

# Hypoadrenia or “A Bit of Addison’s Disease”

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In the fully developed form of Addison’s disease, first described in 1855 and now usually called acute adrenocortical failure or adrenal insufficiency, the signs and symptoms are unmistakable. They are weakness, tiredness, low blood pressure and pigmentation which is especially prominent in scars, flexures and inside the mouth. By the end of the nineteenth century it was generally agreed that the adrenal glands were essential to life and that they consisted of two glands, the medulla and cortex, in a single capsule. The discovery of the pressor effects of adrenal extracts in 1895, and isolation and synthesis of adrenaline in the subsequent decade diverted the attention of clinicians and physiologists away from the adrenal cortex.<sup>1</sup> Adrenaline raised the blood pressure and increased muscular strength and, since these were the antithesis of the symptoms of Addison’s disease, many concluded that Addison’s disease was adrenaline deficiency. Final proof that Addison’s disease was due to failure of the adrenal cortex did not come until the early 1930s,<sup>2</sup> and even then there were major difficulties in diagnosis in patients with “doubtful pigmentation, loss of weight, fatigability, weakness and hypotension”.<sup>3</sup> These, with the exception of pigmentation, are common and non-specific and in the context of neurasthenia form part of what Sicherman has described as “the staggering variety of symptoms that had long taxed the ingenuity and patience of physicians”.<sup>4</sup> They were seized on by some pioneer endocrinologists in the period 1902–1925 to construct a disease, “hypoadrenia”, or a *forme fruste* of Addison’s disease.

The history of medicine is replete with “new” diseases which, like comets, have made a dramatic entry, shone brightly for a time in the medical firmament, and then faded and died (or had their symptoms reconstructed in a different way). Examples from the last century include visceroptosis, suppressed gout, autointoxication and neurasthenia, while

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<sup>1</sup> Throughout this paper I have used the modern English spelling “adrenaline” for the hormone of the adrenal medulla. The name “Adrenalin” was the registered trade name of Parke, Davis and Co. from

1901 onwards. In the period 1895–1925 many other names were used, including adrenin, suprarenin and epinephrin. The nomenclature is discussed in E M Tansey, ‘What’s in a name? Henry Dale and Adrenaline, 1906’, *Med. Hist.*, 1995, 39: 459–76.

<sup>2</sup> R Gaunt, W J Eversole, ‘Notes on the history of the adrenal cortical problem’, *Ann. N. Y. Acad. Sci.*, 1949, 50: 51–21.

<sup>3</sup> G A Harrop, ‘Diagnosis of Addison’s disease (including use of salt free diet)’, *J. Am. Med. Assoc.*, 1933, 100: 1850–5.

<sup>4</sup> B Sicherman, ‘The uses of a diagnosis: doctors, patients and neurasthenia’, *J. Hist. Med.*, 1977, 32: 33–54.

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the first half of the present century has supplied hypoadrenia, focal sepsis<sup>5</sup> and reactive hypoglycaemia.<sup>6</sup> These extinct illnesses had many features in common; the number of possible symptoms was usually great and they were both common and non-specific. For example, the popularizer of neurasthenia, the New York neurologist George Beard (1839–1883), could list over 50 from extreme weakness and fatigue to sexual impotence and backache.<sup>7</sup> The diagnoses were the creation of enthusiasts who set out to make sense of illness within a new theoretical construct, often a new branch of medicine which was struggling to become established and differentiated from the mainstream. This was well expressed by Edmund D Pellegrino, who wrote:

The physician easily develops an inflated estimation of the value of his own expertise or special therapeutic manoeuvre. The tendency to overutilize the techniques with which he identifies is frequently manifest. Given the nature of the dominant professional ethos, once a patient has come to him, the physician feels useless unless he “rules out” every possibility of a disorder in his domain before releasing the patient . . .<sup>8</sup>

The desire of physicians to respond to public demand and make a living should not be underestimated but, although they might later become tarnished by commercialism, these diseases were not the inventions of quacks; all had their roots in theories which were accepted at the time but often continued to grow even when new and contrary facts appeared. For doctors they were intellectually plausible and for patients such diagnoses legitimized their illness and, in stark contrast to the therapeutic nihilism preached by leaders of the profession in the early 1900s, satisfied their desire for treatment.<sup>9</sup>

This paper documents the rise and fall of hypoadrenia, a construct in which, although many of the clinical theories were later described as “immature and fantastic”,<sup>10</sup> the physiological basis had initially seemed secure.

## Addison’s Disease and Adrenaline

In the era of anatomy the position of the adrenal glands above the kidney, their small size and lack of a duct, led to them being regarded as vestigial organs.<sup>11</sup> Thomas

<sup>5</sup> The doctrine of focal sepsis originated with Frank Billings in Chicago in 1915 and was adopted with enthusiasm in many parts of the world. The recommendation for any disease of unknown aetiology was to search for and remove any possible focus of infection. As a result, during the next 25 years, millions of unnecessary dental and surgical procedures were carried out. P B Beeson, R C Maulitz, ‘The inner history of internal medicine’, in R C Maulitz, D E Long (eds), *Grand rounds: one hundred years of internal medicine*, Philadelphia, University of Pennsylvania Press, 1988, pp. 32–3.

<sup>6</sup> G F Cahill, J S Soeldner, ‘A non-editorial on non-hypoglycemia’, *N. Engl. J. Med.*, 1974, **291**: 905–6. J Yager, R T Young, ‘Non-hypoglycemia is an epidemic condition’, *ibid.*, 1974, **291**: 907–8.

<sup>7</sup> George Beard, *A practical treatise on nervous exhaustion (neurasthenia), its symptoms, nature, sequences, treatment*, New York, W Wood, 1880.

See also, Charles E Rosenberg, ‘The place of George M Beard in nineteenth century psychiatry’, *Bull. Hist. Med.*, 1962, **36**: 245–59.

<sup>8</sup> Edmund D Pellegrino, ‘Sociocultural impact of modern therapeutics’, in M J Vogel and C E Rosenberg (eds), *The therapeutic revolution: essays in the social history of American medicine*, Pittsburgh, University of Pennsylvania Press, 1979, p. 255.

<sup>9</sup> I have drawn on several useful discussions of the definition of disease in Charles E Rosenberg, Janet Golden (eds), *Framing disease, studies in cultural history*, New Brunswick, Rutgers University Press, 1992.

<sup>10</sup> R G Hoskins, ‘Some recent work on internal secretions’, *Endocrinology*, 1922, **5**: 621–2.

<sup>11</sup> F I Ibanez, ‘The history of endocrinology as seen through the evolution of our knowledge of the adrenal glands’, *Int. Rec. Med.*, 1952, **165**: 547–604.

Addison's 1855 monograph on the constitutional and local effects of disease of the suprarenal capsules was the first indication that they might be important. He described a clinical entity in which the main features were "anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin". Addison noted that the pigmentation or "singular discolouration" increased with time and might, in the early stages, be so slight as to go unnoticed. He also emphasized that the disease came on gradually, so that "the individual has considerable difficulty in assigning the number of weeks or even months that have elapsed since he first experienced indications of failing health and strength".<sup>12</sup> Addison's paper had an immediate impact, especially in France where, at a meeting of the Academy of Medicine in Paris in August 1855, Armand Trousseau (1801–1867) proposed that it should be called Addison's disease.<sup>13</sup> In 1856, after 60 extirpation experiments on dogs, cats, hares and guinea pigs, the physiologist Charles-Edouard Brown-Séguard (1817–1894) concluded that the adrenals were essential to life and that their function was to destroy a substance which otherwise transformed itself into pigment.<sup>14</sup> Brown-Séguard's conclusions were disputed by many, including the English physiologist George Harley (1829–1896).<sup>15</sup> At a meeting of the Pathological Society in London in 1857 Harley showed a "living and apparently healthy" white rat from which he had removed the adrenals four months earlier.<sup>16</sup> In 1858 Harley was awarded the Triennial Medal of the Royal College of Surgeons for his work on the histology of the suprarenal capsules, in which he clearly differentiated between the cortex and medulla, and wrote that:

Upon histological grounds, Kölliker says that he would regard the function of the cortical and medullary substances as distinct from each other. The former portion of the organ, he thinks, is probably in some way connected with the blood glands; while the latter substance, in consequence of its richness in nerves, and its containing cells resembling ganglion corpuscles, he regards as probably an apparatus connected with the nervous system.<sup>17</sup>

Opponents ascribed the death of Brown-Séguard's animals to operative trauma or peritonitis but by 1895 when Humphry Rolleston gave the Goulstonian Lectures on the suprarenal bodies the medical community had accepted Brown-Séguard's conclusions.<sup>18</sup>

<sup>12</sup> Thomas Addison, *On the constitutional and local effects of disease of the supra-renal capsules*, London, Samuel Highly, 1855, p. 4. Addison's original presentation of patients with a peculiar anaemia (i.e. weakness) had been made to the South London Medical Society in 1849 when he emphasized that in two cases the only abnormality was disease of the suprarenals. *Lond. Med. Gaz.*, 1849, 43: 517–18.

