. The amount of haemorrhage and the rapidity both play a role (Gowers, 1888).

One of the best reviews of experimental coma is Theodore Kocher's book on cerebral concussion, cerebral pressure and surgical procedures in cerebral disease (Kocher, 1901). As the terms commotion and concussion will appear several times in this section, in particular to compare the experimental and clinical situation, a short discussion on the history of these terms is justified. Concussion has been referred to both a clinical state and to the event that bring about that state. It was already found in translations of the Hippocratic corpus, but it was not clear what exactly was meant. Rhazes (850–923) is mentioned as the first to use it in the modern sense, meaning an abnormal physiological state. Lanfrancus (b. 1306) mentioned symptoms following a concussive injury that could disappear rapidly. He explained this by a transient paralysis of cerebral function, thought to be caused by the brain being shaken, thereby introducing the concept commotion. Berengarius da Carpi (c. 1460-c. 1530) postulated that the condition was caused by the thrust of the brain against the skull. Ambroise Paré (1509–90) is usually referred to have discussed both terms. A variety of theories emerged during the subsequent centuries, including the discovery of the petechial haemorrhagic lesions in severe injury (McCrory and Berkovic, 2001).

In the introduction of his book, Kocher (1901) pointed to the difficulty to exactly distinguish compression, concussion and commotion. He argued that an exact distinction could rarely be made. The use of the terms depended on the characteristics of the impact on the brain, being forceful or weak, sudden or slow, massive or circumscribed. Furthermore, the duration of the loss of consciousness should be considered. The term concussion was used with sudden, more circumscribed injury, resulting in localized hemorrhagic brain lesions, whereas commotion was associated with sudden, more massive injury, not leading to localized lesions, although microscopic lesions could be found. From the clinical point of view, the most important or 'pathognomonische' symptom of commotion was sudden loss of consciousness at the moment of injury. The duration of the loss of consciousness determined whether the commotion was complicated by concussion and compression or not (Kocher, 1901, p. 1–4 and 285–7).

Although several scientists had worked on the subject before, Kocher praised the experiments by 'Cushing from Baltimore', in Kronecker's lab [Kronecker was physiologist at the same university in Berne; Cushing continued it for a while in the laboratory of the Italian physiologist Angelo Mosso (1846–1910) in Turin]. To increase intracranial pressure (ICP), he used mercury rubber bags extradurally as well as subdural or subarachnoid injections of a salt solution. In particular, by the latter method, he found the well-known relationship between increasing ICP and blood pressure. In a chapter on symptomatology, Kocher emphasized the distinction between pressure and toxic effects leading to 'coma'. He tried to find the localization responsible for disorders of consciousness. He noted that the cause was not always found in the cerebral convolutions. Focal lesions of parts of the brain could also be the cause of disorders of consciousness, referring to experiments by several German and English authors. The cerebral cortex was supposed to play an important part, although he realized that acute damage of one hemisphere did not result in 'coma'. Like many physicians, including Trousseau, before him, Kocher was impressed by the temporary coma in commotion and he reviewed experiments by Kussmaul and Tenner inducing cerebral 'anaemia' by artery ligation that resulted in temporary coma. He also mentioned Duret's and other's experiments with respect to *Choc cephalorachidien* applying sudden injections within the skull. They held lesions of the aqueduct and fourth ventricle wall, caused by a forceful rise in CSF pressure augmented by a Bernoulli effect, responsible for commotion, but Kocher observed damage in these structures without commotion. Therefore, the previous belief of having solved the enigma of *commotio cerebri* by Duret's experiments was not justified. Duret's experiments and surgical observations on *contre-coupe* lesions learned that loss of consciousness only resulted, when a certain number of neural cortical elements at a certain site were damaged (Kocher, 1901, pp. 306–9).

