Fixed and dilated: the history of a classic pupil abnormality

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The aim of this study was to investigate the development of ideas about the nature and mechanism of the fixed dilated pupil, paying particular attention to experimental conditions and clinical observations in the 19th century. Starting from Kocher’s standard review in 1901, the authors studied German, English, and French texts for historical information. Medical and neurological textbooks from the 19th and 20th centuries were reviewed to investigate when and how this information percolated through neurological and neurosurgical practices. Cooper experimented with intracranial pressure (ICP) in a dog in the 1830s, but did not mention the pupils. He described dilated pupils in clinical cases without referring to the effect of light. Bright demonstrated to have some knowledge of the pupil sign (clinical observations). Realizing the unreliability of the pupil sign, Hutchinson in 1867–1868 tried to reason in which cases trepanation would be advisable. Von Leyden’s 1866 animal experiments, in which he increased CSF volume by injecting protein solutions intracranially, was the first observation in which the association between fixed dilated pupils and increased ICP was established. Along with bradycardia and motor and respiratory effects, he noticed wide pupils were usually present in a comatose state. Asymmetrical dilation could not always be attributed to increased ICP, but to an oculomotor nerve lesion. Pagenstecher in 1871 extended knowledge by meticulously studying consecutive pupil phenomena with increasing pressure. In 1880, von Bergmann emphasized the significance of the ipsilateral dilation in experiments as well as in clinical cases. He distinguished the extent of pressure increase and its duration. Probably confusing irritation (epileptic head turning to the other side with pupil dilation) and lesion effects, he suggested a cortical area responsible for oculomotor phenomena, indicating what is now known as the frontal eye field. Naunyn and Schreiber (1881) understood the relationship between increased ICP with pupil dilation and decreased pulse frequency and blood pressure, warning not to decrease the latter. Concentrating on experimental traumatic effects, Duret (1878) investigated compression and commotion, in which he distinguished two phases, notably pupil constriction by bulbar lesions, due to CSF shock, followed by dilation from congestion and inflammation, due to blood around the oculomotor nerve. The key observation of a fixed dilated pupil as a sign of acute mass effect came gradually and after some localization stumbles. Following the period of extensive experimental research in ICP, the results of which were translated to clinical observations, the prognostic significance was gradually acknowledged by authors of neurological textbooks. It is well known that Cushing did similar experiments in Berne (1900–1901), and later suggested he would not have done so if he had studied the literature.

KEY WORDS history of medicine; pupil; dilated; clinical; experimental; coma; intracranial pressure

ABBREVIATION ICP = intracranial pressure.


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understood and speculatively explained, and the notorious pupil sign (fixed and dilated) is not as robust prognostically as was initially assumed.

In a previous paper in which we studied the historical aspects of coma, we only superficially touched upon the aspect of the fixed dilated pupil. In the present study, we investigate the history of ideas about the fixed dilated pupil, in which we shall pay particular attention to the 19th century. Clinical observations as well as experimental conditions are presented.

**Literature Review**

Our starting point was Kocher’s standard review in 1901 that contains a wealth of references on traumatic brain injury (clinical as well as experimental) and spontaneous mass lesions (in translation: “Brain concussion, brain pressure and surgical procedures in brain diseases”). Working from the references found in this review, we noticed a sufficient coverage of the topic in German, English, and French texts, although some of the references directed our attention to additional publications that were also consulted. We chose to describe the studies per country (combining the German-speaking countries) rather than chronologically, although cross-references between some publications were found. We translated French and German quotations into English where applicable. We did not include Cushing’s work with Kocher and Kronecker in 1901–1902 in Berne, because this research was conducted in the early 20th century and has been described several times elsewhere. Moreover, Cushing was more interested in circulation, intracranial pressure (ICP), respiration, pulse, and blood pressure than in pupil changes.

Medical and neurological textbooks from the 19th and 20th centuries were studied to determine when and how this information percolated through neurological and neurosurgical practices. We selected a representative list of books in English, French, and German from two standard books, notably Garrison’s History of Neurology and the “Diseases of the nervous system” section in Morton’s Medical Bibliography, and consulted several other standard texts.

**Early German Experimental Studies**

The work of a number of prominent German clinicians in the 19th century is presented here. They were aware of each other’s experiments and often refuted or confirmed observations.