<sup>13</sup> L G Wilson, 'Internal secretions in disease: the historical relations of clinical medicine and scientific physiology', *J. Hist. Med. Allied Sci.*, 1984, 39: 263–302.

<sup>14</sup> C E Brown-Séguard, 'Recherches expérimentales sur la physiologie et la pathologie des capsules surrénales', *C. R. Acad. Sci.*, 1856, 43: 422–5. For a description of Brown-Séguard's remarkable career, see Michael J Aminoff, *Brown-*

*Séguard, a visionary of science*, New York, Raven Press, 1993.

<sup>15</sup> Before being appointed Lecturer in Physiology at University College, London, in 1856 Harley had spent five years abroad in Paris (with Claude Bernard), Würzburg (Justus von Liebig), and Giessen (Carl Ludwig), as well as Berlin and Vienna. His daughter, Mrs Alec Tweedie, wrote a biography: *George Harley FRS: the life of a London physician*, London, The Scientific Press, 1899.

<sup>16</sup> 'Pathological Society of London', *Lancet*, 1856, ii: 550.

<sup>17</sup> George Harley, 'The histology of the suprarenal capsules', *Lancet*, 1858, i: 551–3, 576–8, on p. 578.

<sup>18</sup> H D Rolleston, 'The Goulstonian Lectures on the suprarenal bodies', Lecture 2, *Br. med. J.*, 1895, i: 687–91. Lecture 3, *Br. med. J.*, 1895, i: 745–8.

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It later became apparent that adrenalectomy is not necessarily fatal in rats because they often have accessory adrenal cortical tissue elsewhere in the abdomen (Marchand's rests).<sup>19</sup>

There was much discussion about the function of the adrenals, with some holding that they neutralized or destroyed toxins formed in the blood from effete blood-pigments, while others believed they secreted into the bloodstream something which was "necessary to the economy".<sup>20</sup> The breakthrough for the secretion theory was the 1895 finding of the physician George Oliver (1841–1915) and the physiologist Edward Schäfer (1850–1935) that suprarenal extracts had a powerful, but transient, pressor effect and caused the heart to beat more rapidly and forcefully.<sup>21</sup> Since one characteristic of Addison's disease was "a remarkable feebleness of the heart's action", they hypothesized that the adrenals continuously discharged into the blood something essential for the maintenance of vascular tone. A year later they made an extract of the adrenals from two cases of advanced Addison's disease which "yielded no active principle at all". They also proved to their own satisfaction that "extracts of the cortex of the gland are quite inactive, the active principle being confined strictly to the medulla".<sup>22</sup>

The active principle was a very potent compound—what impressed Schäfer and his contemporaries was that as little as 5.5 mg of dried suprarenal extract produced a maximal effect on the heart and arteries of a 10 kg dog.<sup>23</sup> In 1899 J J Abel of the Johns Hopkins Hospital isolated an extract which he called "epinephrin"<sup>24</sup> and, at the same time, Otto von Fürth isolated a similar compound which he called "suprarenin".<sup>25</sup> In 1901 Takamine<sup>26</sup> and Aldrich<sup>27</sup> independently devised a method of isolating the pure active principle which was marketed by Parke, Davis in 1901 under the trade name Adrenalin. By analogy with the remarkable success of thyroid extracts in the treatment of myxoedema introduced in 1891 and completely accepted by 1893,<sup>28</sup> it was expected that suprarenal extracts would cure Addison's disease. In the *International Medical Magazine* in February 1896 William Osler reported six cases including one "greatly benefited by the use of the supra-renal extract". However, later in the same year at a meeting of the Johns Hopkins Medical Society he described a 21-year-old girl who died eight days after starting treatment with glycerin adrenal extract and mentioned that his earlier apparently successful patient was

<sup>19</sup> M A Goldzieher, *The adrenals: their physiology, pathology and diseases*, London, J and A Churchill, 1929.

<sup>20</sup> F P Kinnicutt, 'The therapeutics of the internal secretions', *Am. J. med. Sci.*, 1897, **114**: 7–23.

<sup>21</sup> G Oliver, E A Schäfer, 'The physiological effects of extracts of the suprarenal capsules', *J. Physiol.*, 1895, **18**: 230–76. Schäfer's role in the development of endocrine research is described in Merriley Borrel, 'Setting the standards for a new science: Edward Schäfer and endocrinology', *Med. Hist.*, 1978, **22**: 282–90.

<sup>22</sup> E A Schäfer, 'Oliver Sharpey Lectures on the present condition of our knowledge regarding the functions of the suprarenal capsules', *Br. med. J.*, 1908, **i**: 1277–81, 1346–51, on p. 1347.

<sup>23</sup> E A Schäfer (ed.), *Textbook of physiology*, Edinburgh and London, Young J Pentland, 1898, vol.1, p. 957.

<sup>24</sup> J J Abel, A C Crawford, 'On the blood pressure raising constituent of the supra-renal capsule', *Bull. Johns Hopkins Hosp.*, 1897, **8**: 151–7.

<sup>25</sup> O von Fürth, 'The catechol-like substance of the suprarenal', *J. Chem. Soc. Abstr.*, 1900, **78**: 292.

<sup>26</sup> J Takamine, 'Adrenalin, the active principle of the suprarenal glands and its mode of preparation', *Am. J. Pharm.*, 1901, **73**: 523–31.

<sup>27</sup> T B Aldrich, 'A preliminary report on the active principle of the suprarenal gland', *Am. J. Physiol.*, 1901, **5**: 457–61.

<sup>28</sup> G R Murray, 'Note on the treatment of myxoedema by hypodermic injections of the thyroid gland of a sheep', *Br. med. J.*, 1891, **i**: 796–7, and Editorial, 'Thyroid extract in myxoedema', *Br. med. J.*, 1893, **i**: 252.

“weak and failing”.<sup>29</sup> Osler used a glycerin extract of hog’s adrenals, while others used Adrenalin but by the early years of the century it was agreed that neither could keep a patient with Addison’s disease alive.<sup>30</sup>

Nevertheless, adrenaline was a useful drug. In 1897 Oliver put a fragment of adrenal medulla on a small artery in the mesentery of a frog and found that it “constricted so markedly that blood no longer flowed through it”.<sup>31</sup> This suggested that it might be useful as a styptic, and Schäfer and Oliver used their extract to stop bleeding from wounds during vivisection experiments, and even to stop one of Schäfer’s nosebleeds.<sup>32</sup> By 1904 it was widely used to stem epistaxes, control haemorrhage after dental surgery, or to produce a bloodless operating field. Other uses were for asthma or to raise the blood pressure in heart failure or surgical shock.<sup>33</sup>

### Which Part of the Adrenal was Essential to Life: Cortex or Medulla?

When Oliver and Schäfer discovered the vasopressor effects of suprarenal extracts in 1895, the histological distinction between the cortex and medulla was well known, although this did not necessarily imply that they had separate functions. Rolleston, for example, thought that they were a single functional organ with the cortex and medulla performing the same work but to a different degree. He did nevertheless concede that “the cortex is regarded as being glandular or haematopoietic and the medulla as being nervous and connected to the sympathetic”.<sup>34</sup>

Initially, Schäfer and his pupil Swale Vincent believed the function of the suprarenals was to maintain vascular tone and to a lesser extent assist in muscular contraction and combat fatigue of the muscles (the “tonus” theory). Since the main features of Addison’s disease were asthenia and low blood pressure, it was not surprising that physicians (and many physiologists) deduced that Addison’s disease equalled adrenaline deficiency. Their explanation for its disappointing results in treatment was its short half life in the circulation and the consequent impossibility of replacing it through the twenty-four hours.

