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Struggling with Imperfect Instruments: A Brief History of Experimental Traumatic Brain Injury

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Most of our knowledge comes from close patient observations and from laboratory experiments we consider worth testing and possibly extrapolating to the clinical setting. Clinical knowledge of traumatic brain injury (TBI) has a long history with a number of major works. Worth remembering is the work of German surgeon Ernst von Bergmann (1836–1907), who was born in Latvia, trained in Russia, and from a prominent family of Prussian lineage and who embraced every societal norm. He is best known for his introduction of aseptic surgery, but he provided major novel information in one of the first extensive works on major brain injuries (*Kopfverletzungen* [1]; Fig. 1). The book stood out as one of the earliest detailed descriptions of anticipated changes in level of alertness after major TBI. Von Bergmann was particularly interested in neurologic localization so he could work efficiently and accurately, and the book has a plethora of examples. As expected, the book covers basal skull fractures, depressed fractures, and treatment of cerebrospinal leaks, but it becomes most relevant in chapter 5, in which he describes in great detail the clinical signs, clinical course, and treatment of intracranial pressure ("*Symptomatologie, Diagnose, Verlauf und Behandlung des Hirndrucks*").

Like so many others before and after him, von Bergmann offered little information about the mechanics of the process. Animal studies afforded better understanding of the mechanism of TBI, and some insight was achieved in the late 1900s and continued into the following century. Earlier observations were either inexplicable (e.g., how repeated blows to the head could kill an animal without any observable head injury) or explained by respiratory arrest alone [2]. The surgeon S.P. Kramer postulated that "The old idea that the symptoms of concussion are produced by the transmission of the blow to the brain in the form of oscillations which disturb the relations of the molecules of the brain must be abandoned" [3]. After his trauma experiments using a falling weight, Kramer concluded that a compressing blow to the head increased intracranial pressure, because force would transmit in different directions. Traditionally, it was thought that this blow, through the conversion to a hydrodynamic force, acted as a crushing power, producing tears and hemorrhages throughout the brain; however, Kramer found no corroborating evidence and concluded that it was a so-called syncopal death "produced by a paralysis of the respiratory centres, the cardiac centres remaining intact. This fatal result may in many cases be prevented by the prompt institution of artificial respiration" [3].

G. Gavin Miller (Department of Physiology and Experimental Medicine of McGill University in Montreal) also confirmed that experimental trauma to the brain could occur without evidence of histologic findings [4]. Derek Denny-Brown and William Ritchie Russell cited Jonathan Hutchinson, who proclaimed in 1877, "lesions are found, it is true, but they are to be regarded, I must repeat, as indications of the violence of the shake, and not as causes of death, nor perhaps even as serious complication," and that vacuous statement became a strong incentive for their experimental study. Their studies (Fig. 2) marked a