**Von Leyden’s Experiments (1866)**

In his authoritative book on cerebral trauma and experimental coma, the Swiss surgeon Theodor Kocher (1841–1917) mentioned Ernst von Leyden’s (1832–1910; Fig. 1) 1866 paper on the physiology and pathology of the brain among the key references with respect to the study of ICP. Von Leyden, at the time working in Königsberg (later a professor in Strasbourg and Berlin), was particularly interested in “brain pressure and brain movements,” which was the subtitle of the paper. In his famous experiments on pathological cerebral pressure under morphine narcissis, he increased CSF volume by injecting protein solutions up to a pressure of 180–900 mm Hg. Blood pressure was not measured, even though the German physiologist Carl Ludwig (1816–1895) was already working with invasive procedures using his kymograph that he invented in the 1840s. Von Leyden observed a diminution of the pulse frequency that could be prevented by sectioning of the vagus nerves. When the pressure was decreased again, functions returned. Von Leyden summarized the changes he found in increased ICP, which we list in Table 1. Von Leyden was probably the first investigator to observe dilated pupils by experimentally raising ICP. Equally important, he also noted that the cornea became insensitive to touch. With increasing pressure the pupils first became narrow, followed by dilation. He noticed that the dilation was not always symmetric, and it was the only pressure symptom that showed a difference between both sides. In experiment no. VII, for instance, he mentioned that the pupil on the left was dilated maximally, and on the right constricted. He explained this by supposing that, “it is not impossible that the distribution of the pressure within the skull does not occur equally.” He realized that “the symptoms of the visual system discussed here belong to the most important diagnostics for the brain. Enlargement of the pupils should be considered a sign of considerably increased brain pressure.” He deduced that asymmetrical dilation could not always be attributed to increased...
### TABLE 1. Summary of von Leyden's experimental findings in increased ICP*

<table>
<thead>
<tr>
<th>Finding</th>
<th>ICP (mm Hg)</th>
<th>Cause</th>
<th>Conclusion</th>
<th>Notes</th>
<th>Additional Observations</th>
<th>Analogy in Humans†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>&gt;50</td>
<td>Dura mater compression</td>
<td>Headache as symptom of increased pressure</td>
<td>Depending on the depth of morphine narcosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in consciousness</td>
<td>&gt;130</td>
<td>Diminution to complete coma</td>
<td>Observation limited by morphine</td>
<td>Corneal insensitive to touch/pain in deep coma</td>
<td>More variability in humans, including delirium, diminution of intelligence</td>
<td></td>
</tr>
<tr>
<td>Cramps</td>
<td>&gt;120</td>
<td>No paresis</td>
<td></td>
<td></td>
<td>Opisthotonus; stretching of hind limbs</td>
<td></td>
</tr>
<tr>
<td>Senses, pupil enlargement</td>
<td>&gt;130</td>
<td>Sometimes by local third nerve affection</td>
<td>Asymmetrical due to unequal pressure w/ skull†</td>
<td>After cramps, in coma; sometimes nystagmus-like movements</td>
<td>Not always symmetrical &amp; then possibly by local affection of third cranial nerve</td>
<td>Most important diagnostic sign for increased pressure</td>
</tr>
<tr>
<td>Circulation, decreasing (&amp; then increasing) pulse frequency</td>
<td>&gt;70–90</td>
<td>Vagus excitation (&amp; then loss of function)</td>
<td>No decrease in case of vagus nerve transection</td>
<td>Increasing pulse fluctuations by intracranial arterial compression in diastole</td>
<td>Pulsating headache in meningitis due to fluctuations</td>
<td></td>
</tr>
<tr>
<td>Respiration: irregular, to deep, to very irregular, to long apneas</td>
<td>Increasing</td>
<td>Death due to “paralysis of respiratory centre”</td>
<td>Cardiac arrest because of anoxia</td>
<td>Animal would not die by increased pressure in case of artificial respiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive tract</td>
<td></td>
<td></td>
<td>Vomiting rare, defecation sometimes</td>
<td></td>
<td>In contrast to humans</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td></td>
<td>No incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Von Leyden mentions meningitis and brain tumor as examples of human conditions in which ICP is increased. He added that it is not always clear whether symptoms are due to general action of increased ICP or to local affections, as in the case of asymmetrical pupillary enlargement.†

† Von Leyden wondered whether this would be the explanation of unilateral dilation.
ICP, but rather to an oculomotor nerve lesion. In the discussion he also added that the phenomenon was usually associated with coma.

Pagenstecher’s Experiments (1871)

In his Experimente und Studien über Gehirndruck published in 1871, Friedrich Pagenstecher, a surgeon in Heidelberg, criticized von Leyden by stating: “About the pupil phenomena in brain pressure, we learn very little from Leyden’s studies.” Pagenstecher referred to the clinical description of Jonathan Hutchinson (1867–1868, see below). From his experiments, Pagenstecher concluded that pupil phenomena were not observed in cases without greatly increased brain pressure. Along with the other symptoms that become more severe, the following pupil symptoms were observed: 1) moderate constriction of the pupil on the operated side, only of short duration; 2) equal constriction of both pupils, usually of short duration and once for 5 hours; 3) dilation of the pupil on the operated side up to almost disappearance of the iris; and 4) equal dilation of both pupils up to the maximum. Symptoms 2–4 were always accompanied by sopor and coma. During convulsions, symptom 4 was always present. The wide pupil was always fixed to light. Pagenstecher could not explain the early pupil constriction, which remained unexplained (Fig. 2).