When Schäfer tried to decide on the relative importance of the cortex and medulla in 1908 he had no doubt that the cortex was an internally secreting gland and that it “possessed a function and an important one (because) of the two parts of the gland the cortical is the most constant in the vertebrate subkingdom”.<sup>35</sup> In many fish the cortex and medulla are represented by separate organs, the cortex by a single inter-renal body and the medulla by paired organs on either side of the vertebral column. When Swale Vincent removed the inter-renal bodies in eels, the fish survived in apparent good health,<sup>36</sup>

<sup>29</sup> W Osler, ‘Case of Addison’s disease. Death during treatment with the suprarenal extract’, *Johns Hopkins Hosp. Bull.*, 1896, 7: 208.

<sup>30</sup> R Saundby, ‘Addison’s disease’, *Medical Annual*, Bristol, John Wright and Sons, 1900, pp. 68–9.

<sup>31</sup> G Oliver, ‘The action of animal extracts on the peripheral vessels’, *J. Physiol.*, 1897, 21: xxii–xxiii.

<sup>32</sup> Schäfer, op. cit., note 23 above, p. 1348.

<sup>33</sup> ‘Adrenalin’, *Medical Annual*, Bristol, John

Wright and Sons, 1904, pp. 3–5.

<sup>34</sup> Rolleston, op. cit., note 18 above, pp. 631–2.

Leonard G Wilson (op. cit., note 13 above, pp. 287–8) regards Rolleston’s views on the unity of adrenal function as “somewhat astonishing” but they are only so with the benefit of hindsight.

<sup>35</sup> Schäfer, op. cit., note 22 above, p. 1350.

<sup>36</sup> S Vincent, ‘The nature of the suprarenal body of the eel and the effect of its removal’, *J. Physiol.*, 1897–8, 22: 48–9.

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whereas when the Viennese endocrinologist Artur Biedl (1869–1933) removed them from some torpedo rays, all died in three weeks of “general prostration”. Biedl concluded that his experiments proved that “the complete destruction of the interrenal tissue is incompatible with the continuation of life”.<sup>37</sup> Biedl had also found that rabbits and dogs could live with one-eighth or less of their suprarenal tissue provided the portion left was cortical. His view was that “the muscular asthenia of Addison’s disease is to be explained (on the adrenaline view) only by the most complicated hypotheses”. Schäfer disregarded Biedl’s findings because he did not believe the surgery was possible and laid more weight on the results of his co-worker Swale Vincent. Where Addison’s disease was concerned, Schäfer felt that some of the symptoms were due to absence of the medullary secretion but that others “such as the extreme wasting (when not due to general tuberculosis) and the malnutrition which is expressed in the abnormal pigmentation of the skin and mucous membrane” were probably the result of disease of the cortex.<sup>38</sup> A further confounding factor was the possibility that the cortex had something to do with sexual maturation. There were several reports of the association of adrenal cortical tumours with precocious puberty.<sup>39</sup> These cases were dramatic; the Viennese endocrinologist Wilhelm Falta described a 5½ year old boy with “testicles as large as pigeon’s eggs” who was so big and muscular that he had to be admitted to an adult ward, while an 11-year-old girl who died of metastatic adrenal cancer was so well developed sexually that she “looked like a forty-year-old woman”.<sup>40</sup>

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Unless one assumed that the adrenals were subject to an all or none law, the existence of Addison’s disease had to imply that there would be milder forms characterized by weakness, lethargy, low blood pressure and gastric irritability. Indeed, none other than Thomas Addison had suggested that “were we better acquainted with its symptoms and progress, we should probably succeed in detecting many cases which in the present state of our knowledge may be entirely overlooked or misunderstood”.<sup>41</sup> In the 1909 edition of his textbook, William Osler emphasized the difficulty of making a diagnosis early in the course of the disease. For him, the three most important symptoms were pigmentation, gastrointestinal upset and asthenia but even for the most characteristic sign, pigmentation, he listed thirteen other causes.<sup>42</sup>

The concept of a minor degree or *forme fruste* of Addison’s disease seems to have originated in France, where Édouard Boinet coined the name “Addisonisme” to distinguish it from the full blown disease “Maladie d’Addison”.<sup>43</sup> His compatriot Émile

<sup>37</sup> A Biedl, *The internal secretory organs: their physiology and pathology*, London, John Bale and Sons and Danielson, 1913 (translation of the 1910 German version), p. 152. Biedl became a full professor at the early age of 29 and was one of the pioneers of clinical and experimental endocrinology in Continental Europe. His monograph on internal secretions was first published in 1903 and by 1910 had grown to two large volumes.

<sup>38</sup> Schäfer, op. cit., note 22 above, p. 1351.

<sup>39</sup> W Bulloch, J H Sequeira, ‘On the relation of the suprarenal capsules to the sexual organs’, *Trans. Pathol. Soc. Lond.*, 1905, **56**: 189–208.

<sup>40</sup> W Falta, *The ductless glandular diseases*, Philadelphia, P Blakiston Sons, 1915, p. 358.

<sup>41</sup> Addison, 1855, op. cit., note 12 above, pp. 6–7.

<sup>42</sup> W Osler, *The principles and practice of medicine*, New York, D Appleton, 1909.

<sup>43</sup> É Boinet, ‘De l’Addisonisme’, *Arch. Gén. Méd.*, 1904, **194**: 2324–52.

Sergent described a test by which it could be recognized, “la ligne blanche surrénale”.<sup>44</sup> This white line was produced by running a soft blunt object (e.g. the finger tip) lightly over the skin of the abdominal wall in a square round the navel. The line appeared in 3 to 6 seconds, lasted 2 to 5 minutes and was thought by Sergent to be due to hypotension. Technique and good lighting were essential in eliciting this sign and the bona fide white line had to be distinguished from “certain white lines accompanied by red lines appearing simultaneously, encircling them or being encircled by them, and preceding or following them”.<sup>45</sup>

Hypoadrenia was imported into the USA and pushed to its limits by the grandly named Charles Eucharist de Medici Sajous (1852–1929).<sup>46</sup> He was educated in France and then at the University of California. At the age of twenty-five he graduated from Jefferson Medical College of Philadelphia and soon became a Lecturer in Laryngology there. His first articles were confined to his speciality and were followed by two manuals, *The curative treatment of hay fever*<sup>47</sup> and *Lectures on the diseases of the nose and throat*.<sup>48</sup> In 1888, with the aid of 70 associate and 200 corresponding editors from all over the globe, he published *The annual of the universal medical sciences*, which during the next eight years ran to 34 volumes.<sup>49</sup> Between 1892 and 1897 he gave up his practice to go to Paris, where he worked in Brown-Séguard’s unit. On his return to Philadelphia in 1898 he inaugurated another compendium, *The analytical cyclopaedia of practical medicine*, designed for the general practitioner, which was still being published in 1925 when 70,000 sets had been sold.<sup>50</sup>

In 1903 Sajous entered the nascent field of endocrinology with an 800-page book, *The internal secretions and the principles of medicine*, dedicated to the memory of Brown-Séguard. In the introduction he claimed that as a result of editing the *Annual of the universal medical sciences*, he had been brought face to face with “the yearly crop of contradictory theories upon each disease, mode of treatment, etc”. He realized that only “some gigantic flaw” could account for such confusion and quickly discovered that this was “the invalidity of physiology”. He produced a list of 96 features illustrating the failings of physiology, number 96 being: “That the most fatal and distressing diseases of mankind have not been mastered because the cardinal role of the adrenal system in their pathogenesis, prevention and cure, has been overlooked.” His thesis was that the basis of

<sup>44</sup> E Sergent, L Bernard, ‘Sur un syndrome clinique non Addisonien, à évolution aiguë, lié à l’insuffisance capsulaire’, *Arch. Gén. Méd. Paris*, 1899, 2: 27–59.

