

## BROWN-SÉQUARD'S SPINAL EPILEPSY

by

P. J. KOEHLER \*

In 1850, I found that certain lesions of the spinal cord of mammals are followed, after some weeks, by an epileptiform convulsive disorder.<sup>1</sup>

The experiments which led to the discovery of the crossing sensory pathways in the spinal cord, and made Charles-Édouard Brown-Séquard (1817–1894) famous, established the basis of his theories on the origin of epilepsy. This work is not well-known, but Brown-Séquard's spinal epilepsy remained a clinical entity until the beginning of the twentieth century. He observed that spinal epilepsy could be transmitted to the offspring of animals used in experiments. This artificially induced hereditary epilepsy, although criticized by many, was gratefully accepted by Charles Darwin (1809–1882) and used in his own theories.

In this article I examine the development of Brown-Séquard's ideas on epilepsy against the background of contemporary theories of the disease, the nature of heredity and the way the concept was used by Darwin, and the relationship between the two scientists.

### BROWN-SÉQUARD'S SPINAL EPILEPSY

Three or four weeks after spinal hemisection, "seizures" could be observed in the non-paralysed parts of the body including the face. At times these began spontaneously, at others they were caused by stimuli applied to the skin, ipsilateral on the face, as well as by asphyxia. Within 10 to 30 seconds convulsions would follow in these animals, whereas in healthy ones the asphyxia had to last 90 to 120 seconds before seizures were produced.<sup>2</sup> The first convulsions seen after the spinal lesion was made were located only in the muscles of the face and eyes. After some days the laryngeal muscles, the neck, and chest would also become affected and finally the extremities and trunk. A full description of a convulsion was given by Brown-Séquard:

When the attack begins, the head is drawn first, and sometimes violently, towards the shoulder, by the contraction of the muscles of the neck, on the side of the irritation; the

\* P. J. Koehler, MD, PhD, Department of Neurology, Ziekenhuis De Wever & Gregorius, Postbus 4446, 6401 CX Heerlen, The Netherlands.

Part of this paper was presented at the Third European Meeting on the History of Neurology, Veyrier-du-Lac, Annecy, 23–24 May 1991.

<sup>1</sup> C. E. Brown-Séquard, 'Recherches expérimentales sur la production d'une affection convulsive, épileptiforme, à la suite de lésions de la moelle épinière', *Comptes rendus de l'Académie des Sciences*, 1856, **42**: 86–9, p. 86.

<sup>2</sup> *Ibid.*, p. 87.

mouth is drawn open by the contraction of the muscles of the neck, which are inserted upon the lower jaw, and muscles of the face and eye (particularly the orbicularis) contract violently. All these contractions usually occur simultaneously. Frequently at the same time, or very nearly so, the animal suddenly cries with a peculiar hoarse voice, as if the passage of air were not free through the vocal chords, spasmodically contracted. Then the animal falls, sometimes on the irritated side, sometimes on the other, and then, all the muscles of the trunk and limbs that are not paralyzed become the seat of convulsions, alternate clonic and tonic. The head is alternately drawn upon one or the other side. All the muscles of the neck, eyes and tongue contract alternately. In the limbs, when the convulsions are clonic, there are alternative contractions in the flexor and the extensor muscles. Respiration takes place irregularly, on account of the convulsions of the respiratory muscles. Almost always there is an expulsion of faecal matter, and often urine. Sometimes there is erection of the penis, and even ejaculation of semen.<sup>3</sup>

Brown-Séquard noticed three differences between epilepsy in animals and that in humans:

- (1) Some animals cried out when they were irritated during fits, which suggested they remained conscious. Loss of consciousness was considered to be essential in epilepsy. Brown-Séquard argued that often the animals seemed to be deprived of consciousness. In humans, on the other hand, periods without loss of consciousness had been observed during seizures.
- (2) The animals did not foam at the mouth during a seizure while human beings sometimes did.
- (3) In animals the convulsions lasted two or three minutes, followed by a one- or two-minute period in which they could rise and stand. A new seizure might then occur. In humans these rapidly recurring seizures were rare, but might resemble those in animals.

He drew the following conclusions from these observations:

- (1) Spinal cord injuries might cause an epileptiform affection.
- (2) A relation existed between parts of the spinal cord and branches of some of the nerves of the face and neck.
- (3) Epileptiform convulsions might be caused by slight irritation of certain nerves.
- (4) "Even when an epileptiform affection has its primitive cause in the nervous centres, some cutaneous ramifications of nerves have a power of producing convulsions, which other nerves, even directly connected with them, have not."
- (5) "The cutaneous ramifications of certain nerves may have the power of producing convulsions, while the trunks of the nerves lack this power."<sup>4</sup>

Of course such a discovery must have excited this ambitious physiologist and clinician, since he now had an experimental model of epilepsy. A recent example of such a discovery could be the use of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to produce experimental Parkinson's disease.<sup>5</sup> Brown-Séquard did notice a difference between his artificially produced epilepsy and the real disease.

<sup>3</sup> C. E. Brown-Séquard, *Researches on epilepsy: its artificial production in animals and its etiology, nature and treatment in man*, Boston, Clapp, 1857, pp. 7–8.

<sup>4</sup> *Ibid.*, p. 9.

<sup>5</sup> J. W. Tetrad, J. W. Langston, 'The effect of Deprenyl (selegiline) on the natural history of Parkinson's disease', *Science*, 1989, **245**: 519–22.

### *Brown-Séquard's spinal epilepsy*

This convulsive disorder closely resembles epilepsy. However, I believe it differs from that in the way that if, during the seizure, one pinches the animal, it sometimes yelps.<sup>6</sup>

Although the animal's cries could indicate consciousness, which would not occur in true epilepsy, Brown-Séquard stated that they were involuntary reflexes. "If it is not real epilepsy that I produce by damaging the spinal cord, it is at least an epileptiform affection".<sup>7</sup> The epileptiform condition would belong to that group of convulsive diseases where the cause was sought "outside". Brown-Séquard referred to seizures brought about by an "aura", or a nerve lesion caused by, for example, a tumour.