Von Bergmann’s Experiments and Clinical Cases

The German surgeon Ernst von Bergmann (1836–1907) provided additional information in his large tome on head injuries. He mentioned fixed dilated pupils in cerebral trauma as well as in experiments. One of the methods he applied to increase the pressure was described as follows:

... we observed that blood injected into the carotid with a pressure of 500 mm was able to flow into the skull cavity freely, as was shown by the simultaneous increase of the flow velocity in the veins. In contrast, I obtained, in other cases, in which I put defibrinized blood in both carotids of a dog under 800 to 1000 mm, during the injection, stertorous breathing, deceleration of the pulse and pupillary dilation.

Von Bergmann often correlated the results from the experiments with clinical observations. He noticed differences between the left and right pupil in a way that the ipsilateral pupil became narrower at first and then, with increased pressure leading to coma, wider than the contralateral pupil. He compared it with clinical situations, writing about “a patient whom I trepanned for a subdural abscess, and in which this symptom only pointed to a localized disorder. In a similar way, Hutchinson ... found pupillary dilatation on the side at which autopsy demonstrated a hemorrhage between dura and bone.” He also emphasized its duration, i.e., short duration with all “pressure symptoms” may be reversible. With respect to prognosis, he stated that, “only deep coma with absolute muscle paralysis and insensitivity for all stimuli, with pupillary dilation and irregular deep respiration, almost always results in death.”

With respect to human cases, he provided several case descriptions (including those from colleagues and from the medical literature) and the effects of trepanation. Among the cases, we recognize an epidural hematoma with ipsilateral pupil dilation and contralateral paresis cured by trepanation. Partial oculomotor nerve lesions are mentioned ipsilaterally as well as contralaterally. He explained the latter from a probable central cortical cause, but only if it was a small lesion, and reasoned that in more profound hemisphere contusions it would have another explanation. Interestingly, he applied the recent cortical localization theory to explain certain types of oculomotor lesions. Referring to Charcot, Pitres, Ferrier, Hitiz, and several others, von Bergmann suggested that the frontal eye field not only served conjugated gaze reactions (Fig. 3): “Approximately at 1 the areas are situated from which the oculomotor will be affected (elevation of the upper lids, movement of the ball, dilation of the pupils, turning of the head to the contralateral side).” Most probably, he was confused between the general effects of epileptic phenomena (including sympathetic widening of the eyes and pupil dilation) by local irritation and the effects of oculomotor nerve lesions. He demonstrated the suggestion with a clinical case including postmortem findings of frontal lobe lesions. In another case, von Bergmann was confused about the localization of an oculomotor lesion in a case of traumatic basilar meningitis, supposing that usually cranial nerves are resistant against loss of function.

Naunyn, Schreiber, and Falkenheim’s Experiments

Working in Königsberg (in Prussia), where von Leyden had performed his experiments about 15 years previously, Bernard Naunyn (1839–1925) and Julius Schreiber (1848–1932) in 1881 published their experiments in 170 pages, of which more than 50 comprise pressure curves and another 50 comprise tables, describing intracerebral and carotid pressure as well as pulse and respiration. They concluded that with increased ICP, blood pressure should not be decreased (as by bleeding, see below); on the contrary, it should be increased. They mentioned pupillary dilation and referred to von Leyden and Pagenstecher, but also to Henri Duret’s work. Naunyn and Schreiber operated on dogs (under narcosis, using curare and artificial respiration), and used von Leyden’s method to increase the pressure. They did not notice differences between the pupils. Pupil dilation did not always immediately follow after increasing ICP. Sometimes pupil dilation was associated with increased blood pressure. In 1 experiment they repeatedly noticed the association of increased ICP with bradycardia, increased blood pressure, and pupillary dilation, as well as the other way round (if ICP was decreased, bradycardia disappeared, blood pressure returned to normal, and pupils became normal). Interestingly, they concluded that the m. dilatator pupillae (the muscle that dilates the pupil) innervating nerve fibers originated in the medulla oblongata, “thus, from the same part of the central nervous system that plays a main role in the vasomotor innervation” and that “excitation of the medulla oblongata leads simultaneously to contraction of the vessels, i.e. increase of the blood pressure as well as constriction of the pupil dilator and the other way round.”