<sup>45</sup> *Idem*, ‘The white adrenal line: its production and diagnostic significance’, *Endocrinology*, 1918, 2: 18–23. This article is followed by a commentary from Dr Henry Harrower of Los Angeles, who felt the test had been undervalued for many years. Harrower also ran a commercial organotherapy laboratory which produced, *inter alia*, adrenal extracts. See also E Sergent, *Études cliniques sur l’insuffisance surrénale 1898–1920*, 2nd ed., Paris, Maloine et Fils, 1920.

<sup>46</sup> Charles E de M Sajous was born at sea near the coast of France in 1852 while his parents, Count Charles E de Medici and Marie Pierette Sajous, were

returning from America. His obituary is in *J. Am. med. Ass.*, 1929, 92: 1538, but more comprehensive, almost hagiographic, accounts of his life and work can be found in V Robinson, ‘Charles Eucharist de Medici Sajous’, *Medical Life*, 1925, 32(1): 1–21, and Victor Robinson, *Pathfinders in medicine*, New York, Medical Life Press, 1929, pp. 587–95.

<sup>47</sup> C E de M Sajous, *The curative treatment of hay fever*, Philadelphia, F A Davis, 1884.

<sup>48</sup> *Idem*, *Lectures on the diseases of the nose and throat*, Philadelphia, F A Davis, 1885.

<sup>49</sup> *Idem*, *Annual of the universal medical sciences*, Philadelphia, F A Davis, 1888–1896.

<sup>50</sup> *Sajous’s analytical cyclopaedia of practical medicine*, by Charles de M Sajous and one hundred associate editors, Philadelphia, F A Davis.

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life was the secretion of the adrenals which supplied “the oxidising principle to all living tissues”. Taking a giant leap, he concluded that “what are now considered as symptoms of infection or poisoning are all manifestations, more or less severe, of activity or insufficiency of the adrenal system”.<sup>51</sup>

In the *British Medical Journal* a reviewer noted that “he finds that the internal secretion of the adrenals is ‘of overwhelming importance’ . . . [he goes on to say that the] three glands [adrenal, pituitary and thyroid] form together the “adrenal system”, which is “autonomous”; disturbance in the functions of this system is regarded as explaining the symptomatology and giving the clue to the treatment of most diseases, such as Asiatic cholera, pulmonary tuberculosis, tetanus, septicaemia, and hydrophobia, and a multitude of others”. The review concluded, presumably sarcastically, “We think we have quoted enough to give readers an insight into the character of the book before us”.<sup>52</sup> The second volume was published in 1907 and by the fourth edition in 1911 it had grown to 1873 pages in two volumes.<sup>53</sup> The tenth and last edition was published in 1922.<sup>54</sup> Like the *British Medical Journal* reviewer in 1903, the *Lancet* reviewer of the fourth edition in 1912 was unimpressed, writing:

So far as the new physiology is concerned, we must confess that, taken in bulk, it is rather too big a dose . . . the arguments, though supported by a vast amount of painstaking research in the byways of physiological literature, seem rather flimsy. Thus it hardly follows that because iodine and phosphorus react chemically, therefore the thyroid secretion, containing iodine, is the controlling agent in vital phosphorus metabolism.<sup>55</sup>

Sajous’s published articles total 66, of which 29 are from the *Cyclopaedia* and 12 from the *New York Medical Journal*, of which he was managing editor from 1911 to 1919.<sup>56</sup> Had there been a citation index in the first two decades of the twentieth century Sajous would have scored poorly, since he was a synthesizer and hypothesizer rather than an original worker. The history of the Thomas Jefferson University damns him with faint praise in saying, “His major contributions were broad concepts and appreciation of the importance of internal secretions in health and disease. His specific observations were of lesser importance”.<sup>57</sup> In the *Dictionary of American Biography* he is described as “a voluminous writer and indefatigable editor”, but his book on *Internal secretions* is “marred by the uncritical enthusiasm with which its author indorsed [*sic*] the views of many writers whose statements were not based on exact scientific observation”.<sup>58</sup> Writing in 1929 Goldzieher felt that Sajous’s books “submerge the comparatively scanty facts in too much clinical discussion and prevent the reader from getting an adequate conception of our actual knowledge of the topic”.<sup>59</sup> Lest it be thought that Sajous was a solitary maverick in the field of adrenal disease, it should be noted that he was elected as the first

<sup>51</sup> C E de M Sajous, *The internal secretions and principles of Medicine*, Philadelphia, F A Davis, 1903, vol. I (800 pages, 42 illustrations).

<sup>52</sup> Anon., *Br. med. J.*, 1903, ii: 196.

<sup>53</sup> C E de M Sajous, *The internal secretions and the principles of medicine*, Philadelphia, F A Davis, 1911, 4th ed., two vols., 1873 pages.

<sup>54</sup> *Idem*, *The internal secretions and the principles of medicine*, Philadelphia, F A Davis, 1922, 10th ed.

<sup>55</sup> Anon., *Lancet*, 1912, i: 803.

<sup>56</sup> Robinson, in *Medical Life*, op. cit., note 46 above, pp. 17–21.

<sup>57</sup> F B Wagner, *History of Thomas Jefferson University*, Philadelphia, Lea and Febiger, 1989, p. 370.

<sup>58</sup> *Dictionary of American Biography*, ed. Dumas Malone, New York, Scribner Press, 1934, vol. 16.

<sup>59</sup> Goldzieher, op. cit., note 19 above, p. 321.

President of the American Association for the Study of Internal Secretions (later the Endocrine Society) in 1917.<sup>60</sup> In 1911 in the fourth edition of his book, Sajous begins by pointing out that before the first edition in 1903 the adrenals were thought to have only two functions, (i) sustaining the vascular tone (Oliver and Schäfer) and (ii) neutralizing toxic products of muscular activity and other poisons (Abelous and Langlois). Neither theory explained many of the clinical features of Addison's disease so, according to Sajous, there must be an important missing factor, and this "my labors seem to me to have supplied". The missing factor was that insufficient adrenal function leads to "inadequate oxidation and therefore imperfect tissue metabolism and nutrition, and also impairment of the auto-protective functions of the body at large". He proposed three clinical forms of hypoadrenia:

1. *Functional hypoadrenia*, a form in which the adrenals, though not the seat of organic lesions, are functionally deficient because of tardy development, debilitating influences such as fatigue, starvation, etc. and old age;

2. *Progressive hypoadrenia or Addison's disease*, a form in which the functions of the adrenals or their secretory nerves are progressively impaired by organic lesions, tuberculosis, cancer, fibrosis etc.;

3. *Terminal hypoadrenia*, a late complication of infectious diseases and toxæmias, owing to exhaustion of the secretory activity of the adrenals during the earlier and febrile stage of the causative disease.

