INCREASING SYSTOLIC AND pulse pressure with bradycardia and respiratory irregularity are signs of increased intracranial pressure, leading to cerebral herniation and fatal brainstem compression. This phenomenon, the vasopressor response, is generally known as the Cushing reflex based on Harvey Cushing’s experimental work in Europe in 1901 and 1902. However, similar experiments had been carried out decades earlier by others, notably Paul Cramer, Ernst von Bergmann, Ernst von Leyden, Georg Althann, Friedrich Jolly, Friedrich Pagenstecher, Henri Duret, Bernard Naunyn, and Julius Schreiber. Cushing initially failed to give credit to the work of these predecessors. Nonetheless, he studied the brain’s reaction to compression more carefully than previous researchers and offered an improved explanation of the pathophysiology of the phenomenon named after him.

KEY WORDS: Cushing reflex, Herniation, Intracranial pressure, Medical history, Vasopressor response

“The man who seeks one thing in life, and but one, May hope to achieve it before life be done; But he who seeks all things, wherever he goes, Only reaps from the hopes which around him he sows A harvest of barren regrets.”

(Lord Lytton, 1831–1891)
one-quarter to one-sixth of the size of the intracranial space. In 1866, Ernst von Leyden in Königsberg recorded ICP in dogs through a trephine opening in the skull with the dura left intact (36). In addition, similar experiments were performed independently and published in 1871 by Georg Althann in Tartu (Dorpat), Estonia (2), by Friedrich Jolly in Würzburg (20), and by Friedrich Pagenstecher in Heidelberg, Germany (Fig. 2) (30). Other physicians involved in the full elucidation of the vasopressor response were Henri Duret in Paris (11) and Bernard Naunyn and Julius Schreiber in Tartu (29). In his 1878 medical dissertation, Duret showed that global ischemia from increased ICP is delayed by increased arterial pressure (11). Three years later, Naunyn and Schreiber wrote that, in the case of an intracranial mass lesion, “the

oppressed brain adapts to the available space by displacement and resorption of cerebrospinal fluid. It is the resorption of the latter which, at the same time, allows the regression of signs of increased brain pressure” (29).

In 1880, von Bergmann published a more extensive work on head injuries, Die Lehre von den Kopfverletzungen, describing in detail the laboratory experiments behind the vasopressor response (Fig. 3) (34). One of the editors was Theodor Kocher. In 1887, when von Bergmann was professor and chairman of surgery at the Charité Hospital in Berlin, he wrote another monograph on the surgical treatment of brain disorders, Die chirurgische Behandlung von Hirnkrankheiten. The following is an excerpt from the third edition, published in 1899:

“The decreased cerebral blood flow following the increase in intracerebral or cerebrospinal fluid pressure, explains the symptoms of increased intracranial pressure. The initial headaches, with or without irritability, are followed by nausea and vomiting, confusion, somnolence and loss of consciousness. The slowing of the pulse is the most reliable sign of increased intracranial pressure. The respiration also slows down and becomes irregular, as in Cheyne-Stoke’s phenomenon. These symptoms are followed by two not less typical; the papilledema and the

---

**FIGURE 1.** Title page of Paul Cramer’s thesis on intracranial pressure. (From, Cramer P: Experimental Studies of Blood Pressure [in German]. Dorpat, Verlag von C Mattiesen, 1873 [6]).

**FIGURE 2.** Friedrich Pagenstecher’s compression pump. (From, Pagenstecher F: Experiments and Studies on Intracranial Pressure [in German]. Heidelberg, Carl Winter’s Universitätsbuchhandlung, 1871 [30]).

**FIGURE 3.** Henri Duret’s description of the vasopressor response. A, pulse; B, injection pressure; C, blood pressure; D, respiration rate. (From, Von Bergmann E: The Surgical Treatment of Brain Disease [in German]. Stuttgart, Verlag von Fedinand Enke, 1880 [34]).
increase in arterial blood pressure. With further increase of the space occupying pathological mass inside the cranial cavity, deep coma follows, the pupils become dilated without reaction to light and the pulse becomes weak and fluttering. The end stage is general circulatory and respiratory paralysis followed by primary respiratory arrest and death. The reduced intracranial perfusion paralyzes the cerebral cortex and stimulates the vagus center and the vasomotor center” (35, pp 111–112).