Six years later in 1887, Bernard Naunyn published a new paper, this time in cooperation with Hugo Falkenheim (1856–1945). In addition to von Leyden’s and von
Bergmann’s experiments, they refer to other authors who were interested in and registered normal subarachnoid pressure, including Axel Key (1832–1901) and Gustaf Retzius (1842–1919), and Heinrich Quincke (1842–1922; see Frederiks and Koehler, 1997). Falkenheim and Nauyn described the production and resorption of CSF, as well as the influence of blood pressure and venous pressure, measured in dogs. They emphasized the term “brain pressure,” defining it as the pathological pressure in the CNS by abnormally increased subarachnoid pressure. They distinguished direct signs (such as pulse deceleration, slow irregular breathing, headache, loss of consciousness, cramps, and pupillary anomalies) from indirect signs (such as papilledema, and general mental and physical weakness). They were able to list approximately the same symptoms and were mainly interested in consciousness, respiration, and vasomotor changes. They only casually mention “anomalies of the pupil movement.”

**Early French Experiments**

Although some early trepanation experiments were conducted early in the 19th century, more serious French ex-
peers had to await the second half of the century. Henri Duret (1849–1921; Fig. 4) in the mid-1870s studied cerebral vasculature and then commenced his experiments with respect to cerebral trauma, culminating in his famous 1878 doctoral thesis that, with the aid of David Ferrier, also appeared in the first volume of Brain.

Duret wished to explain what exactly happened in commotion, compression, and contusion, terms that had been used for some time. One of the most important concepts he introduced was that of “choc céphalo-rachidien” (cephalospinal shock). Therefore, he investigated the effects of blows on the head, of increased ICP, as well as those of damage of the dura mater. Following one of his early 1877 CSF shock experiments in animals (no IV: blow on the forehead), he observed loss of consciousness, tetany, rigidity, stertorous breathing, slow and then increasingly faster breathing, middle-wide pupils, and loss of sensitivity. A few days later the pupils became small and the animal died. Next to hemispheric damage, he also observed congestion in the brainstem: “The existence of hemorrhagic lesions in the superior part of the bulbar base [most probably IV ventricular base], proves that the blows to the skull may have a considerable effect on the bulbus. The bulbar lesions are localized at one of the way-outs of the CSF.” (Fig. 5).

Duret mentioned that these bulbar sites contain the motor nuclei of the eye and facial muscle nerves. He related these pathological findings to what had been observed in similar cases, numerous times, with respect to facial and eye phenomena, including “convulsive dilatation and constriction of the pupils.” Duret’s studies led Kocher to apply the eponym “Duret’s hemorrhages.” Duret named the pathophysiological theory of the “choc du liquide céphalo-rachidien” (CSF shock) and distinguished two phases: 1) the period of the actual shock, including tetany and resolution, and 2) a period of congestive and inflammatory reaction. During this first phase, the pupils contract. This phase may last from seconds to 15 minutes depending on the strength of the blow: “Thus, at the moment of the shock, and during some instants after that, it is probable that not a drop of blood passes through the cerebral vessels.” It is followed by the resolution phase. The muscle contractures disappear gradually. The animal remains comatose for a while, without movement or sensitivity and with rapid respiration. In light “shock” it recovers. In severe “shock” the reactive period starts, i.e., inflammatory reaction. The animal remains somnolent or comatose. Duret explained the first period by reflex contracture, because of the rapid occurrence. He believed that this reflex contracture is caused by a disorder in the brainstem, in particular the restiform bodies (with a high density of sensory fibers in his opinion) injured by the CSF shock. He believed it had been proven that a blow to the skull may be transmitted to the brainstem, which he considered evident because of the lesions of that organ. The lesion of the restiform body was believed to result in a reflex tetany. All muscles were put into motion by the reflexive discharge: muscles of the limbs, trunk, eyes, and pupils. The respiratory arrest was also due to contracture of the diaphragm and respiratory muscles. The phenomena observed in human commotion were explained by this CSF shock.

In another experiment in which epidural wax was inserted, Duret distinguished between the effects of the CSF shock that could be stopped by puncture of the occipitoatlantoid membrane (by which CSF may be removed) leading to recurrence of respiration, and the effects of increased ICP that only disappear after trepanation and removal of the wax leading to disappearance of the coma and the dilated pupils. With repeated blows, he demonstrated pupillary constriction followed by dilation and death. He explained the constriction by the CSF shock (bulbar lesion) and the dilation by the accumulation of blood around the third cranial nerve. The resolution phase of the shock period was explained by vascular disorders, starting with a general spasm of the vascular system followed by spasm of the cerebral vessels. The movements of the brain (the pulsations) also stopped for minutes. For the latter he referred to observations by others, among them von Bergmann, who noted paleness of the brain (from general spasm) and barely visible retinal arteries (from spasm of the cerebral vessels).