Brown-Séquard was not the first to relate epilepsy to spinal cord lesions. Early-nineteenth-century concepts of epilepsy followed Marie-Jean-Pierre Flourens' (1794–1867) theory of the non-irritability of the cerebrum and cerebellum. Epilepsy was thought to originate in the medulla oblongata and spinal cord, which were irritable.<sup>8</sup> Flourens' finding was one of the reasons why Brown-Séquard tried to explain the loss of consciousness with a complicated theory of constriction of the blood vessels. "How can convulsions . . . be produced by an organ which has lost its principal function?"<sup>9</sup> This problem of the cerebral lobes was crucial. Marshall Hall (1790–1857), the London physician who turned reflex action from a physiologic phenomenon to a biologic principle,<sup>10</sup> favoured the concept of a spinal and brainstem origin of epilepsy. He upheld a reflex theory of the disease and believed a *central* origin existed in the spinal medulla and medulla oblongata. Diseases acting directly on these centres could cause epilepsy. As well as these central origins he discerned *eccentric* causes involving reflex action, for instance, stimulation of the nerves in the intestines. This kind of epilepsy had been known as "sympathetic" epilepsy.<sup>11</sup> The localization of reflex action in the spinal cord and medulla oblongata makes it clear why epilepsy was also thought to originate there. It could not, however, explain the unconsciousness which was thought to be caused by a disorder of the cerebral hemispheres. Loss of consciousness resulted from vascular engorgement or constriction of the brain. According to Hall, the congestion was caused by "laryngismus", "forcible closure of the larynx and expiratory efforts".<sup>12</sup>

Brown-Séquard had searched for descriptions of cases of epilepsy with spinal cord lesions. He noticed that most pathologic examinations in cases of idiopathic epilepsy had been performed on the brain. In the majority the spinal cord had not been examined, and no abnormalities had been found in the brain.<sup>13</sup> "Such a neglect is a great fault particularly since the publication made by Esquirol" (1772–1840), the French physician and psychiatrist. He had found alterations in the spinal cords or their meninges in nine out of

<sup>6</sup> Brown-Séquard, *op. cit.*, note 1 above, p. 88.

<sup>7</sup> *Ibid.*, p. 88.

<sup>8</sup> M. J. P. Flourens, *Recherches expérimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébrés*, Paris, Crerot, 1824, pp. 13–23.

<sup>9</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 42.

<sup>10</sup> E. Clarke, L. S. Jacyna, *Nineteenth-century origins of neuro-scientific concepts*, Berkeley, University of California Press, 1987, pp. 101–56.

<sup>11</sup> O. Temkin, *The falling sickness*, Baltimore, Johns Hopkins Press, 1971 (2nd ed.), p. 278.

<sup>12</sup> M. Hall, *On the diseases and derangements of the nervous system*, London, H. Baillière, 1841, p. 323; cited by Temkin, *op. cit.*, note 11 above, p. 280.

<sup>13</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 10.

ten epileptics.<sup>14</sup> Among other authors Brown-Séquard referred to Antoine Portal (1742–1832), a French physician, who described a case of epilepsy “with a dilatation of the central canal of the spinal cord, which was filled with water”, obviously one of the first descriptions of syringomyelia. Giovanni Battista Morgagni (1682–1771) had already observed that epilepsy could be “generated” by disease of the spinal cord.<sup>15</sup> In a seventeenth-century case, also noted by Brown-Séquard and originally described by Nicolaes Tulp (1593–1674), the aura originated in the big toe. The patient was cured by the toe being burnt with a red-hot iron.<sup>16</sup> Tulp, a physician working in the Hippocratic tradition, of course interpreted the aura as the place from where bad vapours went to the brain. Treatment with a ligature around the toe and cupping had been unsuccessful in Tulp’s patient.<sup>17</sup>

The frequency of spontaneous seizures in Brown-Séquard’s animals was related to the amount of space they had in their cages. Animals kept in small compartments and supplied with enough food suffered from more seizures than those in the reverse situation. Autopsies of the epileptic animals revealed congestion at the base of the brain and of the Gasserian ganglion on the same side as the spinal cord lesion.<sup>18</sup>

Brown-Séquard concluded in a chapter on epilepsy in his *Course of lectures*, delivered to the Royal College of Surgeons in May 1858, that the spinal cord in animals might be the *cause* (“I do not say the *seat*”) of an epileptic affection.<sup>19</sup> The fits could be produced in humans as well as in animals by an irritation of some part of the skin, and also from a source inside the body.

Brown-Séquard thought that these theories were proved by the fact that the “aura epileptica” could be prevented by several means from reaching the brain. However, the term “aura epileptica” did not have the same meaning as it does now. Brown-Séquard meant by it certain parts of the body, especially the skin, which were involved in the production of epileptic seizures. On another occasion Brown-Séquard explained that there was only one type of aura epileptica, “if we leave to this word the meaning which it has had for centuries, i.e., a local sensation preceding a fit”. Brown-Séquard was referring to the suggestion of Moritz Romberg (1795–1873), the author of one of the first neurological textbooks, that sensory as well as muscular auras existed.<sup>20</sup> Brown-Séquard explained the motor phenomenon as follows: muscular cramp should be considered a reflex of sensory irritation. Thus the *interpretation* of the term “aura epileptica” was different from that today. Brown-Séquard regarded it as a *cause* of a seizure, whereas now it is considered to be an *epiphenomenon*, dependent on the location in the brain where the neurones start to discharge. Brown-Séquard’s theory formed the basis of his therapeutic advice. Brown-Séquard stated that even in idiopathic epilepsy “there may be found an

<sup>14</sup> J. E. D. Esquirol, *Des maladies mentales*, 2 vols, Brussels, J. B. Tircher, 1838, vol. 1, p. 34, cited by Brown-Séquard, *op. cit.*, note 3 above, p. 10.

<sup>15</sup> Brown-Séquard, *op. cit.*, note 3 above, pp. 9–12.

<sup>16</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 21.