Cushing’s first reactions to the city of Bern were expressed in a letter to his father postmarked November 5, 1900:

“Bern itself is the most picturesque town I have seen—has an interesting history—was one of the old walled towns of this part of Switzerland and the old gates, the peculiar 17th century architecture, the arcaded streets etc. are curious and interesting. I am starting with German again with some difficulty since I find my trolley wheel from short custom runs easiest on the French wire . . .” (13, p 177)

Soon after his arrival, Cushing asked Kocher for a problem with which to work. Kocher promised one, but treated the young American coldly. After 3 weeks, the impatient Cushing decided to leave Bern and try his luck in Heidelberg (13, 14). He had already talked to Hugo Kronecker (1839–1914), a distinguished professor of physiology and a pioneer in blood pressure studies. Kronecker was impressed by Cushing and told Kocher that he was welcome to do his experiments at the physiological institute. After almost a month in Bern, Cushing finally received a formal proposition, in English, from Kocher:

“1. Will you try, with the aid of Bertels in Kronecker’s laboratory, to decide the question, if in compression of the brain the small veins and capillary vessels are dilated by stasis or compressed? by making an injection during a compression experiment in an animal and without that? Dog or calf would be necessary. That would be an excellent step towards better knowledge.

2. Make 1 or 2 experiments on a calf’s head freshly killed with a solution which would circulate as easily as blood (ask Kronecker what the best liquid would be) and take the pressure in carotids, in sinus long. and transverses, in Vena Jugularis and cerebral pressure according to Hill’s method, to measure the pressure as well as the quantity of liquid floating through a brain in normal state and with artificial compression with a bag of Lysbang. Notice the height of pulsations in the carotid, vena jug. and in cerebral liquor. Professor Guillebeau at the veterinary school would certainly be willing to help you at my recommendation . . .

3. Commotio cerebri. Is there with a commotio cerebri a pouring of blood out of the cranium veins and arteries or not?


The experimental set-up was derived from the work of Leonard Hill in London, who, in 1896, published simultaneous recordings of brain pressure, sinus pressure, cerebrospinal fluid pressure, arterial blood pressure, and venous blood pressure in dogs (19). Cushing used dogs and occasionally cats and monkeys in his experiments (Fig. 4) (4, 7–9). He basically made a large trephine opening medially, opened the dura, and fitted a glass window in the opening in the skull in order to watch the caliber and color of the cortical vessels. Another much smaller opening was made over another part of the cerebrum, cerebellum, or cervical cord with opening of the dura. A metal cannula was screwed into the trephine hole to which an intracranial soft rubber bag was attached. The ICP was raised by filling the rubber bag with mercury. ICP, blood pressure, pulse rate, and respiratory rate were recorded simultaneously. Cushing observed a blanching of the cortical arteries when the ICP increased and an improvement of the cortical anemia when the blood pressure rose. At some point, the animals would die from transforaminal brainstem herniation, rather than transtentorial herniation, because the artificial masses were mostly placed centrally near the vertex. Outside the laboratory, Cushing was soon involved in a variety of social functions with his Swiss hosts and even sported a moustache (Fig. 5).

By the end of March 1901, Cushing left Bern to continue his experiments in the laboratory of one of Kronecker’s former students, Professor Angelo Mosso, in Turin, Italy. With Mosso’s help, Cushing developed new recording methods of the coincidence of blood pressure and degree of ICP in dogs. Instead of raising the ICP by creating an artificial mass, Cushing injected physiological saline into the subarachnoid space, thereby causing a diffuse rise in ICP. The animals died when the arterial
Hospital Bulletin in September 1901 (7, 32). Cushing wrote in his summary:

“As a result of these experiments a simple and definite law may be established, namely, that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vasomotor centre which with great accuracy enables the blood pressure to remain at a point just sufficient to prevent the persistence of an anaemic condition of the bulb, demonstrating that the rise is a conservative act and not one such as is consequent upon a mere reflex sensory irritation” (7, p 93).