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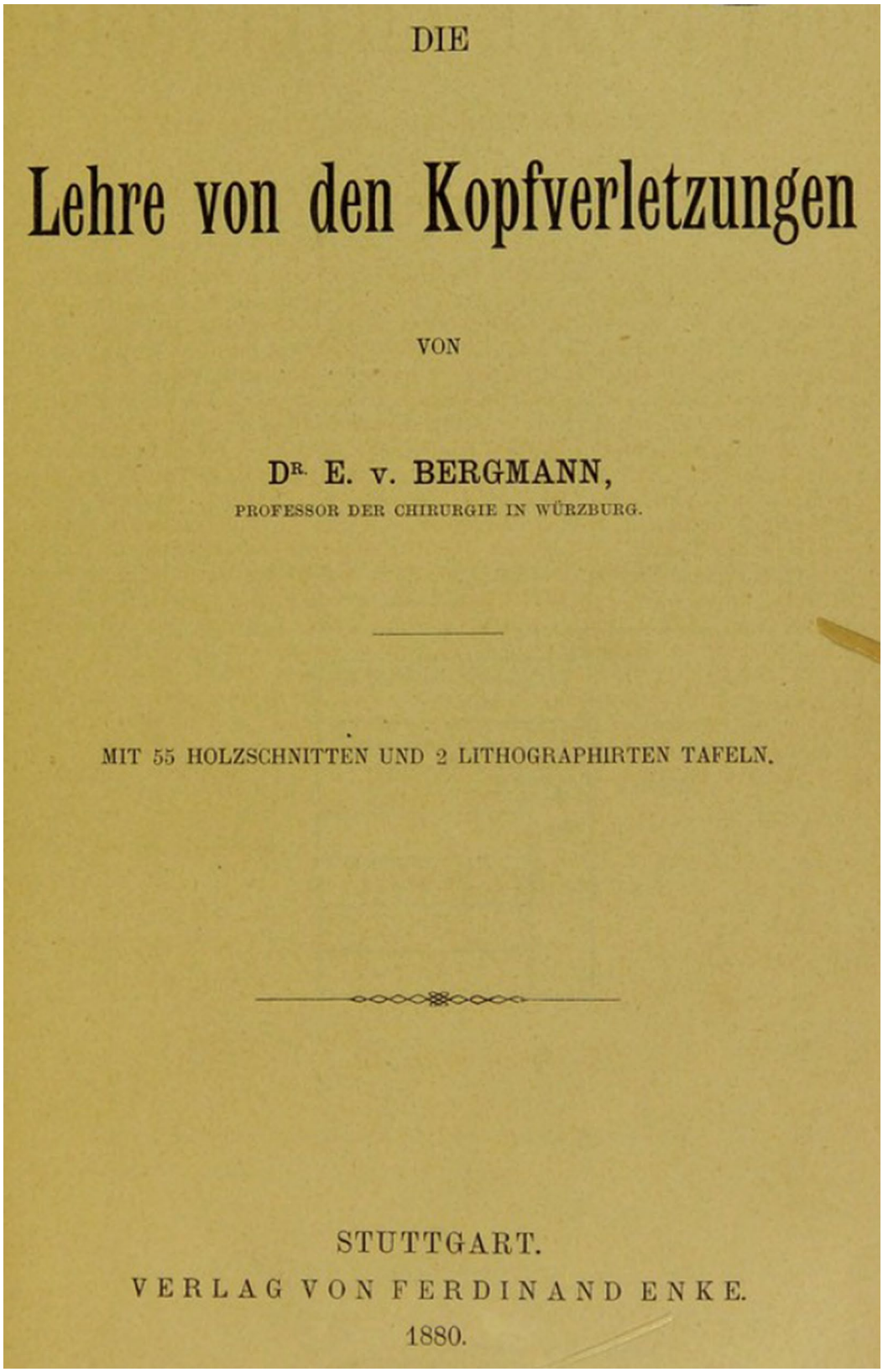

DIE

Lehre von den Kopfverletzungen

VON

Dr. E. v. BERGMANN,

PROFESSOR DER CHIRURGIE IN WÜRZBURG.