<sup>17</sup> N. Tulp, *Observationes medicae*, Leiden, Vivie, 1716 (5th ed.), book 4, case 2. A Dutch physician, anatomist and burgomaster of Amsterdam, Tulp is well-known from Rembrandt’s *Anatomy lesson*.

<sup>18</sup> Brown-Séquard, *op. cit.*, note 1 above, p. 89.

<sup>19</sup> *Course of lectures on the physiology and pathology of the central nervous system*, Philadelphia, Collins, 1860, p. 179.

<sup>20</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 39.

### *Brown-Séquard's spinal epilepsy*

irritation starting from some centripetal nerve, and generating the convulsions".<sup>21</sup> In sympathetic or eccentric epilepsy this location was evident since either the patient felt the aura, or it could be observed. In idiopathic epilepsy an "unfelt irritation" might produce fits. By the term "idiopathic" Brown-Séquard was referring to epilepsy in which no central (as in symptomatic epilepsy) or peripheral (as in sympathetic epilepsy) cause was found. Earlier in the century the term idiopathic epilepsy referred to a cause in the brain itself.<sup>22</sup> In these cases it was important to find where in the body the aura originated, because this would indicate the therapy required. Sometimes it could be found by binding a ligature around a limb just before the seizure. If the convulsion was prevented, the aura probably arose from that limb. In fact, Brown-Séquard thought there was "no radical difference between the symptoms of the sympathetic epilepsy, and those of the pretended [*sic*] idiopathic".<sup>23</sup> Epilepsy was an "increased reflex excitability" of certain parts of the cerebro-spinal axis and a loss of the control that, in normal conditions, "the will possesses over the reflex faculty", "when a wound or any other of the known causes of the sympathetic epilepsy, produces this affection, it does so principally, if not only, by increasing this reflex excitability".<sup>24</sup> The base of the brain, especially the medulla oblongata, was the most frequent seat of increased reflex excitability. Whereas Brown-Séquard recognized a spinal form of epilepsy, the ordinary seat of major epilepsy was in the medulla oblongata.<sup>25</sup> From analogies between experimental epileptic animals and human patients, Brown-Séquard concluded that in humans epilepsy might also be caused by disease of the spinal cord.

... the greatest analogy exists between what we know of the aura epileptica in man and what I have found concerning the property that the skin of the face possesses of producing fits in my animals.<sup>26</sup>

In the animals with experimentally produced spinal cord injuries, Brown-Séquard thought the face to be the starting point of an aura epileptica. In these animals as well as in humans an interruption of nervous transmission between the starting point of the aura and the cerebro-spinal axis, seemed to cure epilepsy. The development of epilepsy in humans was in many cases similar to what took place in his animals: the convulsions at first were limited to a few muscles around the starting point of the aura epileptica; they then extended gradually to many others and at last attacked almost the whole body.<sup>27</sup>

Although Brown-Séquard did not wholly agree with his colleagues' theories, he used parts of them to create a new model for epileptogenesis:

- (1) The increased excito-motory reflex power of Marshall Hall. As already mentioned, Hall explained epilepsy with a reflex theory. His "eccentric epilepsy"

<sup>21</sup> Brown-Séquard, *op. cit.*, note 19 above, p. 180.

<sup>22</sup> The metamorphosis of the concept of idiopathic epilepsy is described by Temkin, *op. cit.*, note 11 above, pp. 285–91.

<sup>23</sup> Brown-Séquard, *op. cit.*, note 19 above, pp. 180–2.

<sup>24</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 35.

<sup>25</sup> Brown-Séquard, *op. cit.*, note 19 above, p. 183.

<sup>26</sup> Brown-Séquard, *op. cit.*, note 3 above, p. 26.

<sup>27</sup> *Ibid.*, p. 27.

was a form of reflex action, the cause of which was at a distance from the nervous centre.<sup>28</sup> It led to secondary changes in the brain accompanied by venous congestion, probably caused by closure of the larynx and expiratory efforts.

- (2) The plethora and anaemia theory of the anatomist and physiologist Jacob Henle (1809–1885): i.e., an increase or decrease in the amount of blood in the vessels at the base of the brain. Henle thought that the loss of consciousness during a seizure was caused by an increase or decrease of blood in the hemispheres. In the plethora form of epilepsy the hemisphere and the base of the brain were congested, whereas in the anaemia form the hemispheres collapsed. The convulsions were thought to be caused by an increased turgor at the base of the brain.<sup>29</sup> A cramp in the muscles of the blood vessels might be the cause of an epileptic attack.<sup>30</sup>
- (3) The humoral theory of Robert Bentley Todd (1809–1860), professor of physiology and pathology at King’s College London. Todd paid attention to “epileptiform” convulsions occurring in patients with uremia and poisoning.<sup>31</sup> He thought that a gradual accumulation of “morbid material” in the blood took place.
- (4) The vasomotor nerve theory of Claude Bernard (1813–1878), and Brown-Séguard himself. This refers to the action of the vasomotor nerves, which Brown-Séguard discovered, parallel with Claude Bernard. In 1852 Bernard had found that section of the cervical sympathetic nerves resulted in paralysis and dilatation of blood vessels in the head.<sup>32</sup> Galvanic stimulation, as Brown-Séguard found out some months before him, resulted in the opposite.<sup>33</sup>

According to Brown-Séguard’s model, in the most common form of epileptic seizures in human beings the following series of events were generated one after another.<sup>34</sup>

- (1) Excitation of certain areas of Hall’s excitomotory part of the nervous system through the peripheral nerves.
- (2) Contraction of the blood vessels of the brain and of the face, spasm of the muscles of the eyes and face, resulting in:
- (3) Loss of consciousness and paleness of the face. Brown-Séguard had shown that the same excitation that produced the first convulsions in muscles of the neck, the eyes, the larynx and the face, also produced contraction of the blood vessels of the “brain proper” (cerebral hemispheres), which was necessarily followed by loss of consciousness. In his *Course of lectures*<sup>35</sup> Brown-Séguard admitted that A. Kussmaul (1822–1902), the physician who among others described a particular

<sup>28</sup> Temkin, op. cit., note 11 above, pp. 278–80.