Duret compared his “choc céphalo-rachidien” with the apoplectic shock in stroke and extensively referred to the work of his teacher Jean-Martin Charcot (1825–1893): “We lend from the lessons of our savant master professor Charcot, the theory on apoplectic shock as it has formulated in 1869 in the lectures at the Salpêtrière that will
follow.” Although it was already known that hemorrhages exceeding a volume of 40–50 cm\(^3\) would result in coma, that did not explain (initial) coma in smaller hemorrhages.\(^{13}\) “We believe to be able to respond: that in the hemorrhagic ictus and the traumatic shock, the mechanism of the observed phenomena is identical.” Smaller hemorrhages near the ventricles cause a CSF shock that damages the brainstem in a similar way as described in traumatic injuries. In the intracranial hypertension studies, the pressure was increased gradually and therefore, Duret reasoned, hardly any phenomena of CSF shock are observed,\(^{13}\) but sometimes some pupillary constriction is noted. In most experiments attention is given mainly to the effects on the arterial tension and pulse. Before death, wide and dilated pupils were observed in most cases. The dilation of the pupils is attributed to paralysis of the third cranial nerves.\(^{13}\)

Duret was well aware of what was done elsewhere. He reproduced some experiments from the work of Pagenstecher (numbers 32 and 33),\(^{14}\) i.e., those with respect to epidural wax insertion at the right parietal area;\(^{13}\) pupillary dilation was noted, and the iris was hardly visible anymore (in a dog). In the second experiment, the left pupil was enlarged and the right one constricted, with the head turned to the right.\(^{13}\) After some time, both pupils become constricted (soporose). The following days he noted deterioration, changing pupils, and finally wide dilated pupils bilaterally. In experiment 39, wax in combination with oil was injected into the subarachnoid space on the left side, resulting in a dilated left pupil.\(^{13}\) The animal survived a few days and the pupils became constricted bilaterally. Duret compared the slower effects in his subarachnoid experiments with the rapid effects in Pagenstecher’s experiments. Of further note is that Duret proposed that the corneal reflex is an excellent device to measure the degree of compression:\(^{13}\) “An excellent way of measuring the degree of compression, applying a sensible method, is the touch of the cornea... Indeed, the brainstem resists the longest time: it is the ultimum moriens of the nervous centers, following the pittoresque word of our erudite master M. Charcot.”

Duret tried to explain the theory by the extraordinary vascular supply of the vertebrobasilar system by numerous collaterals (“coeur basilaire,” or basilar heart).

**British Experimental and Clinical Contributions**

The British contribution was more clinical than experimental, although similar experiments were reported.

**Cooper’s Experiments**

Pagenstecher and Duret both refer to the English surgeon Sir Astley Cooper (1768–1841),\(^{10}\) who investigated the effect of solid materials on the brain. The reference is found on the indicated page of a chapter on “Fracturen des Schädels” (17th lecture). In the original English text, Cooper described how he trephined a dog, “took out a portion of the bone ... separated the dura mater from the bone” and compressed the dura with his fingers. At first there was no reaction, but upon further compression the animal showed signs of pain, became comatose, and fell.” “I kept him in that state for five or six minutes when, upon removing my finger, he got up, turned round two or three times from giddiness, and walked away apparently little worse for the operation.” An accompanying person noticed slowing of the pulse during the experiment. Pupillary changes were not mentioned in this experiment, but he did refer to dilated pupils in clinical cases in lecture XVI “On injuries of the head”;\(^{9}\) “The pulse, however, is not slow unless the body be at rest: for upon the slightest exertion it becomes exceedingly quick: the pupils are dilated...” However, he does not mention whether they were fixed, and from the circumstances it is not clear whether he is referring to the topic of this paper. He was already distinguishing concussion and compression of the brain, the latter from bone compression, extravasation of blood, or “formation of matter within the skull.”\(^{9}\) In another lecture (XVII) he explained the symptoms of compression:\(^{9}\) “The breathing being stertorous, the pulse slow, and the pupils dilated;...when you then find a patient with the apoplectic stertor, slow pulse, dilated pupils, it will generally happen that the brain is compressed.”

In his Lectures, Cooper described the symptoms of concussion, including coma:\(^{8}\) “the pupils of the eyes are generally natural; but if changed, both are a little dilated; or sometimes one only.” In another case, “a friend of Lord Nelson’s ... [who] fell from his horse,” Cooper noticed that he “was totally insensible; the pupils were dilated.... He was bled from the arm to a considerable extent.” Following a temporary improvement, he deteriorated, “his eyes became nearly insensible to light, though one of his pupils was still contracted ... the other ... dilated and immovable.”\(^{8}\) Dilated pupils are mentioned among symptoms of “compression of the brain” in several other cases in this book.\(^{8}\) He rarely noted whether the pupils, if dilated, reacted to light. In a comatose boy, however, he noted “pupils dilated, but contracted on exposure to light.”\(^{8}\)