The main symptoms of functional hypoadrenia were "asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anaemia, slow metabolism, constipation, and psychasthenia". The field was vast since, for Sajous, functional hypoadrenia could, and did, exist in infancy, childhood, adulthood and old age, and he regarded it as self-evident that if one compared the "ruddy, warm, hard muscled, heavy, out-of-door romping child" with the "pale, emaciated, or pasty child", the latter had functional hypoadrenia. In adults it developed when "as a result of the vicissitudes of our existence" the adrenals were exhausted by the strain of exercise or labour. The main symptoms were fatigue and increased susceptibility to infection. Sajous claimed that the infrequency of infections in physicians in spite of frequent exposure proved that "*the normal adult whose adrenals function normally is relatively resistant to infection*" (italics in original). Deficiency of food and excessive work led to hypoadrenia and infection and explained many of the deaths of soldiers on active service. Masturbation and excessive venery were important morbid factors and the pallor and asthenia of the licentious occurred because the "liquid portion of the semen is rich in adrenal principle". The asthenia of old age could also be explained by "the defective supply of adrenal principle", and Sajous thought "It is quite probable that the centenarians owe their prolonged longevity mainly to the integrity of their adrenals". Where treatment was concerned, he recommended general health measures. In infants the answer was breast feeding, and in adults small doses of mercury ("a powerful adrenal stimulant"), rest, and a good diet—but not too much meat, which could precipitate hyperadrenalism! In the aged, Sajous could testify to the wonderful effects that testicular extract had on Brown-Séquard since it

<sup>60</sup> Hans Lissner, 'The Endocrine Society: the first forty years (1917–1957)', *Endocrinology*, 1967, **80**: 5–28.

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“enriched his blood with the pabulum of oxidation, metabolism and general nutrition without impairing his adrenals”. He also recommended that elderly people take the raw juice of 1 lb of uncooked meat every day since this was “a powerful agent for good . . . which more than compensates for the weakened adrenals”. Sajous advised that aged men should be extremely reserved in sexual matters, since “waste of seminal fluid to them means waste of life”.<sup>61</sup> Sajous’s ideas were, as we will see, ridiculed by physiologists but as late as 1931 in the first edition of the *Cyclopaedia* published after his death his views on hypoadrenia are unchanged.<sup>62</sup> By contrast, the chapter on Addison’s disease in the same book by Leonard G Rowntree (1883–1959) of the Mayo Clinic discusses the newly discovered cortical hormone.<sup>63</sup>

The attention of clinicians was further focused on adrenaline by the work of W B Cannon (1871–1945), Professor of Physiology at Harvard, and in particular his 1915 book *Bodily changes in pain, hunger, fear and rage*.<sup>64</sup> His concept of the “fight, flight” reaction grew from his work on the mechanism of swallowing. Serendipitously, he found that if his experimental animals were frightened by rough handling or the barking of a dog, movement of their gastrointestinal tract virtually ceased. After further work he proposed that adrenalin was an emergency hormone which:

Plays an essential role in calling forth stored carbohydrate . . . flooding the blood with sugar; it helps in distributing the blood to the heart, lungs, central nervous system and limbs, while taking it away from the inhibited organs of the abdomen. It quickly abolishes the effect of muscular fatigue and it renders the blood more coagulable.<sup>65</sup>

This theory was, according to the American physiologist Roy Hoskins (1880–1964), “widely and promptly misunderstood and misquoted”,<sup>66</sup> partly because Cannon himself initially thought he was studying a process which was essential to life and because some of the data on which it was based were questionable.

During and immediately after the First World War, the concept of hypoadrenia was extended in a plethora of articles, virtually all of which were based on the premise that through exhaustion the adrenals did not produce enough adrenaline, which led to low blood pressure and asthenia. The subject was reviewed in *Endocrinology* in 1919 by the Italian Nicola Pende (1880–1970), Professor of Medicine in Genoa, who began with the premise that:

Particularly important are those states of hormonal imbalance which are at the border line between health and disease, and which represent either latent or mild endocrinopathic conditions, real *endocrine diatheses* or *endocrinopathic temperaments* [italics in the original]. It is already

<sup>61</sup> Sajous, op. cit., note 53 above, vol. 1, pp. 80–97.

<sup>62</sup> C E de M Sajous, E Bortz, ‘Adrenals: diseases of the’, in *The cyclopaedia of medicine*, Philadelphia, F A Davis, 1931–34, pp. 203–28.

<sup>63</sup> L G Rowntree, ‘Addison’s Disease’, *ibid.*, pp. 138–52.

<sup>64</sup> For details of Cannon’s life and work see H H Dale, ‘Walter Bradford Cannon’, *Obituary Notices of Fellows of the Royal Society of London*, 1947, 5:

407–23, and *Dictionary of Scientific Biography*, New York, Charles Scribner’s Sons, vol. 15, Suppl.1, pp. 71–7.

<sup>65</sup> W B Cannon, *Bodily changes in pain, hunger, fear and rage*, New York, D Appleton, 1915.

<sup>66</sup> R G Hoskins, *Endocrinology*, New York, W W Norton and Co., 1941, p. 31. This book is dedicated to Cannon, “expounder and exponent of wisdom”.

understood that for each of the best known endocrine glands, in addition to frank malfunctions there must be recognized minor degrees of perturbation giving rise to the endocrinopathic habitus.<sup>67</sup>

He then claimed that the hypoadrenal constitution had been first studied in Italy, citing “constitutional anghipotony of A. Ferranini” and “the spurious hyposurrealism of Castellino”. He distinguished four principal types of “irritable heart” in soldiers, all of which came from “a certain irritability of the glands or from an easy exhaustion of their secretory nerves”. Those exposed to repeated explosions developed “Basedowism” with symptoms and signs similar to those of hyperthyroidism. Another group of “functional cardiopathies” occurred in men who had been called back to the colours, and this was attributed to “functional inhibition of the adrenals due to the war”. It recovered quickly when these “rather elderly” soldiers were taken out of the front line. Adrenal asystoly was the name given to a syndrome in which soldiers died suddenly from heart failure and had small adrenals at autopsy.<sup>68</sup> The claimed pathophysiological basis was that the heart stopped because the adrenals normally supplied a physiological stimulus necessary for its contractions—a variant of the tonus theory.<sup>69</sup> Deaths of soldiers from various forms of infectious disease (which would not normally have been expected to be fatal) were thought to have been accentuated by “capsular exhaustion due to the excessive war fatigue”. During the great influenza pandemic of 1919 several authors were impressed that “the most striking and most constant symptoms of influenza (asthenia, prostration and low blood pressure) are also the cardinal symptoms of Addison’s disease”.<sup>70</sup> According to Sajous these terminal symptoms of extreme asthenia, low blood pressure, hypothermia, rapid breathing, cyanosis, weak pulse and tendency to syncope and heart failure, “correspond to those of Addison’s disease” and this was due to hypoadrenia, which should be treated by injections of adrenaline.<sup>71</sup>

### The Association for the Study of Internal Secretions: A Forum for Solving the Adrenal Problem?

The Association for the Study of Internal Secretions was founded by a group called together by Dr Henry R Harrower of Glendale, California, at the meeting of the American Medical Association in June 1916.<sup>72</sup> A business meeting was held at the next American Medical Association meeting in New York in 1917 at which Sajous was elected President with a vice-president, secretary and nine council members. The aims of the society as outlined by Dr Lewellys F Barker (1867–1943)<sup>73</sup> were to bring together people

<sup>67</sup> N Pende, ‘Endocrinopathic constitutions and the pathology of war’, *Endocrinology*, 1919, 3: 329–41, on p. 329. At the age of 82 he published a major treatise, ‘Neuroendocrinologica correlativa’. V C Medvei, *A history of endocrinology*, Boston, MTP Press, 1982, p. 788.

<sup>68</sup> O Josué, ‘L’asystolie surrénale’, *Paris Méd.*, 1916–17, 6: 7–13.

<sup>69</sup> J Carles, ‘Insuffisance surrénale chez le combattant’, *J. Méd. Bordeaux*, 1918, 89: 185–8.

<sup>70</sup> D M Cowie, P W Beaven, ‘On the clinical evidence of involvement of the suprarenal glands in influenza and influenzal pneumonia’, *Arch. Int. Med.*, 1919, 24: 78–88.

<sup>71</sup> C E de M Sajous, ‘Active co-operation between the physiologist and the clinician and comparative analysis of coordinated data in the study of the internal secretions’, *Endocrinology*, 1918, 2: 258–82. This was his Presidential Address given to the Society on 10 June 1918.