<sup>29</sup> J. Henle, *Handbuch der rationellen Pathologie*, 2 vols, Braunschweig, F. Vieweg, 1853, vol. 2, part 2, p. 46, cited by Temkin op. cit., note 11 above, pp. 280–1.

<sup>30</sup> *Ibid.*, pp. 48–9.

<sup>31</sup> R. B. Todd, ‘Clinical lecture on a case of renal epilepsy, and on the treatment of epilepsy in general’, *Med. Times Gaz.*, (new series) 1854, 9: 129–31 and 153–66, cited by Temkin, op. cit., note 11 above, p. 312.

<sup>32</sup> C. Bernard, ‘Sur les effets de la section de la portion céphalique du grand sympathique’, *C. r. Soc. Biol.*, 1852, 4: 168–70.

<sup>33</sup> See C. E. Brown-Séguard, *Notices sur les travaux originaux du docteur Brown-Séguard*, Paris, Masson, 1862, p. 657, and P. J. Koehler, *Het localisatieconcept in de neurologie van Brown-Séguard*, Amsterdam, Rodopi, 1989, p. 54.

<sup>34</sup> Brown-Séguard, op. cit., note 3 above, p. 75.

<sup>35</sup> Brown-Séguard, op. cit., note 19 above, lecture 11, ‘On the etiology, nature and treatment of epilepsy’, pp. 178–86.

### *Brown-Séquard's spinal epilepsy*

kind of respiration in diabetic coma, had come independently to this same conclusion concerning the loss of consciousness.<sup>36</sup> It was not until 1891 that Brown-Séquard demonstrated that loss of consciousness could exist even if the vasomotor nerves to the vessels of the brain were not functioning.<sup>37</sup> He noticed that sleep as well as loss of consciousness in epilepsy could not be prevented by bilateral ablation of the superior cervical ganglion in guinea pigs. He was already suspicious about the theory of cerebral vasospasm causing loss of consciousness since artificial vasospasm caused by faradic stimulation of both sympathetic nerves had not produced this effect. But earlier, in the 1850s, he had supposed that the natural stimulus of these nerves in seizures was capable of producing vasospasm. Bilateral excision of the superior cervical ganglion in humans did not prevent the loss of consciousness in seizures either.<sup>38</sup> Brown-Séquard concluded that the loss of consciousness should be explained by some sort of inhibitory action, according to his well-known theories of *action-à-distance*.

- (4) Due to the loss of consciousness, accumulation of blood at the base of the brain was thought to result in extension of the initial excitation.
- (5) Tonic contraction of the laryngeal, cervical and thoracic expiratory muscles produced the epileptic cry.
- (6) Asphyxia and accumulation of “black” (non-oxygenated) blood in the brain and spinal cord resulted in clonic convulsions.
- (7) Exhaustion of “nervous power and reflex faculty” (irritability and ability to produce reflexes).

That Brown-Séquard recognized the association of epilepsy with brain lesions is demonstrated by a reference he made in his monograph *Recherches on epilepsy* to a case, observed in 1811, of a man with cramps in the little finger of his right hand, which often caused a “Jacksonian march” until a generalized convulsion appeared. At the autopsy an enormous tumour was found in the left side of the cerebrum.<sup>39</sup> In Brown-Séquard’s model the tumour would have produced a specific change in the peripheral nerves, causing a “change of nutrition in the arm” which rendered it able to excite fits of epilepsy.<sup>40</sup> He found it even more probable that this change was not directly caused by the brain, but by “irritation of the sensitive or excito-motory nerves of the scalp, or in consequence of the compression of the base of the encephalon”.

<sup>36</sup> Brown-Séquard referred to Kussmaul and Tenner while quoting from Jacob Moleschott’s book, *Untersuchungen zur Naturlehre*, 1857, vol. 3, part 1. The famous Dutch physiologist was an advocate of materialistic philosophy, who became a lecturer in Heidelberg and later a professor in Rome. See also, A. Kussmaul and A. Tenner, *On the nature and origin of epileptiform convulsions caused by profuse bleeding, and also of those of true epilepsy*, transl. E. B. Bronner, London, New Sydenham Society, 1859, cited by Temkin op. cit., note 11 above, p. 284.

<sup>37</sup> C. E. Brown-Séquard, ‘De la perte de connaissance dans l’épilepsie après l’ablation du ganglion cervical supérieur du nerf grand sympathique, des deux côtés, chez l’homme et chez le cobaye’, *Arch. Physiol. Norm. Pathol.*, 1891, 3: 216–18. It was Michael Aminoff who noticed Brown-Séquard’s change of view concerning this subject: M. Aminoff, *Brown-Séquard. A visionary of science*, New York, Raven Press, 1993, p. 150.

<sup>38</sup> W. Alexander, *The treatment of epilepsy*, Edinburgh, Young J. Pentland, 1889, pp. 27–118, cited by Brown-Séquard, op. cit., note 37 above, p. 218.

<sup>39</sup> Brown-Séquard, op. cit., note 3 above, p. 13. “Jacksonian march” is the term used by the present author.

<sup>40</sup> *Ibid.*, p. 73.