Whereas the Berlin surgeon Bergmann opined that loss of consciousness was caused by disturbance of function of the whole cerebral cortex, Kocher did not agree and gave several arguments including the fact that we dream while we sleep and can remember dreams after awakening. So, in fact he was discussing localization. He believed part of the cortex was damaged in commotion, the part that is in contact with the skull base. He reasoned that loss of consciousness was independent from the bulbar centres (respiration, circulation and vasomotion) (Kocher, 1901, p. 325).

Finally, he concluded that commotion should be ranked between concussion and compression, because compression results in circulatory disorders and concussion in macroscopic disturbances of the brain substance with extravasation of blood. With respect to the cause, it is important that in commotion the pressure increases much faster than in compression: 'Not even a more powerful gradual pressure may bring about what a thrust may' (Kocher, 1901, p. 367). Both Dejerine (1914) and (Lewandowsky, 1910; Braun and Lewandowsky, 1912) referred to Duret's experiments, whereas Lewandowsky and Bouwman and Brouwer (Kock, 1930 also mentioned Kocher's work and review. This short overview on experimental coma also shows, as was recently demonstrated (Fodstad *et al*., 2006), that Cushing was not the only person to experiment on ICP.

Treatment in the early 20th century

Knowledge from these experiments provided new treatment methods. In a chapter on the treatment of increased ICP, Kocher wrote that artificial respiration, autotransfusion and trepanation were the capital means to prevent mortal danger in cerebral commotion. With respect to trepanation, he stated: 'If there is no CSF pressure, but brain pressure does exist, pressure relief must be achieved by opening the skull. Relief of pressure by trepanation is clearly indicated in all cases of brain pressure' (Kocher, 1901, p. 262). He warned ('a formal contraindication') against blood pressure decreasing measures, including bleeding (Kocher, 1901, p. 259). Elevating blood pressure could be indicated and he explained which methods could be used to obtain the effect, including (i) artificial respiration, as he had found that it was impossible to kill an animal by increasing cerebral pressure when applying artificial respiration (Kochler, 1901, p. 260); (ii) increasing the filling of the heart by positioning the patient or compression of the abdomen, or by infusion of salt solution and (iii) by drugs, including atropine, strychnine, etc.

With respect to traumatic coma and treatment in the 1930s, Otto Marburg's overview is illustrating. In Bumke's and Foerster's 18-volume *Handbuch* (1935–7), he summarized the current theories on traumatic commotion in four groups, (i)'Erschütterungtheorie', or impact theory, in which, even without vascular explanation the different 'swing' ability of the bone, grey and white matter may lead to damage, among others at the border between the grey and white matter or at the level of synapses ('Asynapsie' of Henschen); (ii) theories referring to sudden CSF flows (Duret, e.g. see above); (iii) theories based on vascular changes, including Cushing's work on increasing intracerebral pressure in relation to blood pressure and (iv) theories concentrating on the matter of the brain itself, in which a sudden increase of ICP by compression of the brain is supposed. All four theories were discussed and the author believed the reality must be a combination of factors.

With respect to treatment, Marburg mentioned the two most important issues to consider were the increased pressure and regulation of circulation and respiration. Drugs to be used in case of decreased blood pressure included atropine, strychnine, ergotin, ephedrine and caffeine. If ICP was too high, hypertonic salt or glucose was advised. Osmotherapy, however, also had its adversaries. Likewise, lumbar puncture had its advocates and opponents. Trepanation was advised in severe cases. Headache was sometimes treated by exchanging CSF for air by lumbar puncture (referring to Penfield and others). Marburg had observed good results from treating the skull with X-rays in post-commotion complaints (Marburg, 1936).