**Bright’s and Hutchinson’s Observations**

Richard Bright (1789–1858) mentioned “pupils unequally dilated and contracted” among symptoms of con-
cussion," paying attention to the effect of light. He observed a traumatic case between 1828 and 1831. A 38-year-old man working at "a large wharf below London bridge" fell from a height of 11 or 12 feet. The following day his "language was incoherent and speech scarcely articulate, and he complained of pain in the head." He was bled, and the third day "he is in a state of stupor, but may be roused to answer question." The "muscles of the left side of the face are paralyzed... right pupil dilated." Because of "increasing coma," blood is taken from the temporal artery. He died the sixth day and an autopsy was performed. An epidural hematoma was found. In the discussion of this and other cases, Bright did not seem to note any particularity about the ipsilateral dilation of the pupil. In general "the pupils [are] sometimes contracted, at other times dilated, and acting quite irregularly under the stimulus of light." In another case involving a 20-year-old man with apoplexy, Bright described "pupils dilated, and did not contract when a candle was brought near them... I ordered the temporal artery to be opened..."4

The clinical observations reported by Jonathan Hutchinson (1828–1913) in 1867–1868 resulted in the eponym "Hutchinson pupil," attributed to him first by Jacobsen in 1886, when he described several cases with dilated and unresponsive pupils. From his clinical experience, Hutchinson was aware that "the diagnosis of compression is full of difficulty. On the one hand, compression is frequently suspected when it is not present, and on the other, it is sometimes overlooked when really there."27 He tried to reason in which cases trepanation would be advisable and mentioned 4 types of pathophysiological mechanisms, including epidural blood, arachnoid blood, epidural abscess, and "inflammatory effusions within the arachnoid or into the brain substance." In the first situation, "the patient... becomes insensible; but he is pale, with dilated pupils, a rapid, feeble pulse, and irregular respiration... the patient will probably be dead in an hour." He was aware of the "interval of immunity between the accident and the occurrence of symptoms [which] has been long recognized as the chief indication of a ruptured meningeal artery." He also referred to the fact that "the hemiplegia will be on the opposite side [of the blood-clot], a fixed dilated pupil will, I think, generally be present on the same side..."27 In the "arachnoid cases," where the blood was found under the dura, unequal pupils "will rarely be present" and "the patient... may live longer." Compression in the third and fourth pathophysiological conditions, Hutchinson realized, is very hard to recognize. In 1896, Leonard Hill summarized the literature on experimental observations with respect to increasing cerebral pressure, noticing the effects on the pupils ("constriction of the pupils first on the compressed side, followed by dilation"22), but did not pay attention to the pupils in his own experiments. He also referred to his compatriots Spencer and Horsley (1891), who performed experiments with increased ICP. Although describing the effects on the heart, blood pressure, and respiration, they did not mention the effect on the pupils.

### Appearance of the Fixed and Dilated Pupil in Textbooks

With this smattering of experimental and clinical observations—some more enlightening than others—how were these observations described in neurological textbooks and who could make sense of it all? Table 2 demonstrates that dilated pupils were observed early, but its significance and pathophysiological basis was not always understood. In most neurological textbooks (as described above; earlier in surgical texts) the sign is found in chapters on apoplexy and later, approximately after 1900, also in chapters on cerebral trauma. Dilated pupils were noted earlier than fixed pupils. Pupil dilatation and cortical localization were presented by several authors, including Mills.38 He referred to Ferrier’s centers on the “lateral surface of the brain of a monkey;” “center for lateral movements of the head and eyes with elevation of the eyelids and dilatation of the pupil.” Mills pointed to an area that can now be considered the frontal eye field. Similar descriptions are found in the writings of Ross.48 The phenomena and localization correspond to what von Bergmann (Fig. 3) found, probably indicating sympathetic widening of the eyes and pupil dilatation by local irritation (see above).

Following the period of extensive experimental research in ICP, the prognostic significance of the fixed and dilated pupil was soon recognized by authors of neurological textbooks and its pathophysiological mechanism was sometimes mentioned. Around the turn of the century, many books do and some do not mention dilated pupils and its prognostic significance, such as in apoplexy and trauma. Part of the reason for inclusion or exclusion of this topic may be explained by the type of practice they were writing for (chiefly clinical or outpatient clinic practices). In many books, other signs of coma (such as blood pressure, heart rate, and motor phenomena) were considered more important. In fact, if sections in textbooks on pupils were present, pupillary changes in tabes dorsalis, later recognized to result from neurosyphilis, took much more space.