Brown-Séquard recommended that before treatment of a case of epilepsy was started, a search should be made for external causes, such as an irritation of the sensory nerves. Any treatment that would disconnect the aura from the susceptible centre in the brain could be beneficial:

- (1) Ligature of a limb or a finger. This treatment was, according to Brown-Séquard, applied for the first time by Galen (129–200/210). The therapeutic results were illustrated by Brown-Séquard with cases from many sources.
- (2) Section of one or several nerves and amputation (even of a testicle).
- (3) Stretching of the muscles which were the seat of the aura. This treatment was advised in some patients with muscle cramp without epileptic phenomena. The prevention or diminution of asphyxia was also believed to be therapeutically important.
- (4) Cauterization, by various means, of the part of the skin from which the aura originated.<sup>41</sup>

Other treatments that might be of benefit were: the application of blisters or setons in the region where the aura was located (the above mentioned fourth treatment being more effective); drugs, such as strychnine and most particularly atropine and ergot of rye, that influenced the blood vessels and through them the nutrition of the nervous centres; cauterization of the larynx in cases with considerable laryngism; the generation of fever, the old Hippocratic method, and hygienic measures such as preventing sleeplessness.<sup>42</sup>

#### REFERENCES TO BROWN-SÉQUARD'S SPINAL EPILEPSY

“Brown-Séquard’s epilepsy” or “spinal epilepsy” has remained a clinical syndrome for about half a century. Jacob Schroeder van der Kolk (1797–1862), who became the first clinical neurologist and psychiatrist in the Netherlands, referred to Brown-Séquard’s theory of epilepsy and introduced new elements to the reflex theory. He considered the first cause of epilepsy to be the “exalted sensibility and excitability of the medulla oblongata”.<sup>43</sup> Wilhelm Heinrich Erb (1840–1921), professor of neurology in Heidelberg and a pupil of Nikolaus Friedreich (1825–1882), who described hereditary spinal ataxia, wondered if a relation existed between this form of epilepsy and the phenomenon of ankle clonus: “the well-known clonic twitching of the foot which starts on its sudden passive dorsal flexion and is maintained by continuous pressure as long as is desired”.<sup>44</sup>

However, Brown-Séquard’s clinical experience that an epileptic attack could be halted by sudden flexion of the great toe was not confirmed by Erb. He considered, as we do nowadays, that plantar flexion of the whole foot is necessary to stop the clonus. Jean-Martin Charcot (1825–1893) also related ankle clonus in patients with multiple sclerosis to Brown-Séquard’s spinal epilepsy. In one of his *Leçons de mardi* on the permanent contraction of the extremities and spinal epilepsy, Charcot referred to ankle

<sup>41</sup> *Ibid.*, p. 13.

<sup>42</sup> *Ibid.*, pp. 80–2.

<sup>43</sup> J. Schroeder van der Kolk, *On the minute structure and functions of the spinal cord and medulla oblongata, and on the proximate cause and rational treatment of epilepsy*, transl. W. D. Moore, London, New Sydenham Society, 1859, p. 250, cited by Temkin, *op. cit.*, note 11 above, p. 283.

<sup>44</sup> W. Erb, ‘Ueber Sehnenreflexe bei Gesunden und bei Rückenmarkskranken’, *Arch. Psychiat. Nervenkr.*, 1875, 5: 791–6.

### *Brown-Séquard's spinal epilepsy*

clonus: "Gentlemen, the phenomenon of which I just outlined the main features is nothing else than the spinal epilepsy described by Mr. Brown-Séquard".<sup>45</sup>

It was possible to stop the *tremulation* by suddenly flexing the big toe, "as was demonstrated by Mr. Brown-Séquard and as I have observed several times after him".<sup>46</sup> The fact that Erb could not confirm this observation raises the question whether he and Charcot were referring to the same phenomenon.

A. Freusberg, who worked at the physiological institute in Strassburg, referred to the same phenomenon while studying reflex movements and reflex inhibition in dogs.<sup>47</sup> John Hughlings Jackson (1835–1911), who from 1862 worked as an assistant to Brown-Séquard in the National Hospital for the Paralysed and Epileptic in London, referred to the vasomotor part of Brown-Séquard's theory on epilepsy. Loss of function of a part of the nervous system was believed to be the cause of epileptic fits, "probably as Dr. Brown-Séquard points out, the contraction of the blood-vessels diminishing the quantity of the blood".<sup>48</sup> Jackson later classified spinal epilepsy under the lowest level of fits, after he had developed his theories on the hierarchy of centres of the nervous systems, having been influenced by the concept of the philosopher Herbert Spencer (1820–1903) concerning evolutionary levels. From these lowest level, or "pontobulbar fits", Jackson singled out "a condition for fits consequent on certain injuries of the cord or sciatic nerve in guinea pigs".<sup>49</sup>

At the beginning of the twentieth century artificially produced spinal epilepsy in guinea pigs was explained as an exaggerated scratch reflex resulting from irritation of the skin after spinal cord trauma.<sup>50</sup> In 1934 four French authors suggested that lice on the paralysed parts of the body provoked the animal's reaction, which resembled epilepsy.<sup>51</sup> Indeed, Brown-Séquard had observed lice on his experimental animals. This might explain why the frequency of seizures was related to the conditions in which the animals were kept: small cages and enough food made the frequency higher than large cages and insufficient food. However, an exaggerated scratch reflex could not explain all phenomena of the epileptiform manifestation, for example the loss of consciousness. The exact nature of Brown-Séquard's observations remains uncertain, even after repetition of the experiments in the twentieth century.

#### ACQUIRED INHERITANCE

For some years, I have been able to observe a substantial number of new-born guinea pigs that had become epileptic when spinal cord lesions were inflicted. Soon I ascertained in

<sup>45</sup> J. M. Charcot, *Leçons sur les maladies du système nerveux faites à la Salpêtrière*, 2 vols, Paris, Delahaye, 1877, vol. 1, p. 247.

<sup>46</sup> *Ibid.*, p. 246.

<sup>47</sup> A. Freusberg, 'Reflexbewegungen beim Hunde', *Pflügers Archiv für Physiologie.*, 1874, 9: 358–91. Freusberg was a disciple of Friedrich Goltz (1834–1902).

<sup>48</sup> Quoted in Temkin, *op. cit.*, note 11 above, p. 331.

<sup>49</sup> *Ibid.*, p. 340.

<sup>50</sup> T. G. Brown, 'Studies on the reflexes of guinea pigs. I. The scratch reflex in relation to "Brown-Séquard's epilepsy"', *Q. J. exp. Physiol.*, 1909, 2: 243–75.