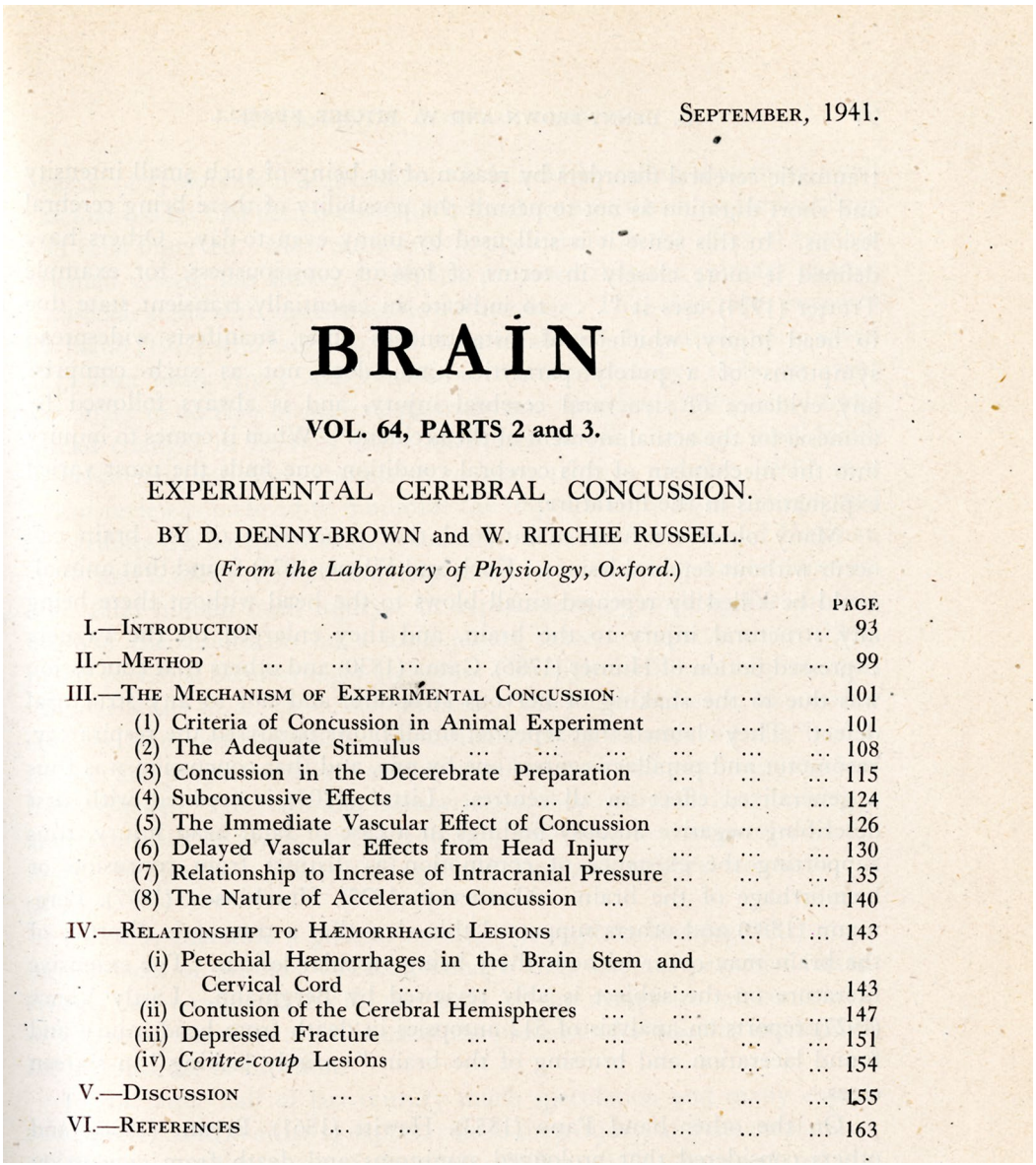
MIT 55 HOLZSCHNITTEN UND 2 LITHOGRAPHIRTEN TAFELN.

STUTTGART.

VERLAG VON FERDINAND ENKE.

1880.

Fig.1 von Bergmann's book on a variety of clinical observations in TBI (Kopfverletzungen)



SEPTEMBER, 1941.

BRAIN

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EXPERIMENTAL CEREBRAL CONCUSSION.

BY D. DENNY-BROWN and W. RITCHIE RUSSELL.

(*From the Laboratory of Physiology, Oxford.*)

Fig. 2 Title page of the experiments by Denny-Brown and Russell

turning point because no prior studies applied systematic elementary mechanics to compute weight, distance, and potential energy of the impact in "gm-cm" units—a unit of measurement equal to the energy exerted, or work done, when a mass of 1 g is raised to a height of 1 cm.

Experimental Cerebral Concussion

Denny-Brown and Ritchie Russell [5] approached experiments in an unique way. In many of their experiments, they sectioned the vagi so that "the blood-pressure curve after concussion then assumed a purer form." They devised a pendulum and calculated the actual speed and momentum for various amplitudes of swing. The head received the velocity of the strike but then was brought to rest after a 2-cm movement using soft padding on a wooden block. They found that a slight blow to the head (in the parieto-occipital region) caused an inspiratory gap, respiratory irregularity, and slowing of the heart rate.