The discovery of the ascending reticular activating system (ARAS)

We have seen the problems Kocher experienced localizing the lesion responsible for coma. Discoveries during the subsequent 50 years provided more insight, in particular the discovery of the function of the brainstem reticular formation. The structure had been largely neglected by early anatomists. During late 19th and early 20th centuries, more attention was paid to spinal reflexes and cerebral localization than to the brainstem. Ramón y Cajal devoted only 10 pages of his large book to the reticular formation (Ramón y Cajal, 1909, p. 949–59; Marshall and Magoun, 1998, p. 249–78). Following studies by Adolf Spiegel on decerebrate rigidity disappearing after transsection of the reticular formation (Spiegel and Bernis, 1925) and subsequent investigations on tonic posture control, the formation gradually gained more attention. The confluence of EEG, invented by Hans Berger in 1929, and stereotaxis (Horsley and Clarke, 1908), coupled with classic histological verification, provided Horace Winchell Magoun and Giuseppe Moruzzi with objective tools to investigate brainstem stimulation in anaesthetized cats. Low-frequency stimulation resulted in a flattened EEG pattern, resembling that of an alerted animal. They found that this 'system of ascending reticular relays' had an effect 'generally upon the cortex' (Morruzzi and Magoun, 1949; Marshall and Magoun, 1998, p. 249–78). Magoun later explained that classical ascending sensory pathways 'contribute polysensory excitation to parallel ascending nonspecific connections . . . . The functions served by these specific and nonspecific cortical input channels are supplementary. The specific one conveys the informational content of the afferent message . . . , the core system . . . provides instead for behavioral and EEG arousal underlying an orientation and attention to the message' (quoted by Marshall and Magoun, 1998, p. 249–78). Although the discovery of the ARAS was not immediately accepted by all investigators involved in the field, it gradually gained more importance in understanding clinical conditions.

Concluding remarks

Probably because of specialization in medicine in the second half of the 19th century, the understanding of the relationship between coma and ICP, the neurosurgical possibilities to treat this and the increasing knowledge on coma made neurologists more aware of the importance of examining comatose patients. Gradually, the subject 'coma' became the subject of special chapters in neurological textbooks starting in the 1940s. Biemond's *Brain diseases* (1946) was among the first books in which a chapter was dedicated to the clinical examination and differential diagnosis of 'coma'. Biemond described the systematic examination of the 'comatose' patient. Except for the well-known phenomena on observation and examination described above, he mentioned the absence of nystagmus, emphasized the examination of brainstem reflexes, including the vestibulo-ocular reflexes and caloric stimulation tests (Biemond, 1946). DeJong's *The neurological examination* (1950) included a separate chapter describing the level of 'coma' (mentioning the nebulous term semi-coma as a 'state of partial or relative loss of response to the environment in which the patient's consciousness may be impaired in varying degrees'). Details on cranial nerve examination emphasizing the value of eye signs in localization and a comprehensive section on differential diagnosis is present. Neurological findings in 'comatose' patients due to a variety of disorders were described with considerable detail, including changes during worsening of 'coma'. How 'coma' could occur was briefly mentioned and specific localizations (thalamus and hypothalamus) were suggested, but he concluded that 'there is no incontrovertible evidence, however, that one site is essential and consciousness is probably a function of the entire organism'.

In the third edition of *Brain diseases* (1961), Biemond added a paragraph on the pathophysiology, referring to the 1957 International Neurology Congress (Brussels) and to Magoun's work (1952) on the brainstem reticular activating system, described above, that finally explained why large cortical lesions were not accompanied by loss of consciousness, whereas small brainstem lesions were (Biemond, 1946; Morruzzi and Magoun, 1949; Magoun, 1952). Despite these first chapters in neurological textbooks, Fisher, in a presentation for the Medical College of Georgia (1960), stated that in 'human coma cases . . . details of the neurologic examination are almost totally lacking' (Fisher, 1969, p. 5).

We have demonstrated that although systematic neurological examination indeed was rarely performed prior to the 1960s, important observations on comatose patients had been made. The understanding of the phenomenon coma and the experiments on ICP in the late 19th and early 20th century, the effects of neurosurgical decompression, together with the discovery of the ascending reticular activating system in the 1940s and 1950s gave an important impetus to the field. The teaching of the neurological examination in coma became a regular part of textbooks in separate chapters. Continuing on the foundations of ICP research and neuroanatomical discoveries, Fisher, Plum and Posner were able to sort through the melange of unrelated signs and recognize certain patterns. Their monographs placed coma at the forefront of clinical signs.

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