<sup>51</sup> P. Pagniez, A. Plichet, P. Salles, R. Laplane, 'Du rôle des poux dans l'épilepsie du Brown-Séquard du Cobaye', *C. r. Soc. Biol.*, 1934, 116: 314–15.

some of the new-born an obvious epileptiform affection, with characteristic seizures, but somewhat different from those in the parents.<sup>52</sup>

In 1859 Brown-Séquard described the hereditary character of the affliction. The epileptiform convulsions of the parents were not the same in the new-born guinea pigs; convulsions could not be produced by pinching the skin of the face as was possible in their parents, though spontaneous convulsions occurred in both. There was another difference too: when the convulsion started the animal trembled, after that it fell on its side and then shook its extremities spasmodically. Half of the epileptic animals were born from mothers that had become epileptic after spinal cord lesions and the other half from fathers treated in the same way. Not all descendants of an epileptic animal became epileptic. Brown-Séquard assumed there was no natural epileptic tendency in guinea pigs, since he had never observed convulsions in any animals that had not been subject to a spinal cord lesion, “and yet the number of healthy guinea pigs that I have kept for months is really immense”.<sup>53</sup>

According to Brown-Séquard these observations were of great value, since they gave new evidence of similarities for those who related human epilepsy to the convulsive affection in mammals determined by heredity. “The more the analogy between these two illnesses becomes evident, the more the study of epilepsy in animals . . . may help the difficult research that is still demanded for human epilepsy”. Brown-Séquard examined the spinal cords of the epileptic offspring macroscopically and microscopically, but did not observe abnormalities. He concluded that it was not the local injury that was transmitted, but the “alteration or general organic tendency of the nervous system produced by the lesion, and that was deeply imprinted in the parents or in one of them”.<sup>54</sup>

The fact that Brown-Séquard presented these observations to the Société de Biologie and published them in 1859 in the *Comptes rendus de la Société de Biologie* and in 1860 in the *Proceedings of the Royal Society of London*,<sup>55</sup> several years after he had observed them, might be of importance. Probably following the second publication, Darwin corresponded on the subject with the professor in anatomy at Harvard University, Jeffries Wyman (1814–1874): “Speaking of inheritance, I was long inclined to entirely disbelieve with you, that mutilations are ever inherited . . .; but I have of late been rather staggered; & now Brown-Séquard’s case of inherited epilepsy from mutilation seems to almost settle the question”.<sup>56</sup> Darwin’s *On the origin of species* was published on 24 November 1859. Even in his lecture on epilepsy, delivered at the Royal College of Surgeons in May 1858 and published in his *Course of lectures*,<sup>57</sup> Brown-Séquard did not mention the hereditary characteristic he had observed in his animals. He gave his first lecture on the subject to the

<sup>52</sup> C. E. Brown-Séquard, ‘De la transmission par hérédité chez les mammifères et particulièrement chez les cochons d’Inde, d’une affection épileptiforme, produite chez les parents par des lésions traumatiques de la moelle épinière’, *C. r. Soc. Biol.*, 1859, **11**: 194–5.

<sup>53</sup> C. E. Brown-Séquard, ‘Hereditary transmission of an epileptiform affection accidentally produced’, *Proc. R. Soc. Lond.*, 1860, **10**: 297–8.

<sup>54</sup> Brown-Séquard, op. cit., note 52 above, p. 195.

<sup>55</sup> The paper was received on 23 December 1859.

<sup>56</sup> C. R. Darwin, letter to Jeffries Wyman, 3 October 1860, see F. Burkhardt (ed.), *The correspondence of Charles Darwin*, 8 vols, Cambridge University Press, 1993, vol. 8, pp. 404–6, p. 405.

<sup>57</sup> See Brown-Séquard, op. cit., note 19 above.

Brown-Séquard's spinal epilepsy

ed a letter from Dr. Livingstone from Sierra Leone, in which he mentioned that Lieut. Goss who had <sup>been</sup> ~~been~~ <sup>been</sup> the country after the wreck of the "Dayspring", had succeeded in recovering some of the M. S. of Mungo Park written upon stray leaves of a table of logarithms.

103  
102<sup>nd</sup> Meeting

20<sup>th</sup> May 1858.

Present 16 Members -

|                                 |                 |
|---------------------------------|-----------------|
| Sir R. Murchison (in the chair) | Sir P. Egerton  |
| M. Brown Séquard                | W. Darwin       |
| Lord Wrottesley                 | W. Bask         |
| Dr. Sharpey                     | W. Bowman       |
| W. Stokes                       | D. Hofmann      |
| W. Whatstone                    | W. Gapiot       |
| W. Horner                       | D. Falconer     |
| D. Hooker                       | Adm. E. Smyth - |
| D. Lyndall                      | (after dinner)  |

D. Brown Séquard informed the Club that he had been for many years engaged in making experiments upon the effects of transfusions of blood in animals in articulo mortis, with the view of

Courtesy the Library of the Royal Society, London.

Figure 1: Part of the report of the meeting on 20 May 1858 of the Philosophical Club of the Royal Society when Brown-Séquard met Darwin.

Société de Biologie in October 1859, so he could not have read Darwin's book before. However, in a letter to Brown-Séquard dated 2 January 1861, Darwin wrote: "I daresay some do not remember it, but a year or two ago I was introduced to you at the Philosophical Club, and had some . . . interesting conversation [with] you".<sup>58</sup> Brown-Séquard had, indeed, been introduced to the Philosophical Club on 20 May 1858 by the physician Henry Bence Jones (1813–1873) at a meeting when Darwin, who had been a member since 1855, was also present (Figure 1).<sup>59</sup> Some important persons in Darwin's circle already were, or would soon become, members: William Benjamin Carpenter (1813–1885), later professor of physiology in London, to whom Brown-Séquard had given a signed copy of his 1857 monograph *Researches on epilepsy* and who later reviewed *On the origin of species*, and had read the last chapter before 19 November 1859;<sup>60</sup> the botanist Joseph Dalton Hooker (1817–1911), who had known Darwin since the 1840s and corresponded with him about the preparation of the *Origin of species*; and Darwin's supporter Thomas Huxley (1825–1895) who had been elected to the club ten days before the meeting. Thus there is some circumstantial evidence that Brown-Séquard might have heard about Darwin's theories in the year (1858) that Alfred Russel Wallace (1823–1913) sent his paper on natural selection to Darwin and their joint paper on the subject was communicated to the Linnean Society by the geologist Charles Lyell (1797–1875) and Joseph Hooker on 1 July 1858. Darwin referred to the hereditary character of epilepsy in some of his books,<sup>61</sup> and he corresponded with Brown-Séquard on the subject:

You say in your note 'that few men are so near agreeing with you as I am'. I cannot tell you how this has pleased me, for I look with profound interest for the judgement of such men as yourself.<sup>62</sup>

There was little interest in evolutionary thought in France, and Lamarck's (1744–1829) theories on evolution did not have a significant following,<sup>63</sup> largely because of the influence of his rival and colleague at the Muséum National d'Histoire Naturelle in Paris, Georges Cuvier (1769–1832), who favoured the fixity of species. Moreover, Lamarck's ideas were developed at a time that was politically as well as culturally unfavourable for them. *On the origin of species* did not cause much excitement in France, where scientists were converted to evolutionism only later during the nineteenth century. In Bowler's words,

<sup>58</sup> C. R. Darwin, letter to Brown-Séquard (1861), McCausland collection 981:96, London, Royal College of Physicians. Formed in 1847 by a group of 47 Fellows of the Royal Society and initially called The 47 Club, the Philosophical Club was one of the Royal Society's dining clubs. See T. E. Allibone, *The Royal Society and its dining clubs*, Oxford, Pergamon, 1976.

<sup>59</sup> 'Notes of the Philosophical Club of the Royal Society', 1847–80, vol. 1, p. 213, Library of the Royal Society.

<sup>60</sup> C. R. Darwin, letter to W. B. Carpenter, see F. Darwin (ed.), *The life and letters of Charles Darwin*, 3 vols, London, Murray, 1887, vol. 2, p. 222.

<sup>61</sup> C. Darwin, *The variation of animals and plants under domestication*, London, Murray, 1868, and *The descent of man and selection in relation to sex*, London, Murray, 1871.

<sup>62</sup> C. R. Darwin, letter to Brown-Séquard (1861), McCausland collection 981:96, Royal College of Physicians of London.

<sup>63</sup> P. J. Bowler, *Evolution, the history of an idea*, Berkeley, University of California Press, 1984, p. 81.

### *Brown-Séquard's spinal epilepsy*

the selection mechanism held no attraction for them. This negative response to Darwinism was conditioned by the legacy of Cuvier. French naturalists . . . found it easier to revive Lamarck's belief that new habits could influence structure directly.<sup>64</sup>

Brown-Séquard, who had been trained in Paris, might have been influenced by the ideas prevalent in France, but he moved to London at the beginning of 1860 to become a physician at the National Hospital for the Paralysed and Epileptic at Queen Square. Thus evolution theories did not reign supreme in France, and were accepted by only a few, such as the famous anthropologist and surgeon Paul Broca (1824–1880), who published his memoir on hybridity a year before *On the origin of species*.<sup>65</sup> In fact, as the subject of changing species was not welcomed by the authorities in the Société de Biologie, Brown-Séquard helped Broca by publishing the article in his recently founded *Journal de physiologie de l'homme et des animaux*. The evolution theory “transformism”, as it was called in France, was frequently discussed in Broca's Société d'Anthropologie, but it was only in 1870 that the members took a stand on Darwin's theory.<sup>66</sup> Although Brown-Séquard knew Broca well, no correspondence on the subject of evolution between the two has been found.<sup>67</sup> However, they met frequently in the late 1850s, and Broca was a co-editor of the above mentioned new journal. Other contacts between Brown-Séquard and the evolutionists took place some years later. He corresponded with Thomas Huxley about a meeting of the British Association for the Advancement of Science in Liverpool (September 1870), at which Brown-Séquard spoke.<sup>68</sup> Huxley defended the ideas which made Brown-Séquard many enemies in anti-vivisectionist circles,<sup>69</sup> and dissuaded Brown-Séquard from going to a scientific meeting in 1876 because of possible problems with the influential anti-vivisectionist movement.<sup>70</sup> Brown-Séquard's 1870 paper given in Liverpool ‘On apparent transmission of abnormal conditions due to accidental causes’ was praised by Huxley, who was the president of the meeting, he said he was

convinced that the observations made by Dr. Brown-Séquard would be referred to as having proved an introduction to a great and new path in science. The great theoretical problem that they had to determine was to know what effect artificial modifications and external conditions had had on living organisms—changes which, by being transmitted hereditarily, became the basis of new races.<sup>71</sup>

<sup>64</sup> Ibid., p. 186.

<sup>65</sup> P. Broca, ‘Mémoire sur L'hybridité et sur la distinction des espèces animales’, *J. Physiol.*, 1858, 1: 432–71 and 684–729, cited by F. Schiller, *Paul Broca*, Oxford University Press, 1992, pp. 221–35.

<sup>66</sup> P. Broca, ‘Sur le transformisme’, *Bull. Soc. d'Anth.*, (2nd series) 1870, 5: 168–242, cited by Schiller, op. cit., note 65 above, pp. 221–35.

<sup>67</sup> Broca supported Brown-Séquard's theories on the crossing sensory paths in the spinal cord at the Société de Biologie in 1855, and wrote a letter of introduction for Brown-Séquard when he went to Philadelphia. See P. Broca, ‘Propriétés et fonctions de la moelle épinière. Rapport sur quelques expériences de M. Brown-Séquard’ (read to the Société de Biologie 21 July 1855), in *Mémoires*, no. 3, Paris, Bonaventura, 1855; and Koehler, op. cit., note 33 above, p. 14.

<sup>68</sup> T. H. Huxley, letters to Brown-Séquard, McCausland collection 999: 6 and 981: 62–7, Royal College of Physicians of London. ‘British Association for the advancement of science. Report of the Meeting at Liverpool, September 14th–21st’, *Lancet*, 1870, ii: 436–8.

<sup>69</sup> See Aminoff, op. cit., note 37 above, p. 58.

<sup>70</sup> Huxley, op. cit., note 68 above 981: 64.