A blow of moderate intensity caused 5-min to 10-min effects but with complete recovery (Fig. 3). Respiration halts for 10 s with gradual recovery. There is a steep rise in blood pressure with gradual decline, an extensor spasm of the limbs with the blow, and a more prolonged

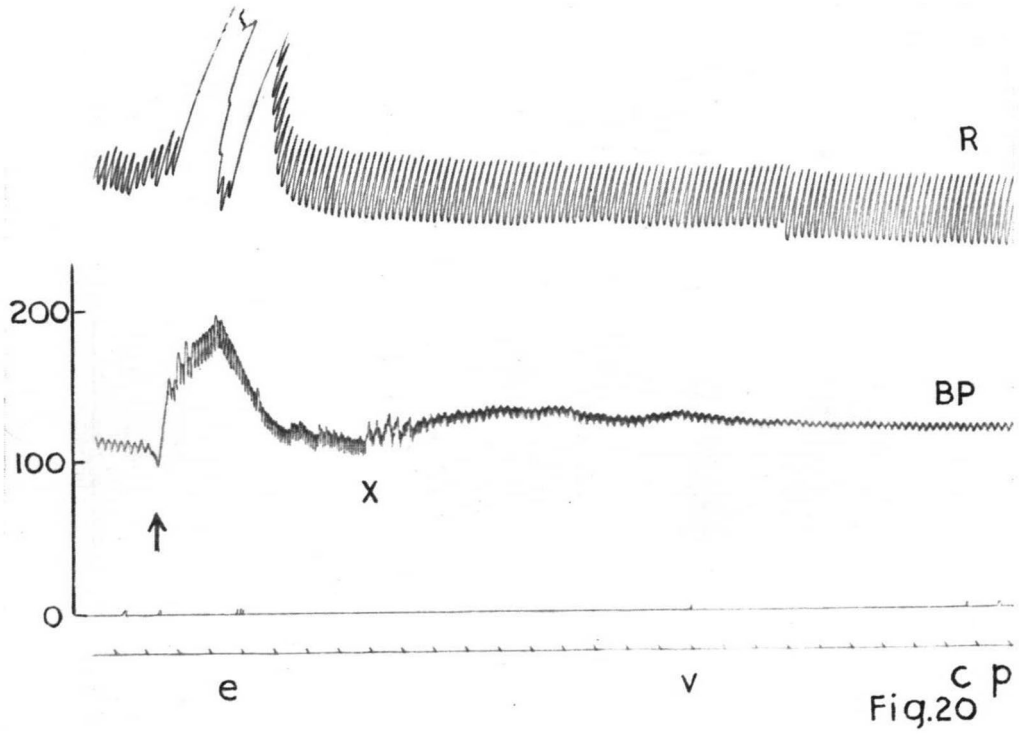

FIG. 20.—Cat, nembutal 0·024 g.p.k. Vagi and right carotid intact. Artificial respiration by pump throughout, and respiration recorded as usual by band around chest. Heavy occipital hammer blow at the arrow. At *e* a spasm of the limbs in extension. At *v* stimulation of the cornea evoked a movement of vibrissæ, at *c* a corneal reflex, and at *p* the pinna reflex returned. Note the return of sinus rhythm at *x*.

Fig. 3 Recordings of a TBI experiment (see text and legend under the figure for a full description)

spasm 12 s later. The corneal reflex disappears for 65 s and then becomes brisk.

Autopsy of the brain revealed a small contusion in the vermis of the cerebellum and around the cervical spinal cord. They concluded that there is a "period of paralysis of the brainstem." The respiratory manifestations start with excitation, reflex paralysis, and complete paralysis. Vagal stimulation produces bradycardia with prominence at a "crest of the rise of blood pressure." Moreover, they explained the pauses in respiration also by vagal stimulation; however, in an animal with sectioned vagi, the respiratory pause still occurred. A rapid peripheral vasoconstriction was interpreted as direct stimulation of the vasomotor center in the medulla.