<sup>72</sup> Lisser, op. cit., note 60 above, pp. 10–11.

<sup>73</sup> Lewellys F Barker was credited with being first to introduce laboratory investigation into clinical medicine. He was also in favour of full-time clinical professorships although, when they were introduced at Hopkins in 1913, he decided to continue in private practice. He was an anatomist by training and, according to Dana Atchley, “He knew no medicine

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“contributing to the progress of the study of the endocrine glands, whether that study be physiological, chemical, histological or what not”. Barker, Osler’s successor as physician in chief at Johns Hopkins Hospital in 1905, noted that in the previous eighteen months nearly 2,000 articles on endocrine function had been published in the world literature, and he proposed that they should set up a journal not only to publish articles by members of the Society but also to abstract the literature. From its first appearance in 1917 the journal *Endocrinology* was quarterly and then from 1921 bi-monthly. All the early volumes had substantial sections devoted to abstracts, and even so-called “trash” was included to allow readers to form their own judgement.<sup>74</sup> The early years of the Association seem to have been marked by considerable tension between clinicians and physiologists and one of the founders, Dr Frank M Pottenger, wrote that:

Our problem was particularly difficult because the existence of the Association depended upon the support of clinicians. Accordingly, there was more or less disappointment expressed by our members, not only by complaint but too often by resignation. This made the financing of the early years exceedingly difficult.<sup>75</sup>

In the first five years, one of the hottest topics was the adrenal glands and, specifically, the relative contributions of the cortex and medulla. For example, in the 1919 volume of *Endocrinology* there were 169 abstracts from the world literature on the general topic adrenaline/adrenal secretion compared with 132 on diabetes. The first volume in 1917 contained two articles by physiologists on the function of the adrenals, which supported Biedl’s view that it was the cortex which was essential to life. The first was by Thomas Swale Vincent (1868–1933), who had been assistant to Schäfer at University College, London, from 1895 to 1899 but was by this time Professor of Physiology at the University of Manitoba.<sup>76</sup> Vincent was a careful worker with a highly critical mind, the effect of whose sceptical views (especially about the unscientific views of clinicians) have been described by Diana Long Hall.<sup>77</sup> In his article Vincent stated unequivocally that the cortex and the medulla were independent glands and that the medulla was not essential to life.<sup>78</sup> In support of the latter proposition he cited his own work with Wheeler in which practically all the medulla had been destroyed in dogs without causing death<sup>79</sup> and the work of Stewart and Rogoff, who had found that removal of one adrenal and section of the nerves of the other (thus virtually abolishing adrenaline secretion) in dogs and

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and never had known any. He built up a huge practice, got some bright young assistants who did the diagnostic work and would merely come in and lay on hands”. Quoted in A McGhee Harvey, *Science at the bedside: clinical research in American medicine 1905–1945*, Baltimore, Johns Hopkins University Press, 1981, pp. 70–1. A more sympathetic assessment is Rufus Cole, ‘Lewellys Franklin Barker (1867–1943)’, *Trans. Assoc. Am. Phys.*, 1944, **58**: 13–17.

<sup>74</sup> R G Hoskins, ‘Endocrinology in retrospect and prospect’, *Endocrinology*, 1920, **4**: 602–5.

<sup>75</sup> Lisser, op. cit., note 60 above, p. 8.

<sup>76</sup> Professor T Swale Vincent, Obituary, *Nature*, 1934, Jan. 27th : 128–9. In 1910 he was asked to write a series of reviews on the ductless glands for

Ascher-Spiro’s *Ergebnisse der Physiologie* and these were expanded into a book, *Internal secretion and the ductless glands*, first published in 1912 which went into three editions.

<sup>77</sup> Diana Long Hall, ‘The critic and the advocate: contrasting British views on the state of endocrinology in the early 1920s’, *J. Hist. Biol.*, 1976, **9**: 269–85.

<sup>78</sup> Swale Vincent, ‘Recent views as to the function of the adrenal bodies’, *Endocrinology*, 1917, **1**: 140–52.

<sup>79</sup> T D Wheeler, S Vincent, ‘The question as to the relative importance to life of cortex and medulla of the adrenal bodies’, *Trans. Royal Soc. (Canada) Ser III*, 1917, **11**: 125–7.

monkeys was compatible with long term survival of the animals in good health.<sup>80</sup> The other article by the physiologist Roy Hoskins, editor of *Endocrinology* from 1917 to 1940 and at this time working at the University of Chicago,<sup>81</sup> made the point that continuous infusion of adrenaline could not preserve the life of an adrenalectomized animal, and included the definite statement that:

Laying all theories aside and facing this single fact, one can scarcely escape the conclusion that adrenin deficiency plays no essential part in the Addison syndrome or its laboratory equivalent, experimental suprarenal deficiency. Adrenin discharge is apparently then merely a reserve source for use in emergencies.<sup>82</sup>

In his presidential address to the Association for the Study of Internal Secretions in 1918, Sajous attempted to rebut these claims by physiologists. Swale Vincent's (1917) view that "There is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite function" was to Sajous an abysmal confession of ignorance and ignored clinical observation which would "always remain a rich mine of physiological facts". Sajous had confirmed from personal experience that 8 to 12 minim doses of adrenaline are "positively lifesaving in uncomplicated toxæmias" and he cited numerous papers in favour of his theory that death in most infectious diseases was due to hypoadrenia.<sup>83</sup>

Lewellys Barker's presidential address in 1919 was also devoted to the adrenals and was notably conciliatory to the polarized camps of clinicians and physiologists.<sup>84</sup> He stressed that both groups had important contributions to make and that it was natural for clinicians to have invented the concept of hypoadrenia for "conditions resembling but not identical with Addison's disease". This attempt at mediation was shattered by an article in *Endocrinology* in May 1921 by the physiologist George N Stewart (1860–1930). Stewart was born in Canada but raised in Scotland. His interest in physiology began when he held a G H Lewes Studentship at Cambridge with Michael Foster from 1889 to 1893. When he wrote this article he was at the Cushing Laboratory of Western Reserve University, Cleveland, where he had been working on the adrenals since 1907.<sup>85</sup> He poured scorn on papers by so-called "clinical endocrinologists", especially the French and Italians, suggesting that "the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded and 'nothing is but what it is not'".<sup>86</sup> Stewart noted that:

<sup>80</sup> G N Stewart, J M Rogoff, 'Quantitative experiments on the liberation of epinephrin from the adrenals after section of the nerves', *J. Pharmacol. Exper. Therapeut.* (Baltimore), 1917, 10: 1–48.

<sup>81</sup> Roy G Hoskins (1880–1964) was Professor of Physiology at Ohio State University from 1920 to 1927 and, from 1927 to 1947, Director of the Memorial Foundation for Neuroendocrine Research in Boston. He was President of the Association for the Study of Internal Secretions in 1926 and the June 1942 issue of *Endocrinology* was dedicated to him.

<sup>82</sup> R G Hoskins, 'The relation of the adrenal glands to the circulation of the blood', *Endocrinology*, 1917, 1: 292–305.

<sup>83</sup> C E de M Sajous, 'Active cooperation between the physiologist and the clinician and comparative analysis of coordinated data in the study of the internal secretions', *Endocrinology*, 1918, 2: 258–82.

<sup>84</sup> Lewellys F Barker, 'Remarks on the functions of the suprarenal glands as revealed by clinical-pathological studies of human beings and by experiments on animals', *Endocrinology*, 1919, 3: 253–61.

<sup>85</sup> *Dictionary of American Biography*, ed. Dumas Malone, New York, Scribner Press, 1936, vol. 18.

<sup>86</sup> G N Stewart, 'Adrenal insufficiency', *Endocrinology*, 1921, 5: 283–306, on p. 299.