### Discussion

In his historical review on the subject, Eugene Flamm attributed the first observations to Gersdorff’s Feldbuch der Wundartzney (1517 and many subsequent editions), because woodcuts by Hans Wächtlin suggested a large pupil ipsilateral to the impression fracture, in some cases combined with an abducted eye.18 Although several other signs of severe head injury have been noticed before and after that period, the author stated that, “yet well into the nineteenth century no writer commented on the occurrence of anisocoria in association with a mass lesion. Certainly no one made the association with compression of the third nerve.” One could argue, however, about Robert Whytt's description in 1763 of a 5-year-old boy with fixed pupils, unresponsive to light, who at autopsy had a fluid collection compressing the optic thalamus.51,52 Moreover, Whytt noted “for, as in syncope, apoplexy, or at the moment of death, when the eye is quite insensible to external objects, the pupil is always greatly dilated.”54 One wonders whether he understood the prognostic significance of the sign during his life and it is doubtful whether he comprehended the pathophysiology. Cooper, in the 1830s, only mentioned dilated pupils, without referring to whether they remain fixed on light, which is of particular importance if dilatation is no-
ter is the work of von Bergmann: with respect to the localization of the lesion responsible for pupil dilation, he was confused by the effect of local (frontal) cortical irritation resulting in epileptic phenomena and the effects of oculomotor nerve lesions. In most cases, however, “fixed” was either mentioned or it could be interpreted as such by the combination of other signs, with the present knowledge. Naunyn and Schreiber already noticed the association between increased ICP, pupillary dilation, bradycardia, and increased blood pressure (and the opposite in 1881). Table 2 reviews whether authors mentioned light-fixed pupils and had insight into the pathophysiology of pupillary dilations. Our reading of the literature is that insight into the mechanism of acute pupillary changes originated in the period in which animal experimentation with ICP began. The beginning of the experiments on ICP coincides with the increasing importance of the experimental method in medicine around the mid-19th century, such as the work by Claude Bernard (1813–1878) and Rudolf Virchow (1821–1902). Von Leyden’s 1866 paper appears to be the first in which experimental studies prove the association between fixed dilated pupils and increased ICP. Various methods for increasing intracerebral pressure were used. We chose to discuss experiments and clinical material according to country, although it became obvious that several investigators also referred to papers published in other countries. Remarkably, but not unexpectedly, experiments were mainly conducted in Germany and France, although Hill and Spencer/Horsley performed experiments in this field in England in the last decade of the 19th century. Duret went further than his German colleagues, wishing to investigate commotion as well as compression. He explained the pupillary phenomena by “choc céphalo-rachidien” leading to damage of the superior part of the bulbus (base of the fourth ventricle). He distinguished between a shock phase, during which the pupils constrict, and a congestive/inflammatory phase causing pupillary dilation, which he attributed to paralysis of the third cranial nerves.

With respect to the significance of the fixed dilated pupil during the 19th century, a gradual increase from clinical observation and associations, to experimental explanation and pathophysiological insight, can be demonstrated. Cooper in the 1830s conducted some primitive experimental work, but without mentioning the pupils. He did observe dilation in clinical cases. Bright, around 1830, was only partially aware of its significance and obviously before the period of knowledge of ICP, bled his patients. Hutchinson (1867–1868) was fully aware of the significance of the fixed and dilated pupil, but realized that this sign was not always reliable to lead the surgeon. After the mid-19th century, when the experimental method was fully accepted, von Leyden (1866) was the first to establish experimentally a relation between fixed dilated pupils and increased ICP. If the pupils were asymmetrical, it could be attributed either to increased ICP or to an oculomotor nerve lesion. Paggensteher (1871) extended the knowledge on this subject by painstakingly studying consecutive pupil phenomena with increasing pressure. Duret (1878) was important in the way that he distinguished between traumatic injury and commotion with brainstem lesions from lesions in which ICP was increased; this distinction had

**TABLE 2. Mention of dilated and fixed pupils in early medical and later neurological textbooks**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Pupil Dilation*</th>
<th>Fixed Pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>19th century</td>
<td></td>
<td></td>
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<tr>
<td>Cheyne, 1812</td>
<td>2†</td>
<td>Yes</td>
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<tr>
<td>Rostan, 1823</td>
<td>1 ? (L’oeil fixe, p. 58)</td>
<td>No</td>
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<tr>
<td>Romberg, 1840–1846</td>
<td>No</td>
<td></td>
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<tr>
<td>Trousseau, 1882</td>
<td>No</td>
<td></td>
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<tr>
<td>Ross, 1882</td>
<td>1‡</td>
<td>No</td>
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<tr>
<td>Hammond, 1872</td>
<td>2 Yes</td>
<td></td>
</tr>
<tr>
<td>Charcot, 1890</td>
<td>— No§</td>
<td></td>
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<tr>
<td>Hughlings-Jackson, 1876</td>
<td>No¶</td>
<td></td>
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<tr>
<td>Gowers, 1893</td>
<td>2 Yes</td>
<td></td>
</tr>
<tr>
<td>Osler, 1893</td>
<td>2 Yes</td>
<td></td>
</tr>
<tr>
<td>Dana (in Dercum), 1895</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Keen (in Dercum), 1895</td>
<td>No</td>
<td></td>
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<tr>
<td>Mills, 1898</td>
<td>3** Yes</td>
<td></td>
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<tr>
<td>Church &amp; Peterson, 1899</td>
<td>No</td>
<td></td>
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<tr>
<td>Oppenheim, 1900</td>
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<td></td>
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<tr>
<td>20th century</td>
<td></td>
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<tr>
<td>Starr, 1907</td>
<td>2 Yes</td>
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<tr>
<td>Purves-Stewart, 1908</td>
<td>No</td>
<td></td>
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<tr>
<td>Marie, 191136,39</td>
<td>2 Yes</td>
<td></td>
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<tr>
<td>Dejerine, 1914</td>
<td>2 Yes</td>
<td></td>
</tr>
<tr>
<td>Lewandowsky, 1910</td>
<td>2 Yes†</td>
<td></td>
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<tr>
<td>Jelliffe &amp; White, 1919</td>
<td>No</td>
<td></td>
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<tr>
<td>Bouman &amp; Brouwer, 1930</td>
<td>2 Yes</td>
<td></td>
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<tr>
<td>Jaensch-Essen (in Bumke &amp; Foerster), 1936</td>
<td>2 Yes</td>
<td></td>
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<tr>
<td>Wilson, 1940</td>
<td>2 Yes</td>
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<tr>
<td>Biemond, 1961</td>
<td>2 Yes</td>
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<tr>
<td>Plum &amp; Posner, 1966</td>
<td>3 Yes</td>
<td></td>
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<tr>
<td>Zülch et al., 1974</td>
<td>3 Yes</td>
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</tbody>
</table>