They countered Henri Duret's theory that a wave of cerebrospinal pressure against the foramen magnum caused contusion. In their experiments, the rise of intracranial pressure with experimental concussion was minimal and unrelated to a rise in systolic pressure, but when a great increase in pressure was produced by injecting fluid or air in the extradural space to a pressure of 100 mm Hg, they discovered the mechanism to be herniation of the medulla and cerebellar vermis into the foramen magnum. Concussions displace tissue, but the rise in intracranial pressure was insufficient to produce that effect. Contrecoup lesions were not seen when the head was fixed at the moment of injury. Their explanation was that "at the degree of acceleration required for their production and the occurrence of concussion the brain, albeit incompressible, suffers appreciable displacement due to inertia or 'fling' even to the point of appearance of a momentary vacuum on the membrane opposite to point struck."

Impact Models in the Twentieth Century

Two studies, Browne et al. [6] and McIntosh et al. [7], led to the redesigning of impact models in compression and acceleration experiments. The lateral fluid percussion model has been the most extensively used and characterized model of experimental TBI. Lateral

fluid percussion–induced injury is created by performing a craniotomy and applying a fluid pressure pulse to the intact dura, which is caused by striking a pendulum against a piston attached to a fluid reservoir, producing displacement and deformation of neural tissue. As such, it does not reproduce the linear and rotational forces that generate concussive injuries clinically; typically, in the real world, an impact to the head leads to rapid acceleration. Models of pure rotational acceleration (without head impact) study the effects of repeated insults to the brain. Closed-head injury models apply force directly onto the intact skull, which causes movement of the unrestricted head, including lateral and rotational forces, as seen in concussive insults. Browne et al. [6] studied the movement of the swine's head circumferential to the brainstem in the coronal plane and transverse to the brainstem in the axial plane and found that both planes of rotational injury resulted in diffuse axonal injury, characterized by widely disseminated multifocal axonal pathological findings throughout the white matter, extending from the frontal lobe to the brainstem.

Ommaya's [8] primate model of head motion, further perfected by Gennarelli et al. [9], became the best characterized model. They placed primates in a helmet connected to a piston that could move the head in a horizontal plane and in a whiplash fashion while standardizing the amount of movement to 60 degrees. Ommaya and Gennarelli postulated that the depth of the structural and functional disconnection determines the severity of impaired consciousness.

Is There a Future for Bench Research?

William Ritchie Russell carefully studied TBI and produced a landmark article about 200 patients in 1932 [10]. In his view of the pathophysiology of diffuse brain dysfunction after head injury, Russell dismissed increased intracranial pressure as an explanation for disturbances of consciousness because increases in cerebrospinal fluid pressure were unrelated to the time interval between the hit and return of consciousness. Russell would go on to develop much more sophisticated ideas in his study with Denny-Brown in 1941 [5]. The physiologic changes from acceleration and compression concussion were similar but differed in degree—compression caused more respiratory effects and fewer cardiovascular effects than acceleration. In addition, compression induced a greater change in intracranial pressure. These differences turned out to be crucial and led to two different methods in TBI research. Nonetheless, irrespective of the type of trauma, distortion and deformation of neuronal tissue are the ultimate results. In addition, and likely for the first time, Denny-Brown and Russell discussed cushioning devices to protect the head from injury: the helmet should be close-fitting, and leverage on the neck must be avoided.

Nonetheless, each of these investigators realized that extrapolation to humans was difficult due to variability of the neuraxis within species and because histologic changes do not necessarily translate to functional impairment.

Animal experiments have been notoriously deficient in predicting the efficacy of human clinical therapies. Improvements in magnetic resonance imaging, pathological studies, and biomarkers, but also studies on ongoing behavioral and cognitive deficits in animals, may change how preclinical work is done [11]. More recently, investigators have employed mouse brain models with detailed 3D vasculature to study the effect of vasculature on brain strains under both diffuse (closed-head impact) and focal injury (through controlled cortical impact loading [11, 12]).

TBI research is diversified because of the many ways in which injury can occur and to what extent. There is closed-head impact, fluid percussion injury, controlled cortical impact, closed-head impact with rotational acceleration, penetrating ballistic-like brain injury, weight-drop, primary blast injury, and captive bolt impact, each producing different degrees of injury and different pathological conditions. Nearly a century after the first studies in the late 1930s, there is still a call for a consortium-based approach and a need to assess therapies in multiple models before introducing them in a clinical trial.

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Ethical approval/informed consent
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