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It is a curious thing that while the great bulk of the experimental evidence emphasizes the importance of the cortex without demonstrating any definite physiological value for the medulla, or at least for its epinephrin secretion, the bulk of clinical writers seem almost to ignore the existence of the cortex. "Adrenal insufficiency" in nine clinical papers out of ten, so far as they have come to the notice of the present writer, seems to connote interference with the output of epinephrin . . .<sup>87</sup>

Stewart emphasized that there was no experimental evidence that fatigue diminished the output of adrenaline and, indeed, no evidence that adrenaline deficiency caused any symptoms. "What", he wondered, "is the use of a clinical observer looking at a sick man and saying 'no doubt he is suffering from capsular exhaustion due to excessive war fatigue . . . ?'"<sup>88</sup> The syndrome of "hypoadrenalism" in soldiers with a variety of infections was simply "the product of an undisciplined imagination".<sup>89</sup> To ram home the illogicality of clinicians and their theory of hypoadrenalism, Stewart pointed out that in 1917 one French physician, Naamé, blamed seasickness on hypoadrenalism due to inhibition of the adrenals by the rolling of the ship, while another, Cazamian, attributed it to hyperadrenalism from stimulation of the adrenals by rolling of the ship.<sup>90</sup> Yet another French doctor had attributed sickness in pilots to hypoadrenalism.<sup>91</sup>

In *Endocrinology* in March 1922 Sajous entered a vigorous defence under the title 'Adrenal insufficiency from the viewpoint of the clinician'. He had long believed that animal experimentation was a blind alley and that suddenly removing both adrenals in a healthy animal was, he contended, not analogous to the situation in hypoadrenia, where "there exist besides, systemic phenomena due to the pathogenic agent, toxins, endotoxins, wastes, the defensive reaction, lesions in other organs including the nervous system, etc, which the trained endocrinologist takes into account".<sup>92</sup> The fact that George Stewart and Swale Vincent admitted not knowing the function of the adrenals simply indicated the inadequacy of physiologists.<sup>93</sup> "Is there not", enquired Sajous, "a more promising field of research, one in which their labours would prove more fruitful?" Hypoadrenia was recognized by "thousands of physicians" and Sajous reiterated his theory that adrenaline took part in pulmonary and tissue respiration by "becoming part of the haemoglobin molecule". The views of experienced clinicians like himself could not be overthrown by artificial physiological experiments. He concluded:

An experience of over forty years as a physiologist (my first chair), clinician, encyclopedist and editor, has only served to emphasize the fact that physiology will become "a great white light" when physiologists will fully realize that its true worth lies in *constructive synthesis* [italics in original] along with contributions from all other branches of medical science.<sup>94</sup>

A similar exchange took place in England between Swale Vincent, who had returned to England as Professor of Physiology at the Middlesex Hospital, and the physician Walter Langdon Brown (1870–1946). In 1920 Langdon Brown who was, like Sajous, an

<sup>87</sup> *Ibid.*, p. 295.

<sup>88</sup> *Ibid.*, p. 301.

<sup>89</sup> *Ibid.*, p. 300.

<sup>90</sup> *Ibid.*, p. 302.

<sup>91</sup> G Ferry, 'Mal des altitudes et hygiène de l'aviateur', *Ann. Méd. (Paris)*, 1919, 6: 124–37.

<sup>92</sup> C E de M Sajous, 'Adrenal insufficiency from the viewpoint of the clinician', *Endocrinology*, 1922, 6: 197–212, on p. 198.

<sup>93</sup> In a review in 1924 Stewart wrote, "The cortex is the part of the adrenal essential to life. How it exercises its function is utterly unknown", *Physiol. Rev.*, 1924, 4: 163, while, in 1917, Vincent wrote, "We do not know why its removal causes death, but it is possible it is due to some defect of muscular metabolism", *Endocrinology*, 1917, 1: 140–52.

<sup>94</sup> Sajous, *op. cit.*, note 92 above, p. 209.

interpreter and commentator, not an innovator, gave a lecture to the Suffolk branch of the British Medical Association on 'The principles of internal secretion'.<sup>95</sup> After restating the Cannon flight/fright hypothesis, he suggested that diseases due to overaction of adrenaline might be "raised blood pressure with glycosuria in later life . . . since they may be induced by overstrain and worry, which irritate the sympathetic". However, he still ignored the findings of the physiologists when he said:

We have a clear-cut example of adrenaline defect in Addison's disease, in which all the symptoms can be attributed to loss of sympathetic action. Failure of its inhibitory action on the stomach would tend to vomiting, and of its stimulating effect on the vaso-constrictor nerves to low blood pressure and a relaxed condition of the peripheral vessels which would lead to pigmentation.<sup>96</sup>

He suggested that prolonged mental and physical conflict or infection might lead to adrenaline exhaustion, which "entered into many war neuroses and other functional states characterised by lack of vascular tone, vasomotor instability, and myasthenia, especially when accompanied by a low blood pressure". For many years Langdon Brown was the only English physician to accept and apply Freud's teachings<sup>97</sup> and in this 1920 lecture he claimed that "the two newest methods of medicine", psychotherapy and endocrinology, were different aspects of the same problem. In his 1927 book, *The endocrines in general medicine*, he declared that endocrinology "provides the missing link between biology and psychology", and in the chapter on 'The adrenals and the chromaffin system' he included Addison's under diseases of the medulla.<sup>98</sup> Christopher Lawrence has suggested that endocrinology must have looked like "a gift" to someone of Langdon Brown's perceptions, since it enabled him to underwrite the autonomy of clinical medicine.<sup>99</sup> Less charitably, one might also say that at a time when endocrine disease could be diagnosed only on clinical grounds it enabled him to build up a large private practice as someone who could recognize minor endocrine disturbances. In 1923 he took the chair at a meeting of the Section of Therapeutics and Pharmacology of the Royal Society of Medicine on 'The present position of organotherapy'.<sup>100</sup> The discussion was opened by Swale Vincent, who the previous year had given the Arris and Gale Lecture at the Royal College of Surgeons entitled 'A critical examination of current views on internal secretion'.<sup>101</sup> In general, Vincent thought, "there has been much loose writing and loose thinking on the whole subject of internal section" while, in relation to the adrenal, "we find ourselves in a veritable quagmire of doubt and difficulty". He reiterated his views about:

The untenable hypothesis that the secretion of the chromaffin tissue maintains, or helps to maintain, the tone of the blood-vessels, and the normal blood pressure has given rise, for example, to the

<sup>95</sup> W Langdon Brown, 'The principles of internal secretion', *Br. med. J.*, 1920, ii: 687-91.

<sup>96</sup> *Ibid.*, p. 687.

<sup>97</sup> Obituary, *Munk's Roll. Lives of the Fellows of the Royal College of Physicians of London 1826-1925*, London, The College, 1955, pp. 491-2.

Langdon Brown spent most of his working life at St Bartholomew's Hospital and it was said that "his fame moved well in advance of his promotion on hospital staffs".

<sup>98</sup> W Langdon Brown, *The endocrines in general*

*medicine*, London, Constable, 1927, pp. 69-76.

<sup>99</sup> C Lawrence, 'A tale of two sciences: bedside and bench in twentieth-century Britain', *Med. Hist.* (this issue).

<sup>100</sup> Royal Society of Medicine: Therapeutics and Pharmacology, 'The present position of organotherapy', *Lancet*, 1923, i: 130-2.

<sup>101</sup> Swale Vincent, 'The Arris and Gale Lecture on a critical examination of current views on internal secretion', *Lancet*, 1922, ii: 313-20.