Cushing stated in a footnote, “reprinted from the Archives Italiennes de Biologie for 1901” (13, p 187). However, Mosso’s paper never actually appeared abroad and there seems to have been no further exchanges with Mosso after that. Cushing went on to present some of his work in the Mütter Lecture, delivered in Philadelphia in December 1901. The following year, he published a second paper in America on the vasopressor response (9).

When Cushing returned to Bern from Italy in June 1901, Kocher and Kronecker shepherded a longer paper for publication in German, but not before Kocher had tried to write his pupil’s paper himself. The self-assured American immediately reacted to the European custom of the professor writing the pupil’s paper: “I was pretty plain with the Professor and told him he could write the article as his, or if he chose to have me publish it, I shall do all the work which he could correct and alter as much as he chose” (13, p 192).

Cushing had his way and Kocher submitted the translated paper to Bernard Naunyn for publication in his journal (8). Naunyn had published a paper on the vasopressor response in 1881 (29) and was a well known continental clinician (14). He had spent some time with Kocher in Bern in 1871 and they knew each other well (24, 28). He wrote an appendix to the paper indicating his surprise that Cushing was, without attribution, confirming his own findings of 20 years earlier:

“Of course, Mr. Cushing goes far beyond the point we did at that time (just like I would do too) when he considers the rise in blood pressure as a sign of activity of a ‘regulatory mechanism.’ Furthermore, our work might not be without significance, particularly since our results were different on some essential points” (8, pp 806–807).

In his memoirs 25 years later, Naunyn wrote:

“In the meantime the extensive experimental work on intracranial pressure took place by Stapel in Königsberg, which I published in 1881 with Schreiber. My self-confidence increased tremendously when in 1902 Cushing’s work about the same subject appeared. Cushing has under no circumstances added anything new to our results. The fact that he does not mention our work with a single word surprised me, even if it was done with Kocher . . .” (13, p 192; 28).
Nauyn also wrote about Kocher:

“His enormous diligence and the fact that his interest was exclusively focused on professional work led to his great success. However, on various occasions his behavior was such that an approach was impossible. With Kocher we did not experience any delight. He always appeared very strange to me” (25, p 51; 28).

In contrast, Nauyn remembered von Bergmann as a happy person with keen interest in experimental pathology and a truly scientific approach to solving medical problems and alleviating human suffering. He never deviated from the path of seeking the truth, and emphasized the importance of being proud and energetic while remaining truthful, honest, and careful (28).

Cushing had acquired good knowledge of the German language during his stay in Bern. He had actually met with Kocher and von Bergmann at the centennial celebration of the Royal College of Surgeons in London in July 1900, which he mentioned in a letter to his father (1, 13). One would assume that he knew about the works of at least von Bergmann through his mentor Kocher before essentially repeating the experiments performed by von Bergmann and others. Decades later, Cushing referred to the Nauyn episode in a letter to his friend, Arnold Klebs.

“You speak of Nauyn’s uncomplimentary allusion to me in his Erinnerungen and remember that he also spoke about Joslin though I don’t recall whether Joslin was treated more or less kindly than I was. 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. My paper was nothing more than thunder for Kocher’s monograph on Hirnerschütterung for Nothnagel’s Specielle Pathologie and as Kocher at the time had the literature at his fingertips, I should have supposed that he would naturally have checked me up. I find in my reprint which I subsequently went over and abstracted that he had less reason for his protest than I feared he might have. But then, this is all past history and we needn’t go into it” (12, 13, pp 192–193).