<sup>71</sup> *Lancet*, op. cit., note 68 above, p. 436.

Although Brown-Séguard had referred to the hereditary character of acquired epilepsy more than once since 1859, it is hard to discover through direct comment his attitude towards evolutionism. We may assume from Darwin's words that Brown-Séguard "agreed with him".

Brown-Séguard's ideas on the hereditary character of experimentally induced epilepsy in guinea pigs were gladly accepted by Darwin who referred to them in some of his books.<sup>72</sup> In a chapter on inheritance he wrote:

But perhaps the most remarkable and trustworthy fact is that given by Dr. Brown-Séguard, namely, that many young guinea pigs inherited an epileptic tendency from parents which had been subjected to a particular operation, inducing in the course of a few weeks a convulsive disease like epilepsy.

Darwin's conclusions were:

On the whole, we can hardly avoid admitting, that injuries and mutilations, especially when followed by disease, or perhaps exclusively when thus followed, are occasionally inherited.<sup>73</sup>

Darwin cited as an example of this the case of certain short-tailed monkeys, in whom a part of the tail which was functionally useless became a rudimentary and distorted hereditary feature as a result of being continuously rubbed.<sup>74</sup> The subject of hereditary transmission in Darwin's theories was not, however, essential. Although, like Lamarck, he believed in "soft heredity" (direct environmental influence on heredity), his theories of evolution by natural selection were separated from any particular mechanism of inheritance. They merely required the presence of inherited variability by whatever means.

How then are we to understand the references to Brown-Séguard's examples of inheritance of acquired epilepsy? He observed epileptiform convulsions in the offspring of his experimental animals. He certainly read Darwin's *Origin of species* and he knew Huxley well. Brown-Séguard could have been influenced during his stay in America by his friend Louis Agassiz (1807–1873), who had worked under Cuvier in Paris and who was the leading opponent of Darwinism. Agassiz's idealistic view was not compatible with theories of natural evolution. But, as evident in correspondence with Darwin, Brown-Séguard agreed with his ideas, and helped to bring the *Origin of species* to the attention of French readers.

It appears that Darwin was quite impressed by Brown-Séguard's position in those days. From 1860–1863, apart from being one of the physicians at the National Hospital for the Paralyzed and Epileptic in London, he also had a large neurological practice. He was considered an expert on epilepsy, and patients came from great distances to see him. In one of his letters Darwin asked for Brown-Séguard's opinion of his book: "I shall be truly glad to read any criticisms from one who stands so very high in one of the very highest branches of science as you stand".<sup>75</sup>

<sup>72</sup> Darwin, op. cit., note 61 above.

<sup>73</sup> Ibid., *The variation of animals*, 1868, vol. 2, p. 24.

<sup>74</sup> Ibid., *The descent of man*, 1875, p. 60.

<sup>75</sup> Darwin, op. cit., note 62 above.

### *Brown-Séquard's spinal epilepsy*

The hereditary character of “Brown-Séquard’s epilepsy” was criticized at the end of the nineteenth century by various scientists, and early this century it was suggested that the experimental animals, after spinal lesions had been made, bit off the toes they could not feel—both their own and those of their offspring—so that they were unable to groom themselves properly and therefore lice accumulated on the skin causing “epileptiform” seizures.<sup>76</sup> In 1930 the hereditary transmission of traumatic foot, eye and ear abnormalities were considered as coincidental congenital anomalies.<sup>77</sup>

Brown-Séquard’s theory of epilepsy evolved partly from the authoritative opinion of Flourens who had found that the cerebrum and cerebellum were not irritable. Brown-Séquard tried to confirm this experimentally. His own experience with the phenomenon of inhibition and dynamogenesis (excitation), led to his concept of *action à distance*, and contributed to establishing his theory of epilepsy, in which he made use of contemporary theories of epileptogenesis. As has been shown, Brown-Séquard used the theories of Hall, Henle, Todd, and Bernard to build his own theory, which, however, has to be considered in the light of the lifelong development of his localization-concept of the nervous system, based on inhibition and dynamogenesis (excitation).<sup>78</sup> He built a network system in which actions from a distance could inhibit or excite other areas of the nervous system. With this concept he was able to explain why lesions in different parts of the nervous system could produce the same effects. According to this theory he changed the original view on the crossing sensory pathways in the spinal cord, by which his name became associated with syndromes following injuries to half the spinal cord,<sup>79</sup> and he also changed his explanation for the loss of consciousness in seizures after he had concluded that sympathetic cerebral vasospasm could not be the cause.

Brown-Séquard’s concept of spinal epilepsy played an important role in the development of mid-nineteenth-century theories of the disease. He remained in the centre of the medical world in France and England, where he picked up contemporary knowledge on epilepsy and, in turn, influenced others. The concept of the hereditary character of acquired epilepsy in experimental animals was published in the same period as *On the origin of species*, and contributed to Darwin’s theories. Some decades later it was shown to be based on a wrong interpretation of observations.

<sup>76</sup> T. G. Brown, ‘An alleged specific instance of the transmission of acquired characters—investigations and criticism’, *Proc. R. Soc. Lond.*, (series B) 1912, **84**: 555–79; see also Aminoff, op. cit., note 37 above, p. 151–2.

<sup>77</sup> E. Guyénot, *La variation et l’évolution*, Paris, Doin, 1930, cited by J. M. D. Olmsted, *Charles-Edouard Brown-Séquard: a nineteenth century neurologist and endocrinologist*, Baltimore, Johns Hopkins Press, 1946, p. 187.

<sup>78</sup> P. J. Koehler, ‘Brown-Séquard’s localization concept. The relationship with Sherrington’s “integrative action” of the nervous system’, in F. C. Rose (ed.), *Neuroscience across the centuries*, London, Smith-Gordon, 1989, pp. 135–8.

<sup>79</sup> *Ibid.*, p. 135–8. See also C. E. Brown-Séquard, ‘Remarques à propos des recherches du Dr. F. W. Mott sur les effets de la section d’une moitié latérale de la moelle épinière’, *Arch. Physiol.*, 1894, **26**: 195–8.