* Classification of understanding pupil dilation: 1 = casual mention, probably without knowledge of prognostic significance; 2 = recognition of prognostic significance; 3 = 2 + understanding the pathophysiology (third nerve compression).
† Cheyne mentions constriction and dilatation; on page 13: “Thus we do not despair until the pupil ceases to contract. With any return of sensibility our hopes rise, and with the diminution of it they are destroyed.”
‡ Dilated and fixed pupil mentioned, e.g., in oculomotor nerve paralysis but not in hemorrhage or coma.
§ We looked in this book on stroke, only brief clinical information, with an emphasis on postmortem; other books are mainly outpatient/nontraumatic patients.
¶ This is not an ordinary textbook; many chapters/papers on epilepsy.
** Mentions “Hutchinson pupil” in “supradural hemorrhage.”
†† Refers to the work of von Leyden, Naunyn, Schreiber, and Falkenheim; only casual mention.

**Commented bilaterally. In several publications, it was not always clear whether investigators just found dilation, or dilation in combination with fixation to light. Pupil dilation could, in some cases, be attributed to sympathetic activation due to pain, fear, or epileptic discharges. An example of the lat-
differing effects on the pupils (constriction and dilation, respectively). The first traumatic injury/comminution was compared with reversible coma in (hemorrhagic) stroke and the latter to larger hemorrhages. The surgeon von Bergmann (1880), in experiments as well as clinical cases, emphasized the significance of the ipsilateral dilation. He delineated the difference between the extent of the pressure increase and its duration. Most probably, he was confused between the general effects of epileptic phenomena (including sympathetic widening of eyes and pupil dilation) by local irritation and the effects of oculomotor nerve lesions. Naunyn and Schreiber (1881) emphasized and understood the relationship between increased ICP, noted by pupil dilation and decreased pulse frequency, and blood pressure. They wrongly explained the relation by localization in the medulla oblongata, but were well aware that blood pressure should not be decreased but increased. The textbooks we studied confirm that, although the authors of textbooks were aware of the prognostic sign, dilation was not always related to fixed dilated pupils and that the pathophysiologival basis of the fixed dilated pupil was not understood for a long time.

When studies on increased ICP are described, papers often start with Cushing’s 1900–1901 experiments in Berlin, and with a few exceptions do not discuss the experimenters described above. In his correspondence to his friend, the Swiss physician Arnold Klebs, Cushing later admitted: "As a matter of fact, when I wrote that paper in Kronecker’s laboratory I had very little chance to study the literature; if I had, I’d probably never have done the work."

The 20th century would bring more insight into the pupillary mechanisms. An important advance came in 1939, when Reid and Cone published their experimental study through trephine holes. In their experiment they could induce and reverse pupillary dilation through manipulation of the ICP. The oculomotor nerves were found to be compressed by the extruded hippocampal gyrus in most cases. Jennett and Stern replicated the experiment in cats. Ropper suggested acute angulation of the third cranial (nucleus level) third cranial nerve damage. Clinicians have resolved and Ropper suggested a bilateral central (at the opposite pupil enlarges with mass effect has also not been

References


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44. Pagenstecher F: Experimente und Studien über Gehirndruck. Heidelberg: Winter, 1871


46. Purves-Stewart J: The Diagnosis of Nervous Diseases, ed 2. London: Arnold, 1908


Author Contributions
Conception and design: both authors. Acquisition of data: Koehler. Analysis and interpretation of data: Koehler. Drafting the article: Koehler. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Koehler. Study supervision: Wijdicks.

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