Here Cushing refers to the fact that Kocher, in 1901, quoted in detail from Cushing’s original manuscript. In Specielle Pathologie und Therapie, Kocher also reproduced several of Cushing’s illustrations, including three in color, from the experiments in his chapter on brain concussion (“Hirnerschütterung”) (21). Cushing must have known that Kocher was going to use his data (17).

Thus, Cushing’s work on the vasopressor response resulted in five published papers in German and English between 1901 and 1903, four of them authored by Cushing and one by Kocher (7–10, 21). If Cushing had not been so persistent, Kocher may have taken all the credit for his experiments. Cushing did not include any coauthors in his reports on the Cushing reflex, but says in a footnote in his first paper that “I am deeply indebted to Professor Mosso in Turin and to Professor Kronecker in Bern for extending to me the privileges of their laboratories while carrying out these observations” (7, p 290).

Perhaps as a result of Nauyn’s criticism, Cushing mentioned in the Mütter Lecture, without distinction, the names (sometimes misspelled) of a variety of European scientists associated with his research “from a bibliographical standpoint” in the following order: Albrecht von Haller, Astley Cooper, Marie-Jean Pierre Flourens, François Magendie, Axel Key, Gustaf Retzius, Ernst von Leyden, Georg Althann, Adolf Kussmaul, François Franck, Bernard Nauyn, Angelo Mosso, Ernst von Bergmann, Victor Horsley, Albert Adamkiewicz, Leonard Hill, and Theodor Kocher (9). Whereas von Bergmann always referred extensively to other scientists in his monographs, neither Kocher nor Cushing seems to have had any scruples failing to give credit to or to acknowledge the works of others on the vasopressor response. Kocher’s motives in this respect are obscure, whereas Cushing’s actions were undoubtedly self-serving. Interestingly, these two strong personalities had a good and lasting relationship, which was probably based on mutual respect.

Many of Cushing’s ideas about vasomotor defenses against compression, vasomotor exhaustion, shock, low blood pressure, and eventual collapse were soon to be challenged and, ultimately, discarded (4). Even if the ambitious American individualist with a penchant for self-promotion ignored his rivals, his solid achievement was to delineate the brain’s reaction to compression more carefully than previous researchers and offer an improved explanation of the pathophysiology of what is known as the Cushing reflex (16, 17). By adopting a more strictly biophysical approach, Cushing laid the groundwork for our contemporary understanding of ICP (25, 26). In 1904 he stated that the key to better results in all brain operations was “control of the increased tension and consequent disturbance of circulation within the closed box of the skull” (16).

“History, as it lies at the root of all science, is also the first distinct product of man’s spiritual nature; his earliest expression of what can be called Thought.”

(Thomas Carlyle, 1795–1881)

REFERENCES

History of the Cushing Reflex

Both historically and practically, this article is an informative and scholarly effort setting the background and contributory efforts of many workers. But, as the authors point out, it was Cushing’s research that established the clinical significance and the neurophysiology of the concept. Justifiably, the authors conclude that it should properly be called the Cushing reflex. Although I can’t recall when or where Cushing expressed the axiom that said, “...it is often not the person who first conceived the idea, but the person who convinced his colleagues of its utility that gets the credit for it.” Such is the case with the Cushing reflex.

Lycurgus M. Davey
New Haven, Connecticut

The authors present a very interesting analysis of research dealing with what we today call the Cushing reflex. Obviously, it was not totally original with Dr. Cushing’s work that was done when he was in Europe in 1900, and the interaction of previous and subsequent investigations along with Cushing’s is of significant interest. I am sure that our readers will enjoy this expansion of knowledge about what continues to be an interesting and fascinating subject.

Edward R. Laws, Jr.
Charlottesville, Virginia

In this superbly presented history of Cushing’s contribution to elucidation of the reflex that bears his name, the authors have adroitly blended vignettes of the personalities of some of the giants of physiological research in the early years of the 20th century with the quest to understand the cardiovascular effects of increased intracranial pressure.

Robert G. Grossman
Houston, Texas