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whole fabric of vagotonia and sympathicotonia.<sup>102</sup> When it became clear that physiological experiments lent no support to these views, a large number of physicians defended the use of organic extracts on the grounds that though they may contain no physiologically active principle, they are found useful empirically.<sup>103</sup>

Summing up, Langdon Brown said that “The cold douche of scepticism with which Professor Vincent had opened the proceedings was refreshing” and, in reply, Vincent said “It was assumed by the President that he had attempted to disparage clinical evidence, but he did not mean to do this, but only to dwell on the necessity of controls and a full record of cases”. Swale Vincent’s cold douche had little effect on Langdon Brown because in November 1923 in a lecture to the British Medical Association at Southend-on-Sea, he again indulged in what Vincent would have called speculation, saying that:

The sympathetic is defensive not only against the external foe, but also against internal invasion by bacteria. Fever is a defensive mechanism largely controlled by the sympathetic through the ductless glands associated with it. This explains why (1) patients with endocrine defects stand infections badly; (2) infections may lead to endocrine exhaustion. [ . . . ] The adrenal medulla from its activating effect on the sympathetic is a fighting gland. And as the adrenal cortex tends to virilism, the owner of a well-developed pair of adrenals is pugnacious and masculine in type, with plenty of drive, not to say aggression. If the adrenals are in defect we see a weakening of all these characteristics, with a tendency for the vagus to get the upper hand, which may precipitate such things as asthma. If the adrenals are in excess we find a liability to anxiety neurosis, and to phobias of all kinds.<sup>104</sup>

## Adrenal Organotherapy

As early as 1896 at least three firms were marketing a wide variety of organ extracts in Britain.<sup>105</sup> Among the preparations available from Burroughs, Wellcome and Co., which “they are now submitting for professional trial”, was suprarenal substance, of which it was said:

A dose of  $\frac{1}{800}$ <sup>th</sup> of a grain of the active principle produces distinct physiological effects on the heart and arteries. The absence of the secretion of the gland causes prostration, inanition, and death. None of the organic extracts at present in use, if we except the proved results of “thyroid”, is likely to prove of more clinical value.<sup>106</sup>

Apart from the use of adrenaline for its vasoconstrictor properties, suprarenal extracts were recommended by doctors and advertisers for conditions in which asthenia and low

<sup>102</sup> This theory, associated with the Viennese physicians H Eppinger and L Hess, held that the whole vegetative nervous system was under hormonal control. The sympathetic was controlled by continuous secretion of adrenaline, and the parasympathetic by “autonomin” or hormone X. Symptom complexes were described which corresponded to vagotonia and sympathicotonia and could be diagnosed by the response to pilocarpine or physostigmine. Their book *Vagotonia: a clinical study in vegetative neurology* was published in 1910 and 1915 in English translation. It was reviewed by Vincent and dismissed as a “highly speculative theory, based on a false analogy and with little or no

clinical or experimental evidence in its favour”. *Endocrinology*, 1917, I: 459–67.

<sup>103</sup> Op. cit., note 100 above, p. 130.

<sup>104</sup> W Langdon Brown, ‘Minor endocrine disturbances and their metabolic and psychical effects’, *Br. med. J.*, 1923, ii: 1073–7, on pp. 1073, 1075.

<sup>105</sup> In the 1896 *Medical Annual* (Bristol, John Wright and Sons), the three firms mentioned were Ferris and Co. (Bristol) who imported from Chaix and Raimy of Paris, Oppenheimer Son and Co. (London), and Burroughs, Wellcome and Co. (London).

<sup>106</sup> *Ibid.*, p. 695.

blood pressure were prominent.<sup>107</sup> Before the First World War any extract (especially if it had been shown to have a definite physiological action) was tried empirically on a wide variety of cases. Thus, for example, thyroid extract was used in “those forms of obesity in which there is a tendency to general softness and flabbiness of tissues” as well as in epilepsy, melancholia and insanity.<sup>108</sup>

The English doctor Ivo Geikie Cobb<sup>109</sup> whose book on internal secretions for general practitioners went through three editions between 1916 and 1921 was clearly a disciple of Sajous, whom he quotes frequently. Thus, he suggests that a boy or girl who developed asthenia, languor, hypophysis and “backwardness at school” after an infection was probably suffering from hypoadrenia and that adrenal extract would “counteract this condition, render the patient more active and banish the indolence”. The same was true in adults after an illness where “delayed convalescence was a marked feature”.<sup>110</sup>

Faced with a fatal illness, especially when the patient was himself a member of the profession, even “respectable” doctors could disregard the physiological evidence as shown by the example of the Muirhead regime. In May 1920 A L Muirhead, a Professor of Pharmacology with a history of tuberculosis, was referred to Leonard Rowntree at the Mayo Clinic.<sup>111</sup> He had suffered from Addison’s disease for several years and was barely able to work.<sup>112</sup> In July 1920 he was given a subcutaneous injection of 1 cc of 1:10,000 adrenalin which produced a sensation of exhilaration and increased strength. For the rest of his hospital stay he had a similar injection of 1/2 cc twice a day, and after two weeks he could “walk a mile instead of only two blocks”. In addition to the adrenaline he had a rectal infusion of dried suprarenal gland (10 gr) every day. This route was chosen because of gastric intolerance. When Muirhead wrote himself up, he said that the pigmentation had completely disappeared. Unfortunately, his progress was not maintained and he died in 1921. However, Rowntree was impressed by the results of the treatment which was “striking objectively as well as subjectively”<sup>113</sup> and the Muirhead regime remained the standard treatment at the Mayo Clinic into the late 1920s.<sup>114</sup>

<sup>107</sup> H A Hare H A, ‘Progress of therapeutics: new remedies’, *Medical Annual*, Bristol, John Wright and Sons, 1898, p. 7.

<sup>108</sup> *Ibid.*, p. 3.

<sup>109</sup> Cobb obtained his MRCS LRCP from St Thomas’s Hospital in 1910 and an MD (Brussels) in 1912. As far as I can discover he never held a hospital appointment in Britain but his continuing interest in the wilder shores of endocrinology is shown by the publication in 1947 of the third edition of his book, *The glands of destiny: a study of the personality*. I have been unable to find an obituary or any other biographical details.

<sup>110</sup> J G Cobb, *The organs of internal secretion: their diseases and therapeutic application*, 3rd ed., London, Baillière, Tindall and Cox, 1921, p. 169. This book arose from a series of articles in the *Medical Press and Circular* in 1916. The one on the internal secretions of digestion was reviewed by Roy Hoskins in *Endocrinology* as “a brief review of the physiology of gastrin and secretin with some dubious data on the value of liver extracts and ‘neo-hormonal’”,

*Endocrinology*, 1919, 3: 63. Another on the therapeutic use of hormones was described by Hoskins as “An attempt to present briefly the indications for the use of a variety of gland products, several of which, in the opinion of most therapeutists, are useless”. *Endocrinology*, 1919, 3: 67.

<sup>111</sup> Rowntree (1883–1959) was Professor of Medicine at the Mayo Clinic from 1920 to 1932 when he went to Philadelphia. He was involved in the early trials of Swingle and Pfiffner’s successful adrenal cortical extracts in 1930. See Norman M Keith, Philip S Hench, ‘Leonard George Rowntree (1883–1959)’, *Trans. Assoc. Am. Phys.*, 1960, 73: 29–31.

<sup>112</sup> A L Muirhead, ‘An autograph history of a case of Addison’s disease’, *J. Am. Med. Assoc.*, 1922, 79: 556–7.

<sup>113</sup> L G Rowntree, ‘Subsequent course of a case of Addison’s disease’, *J. Am. Med. Assoc.*, 1922, 79: 556–7.

<sup>114</sup> *Idem*, ‘Studies in Addison’s disease’, *J. Am. Med. Assoc.*, 1925, 84: 327–40.

## Hypoadrenia

### Solution of the Cortical Problem

In 1929 Swingle and Pfiffner reported that they had extracted “the cortical hormone” using organic lipid solvent and that it could keep adrenalectomized cats alive indefinitely—one of their articles is illustrated by a charming photo of seven cats which had survived 100 days compared to the previous average of 7.5.<sup>115</sup> This was the beginning of the end of an era in which, according to Berkeley, “many clinicians have been so much absorbed with the known facts of the medullary secretion section that they have almost ignored the function of the cortex”.<sup>116</sup> It is certainly true that many physicians such as Sajous, Pende and Langdon Brown, did ignore the physiological evidence in their enthusiasm to make endocrinology an all-embracing discipline which would explain (and cure) everything from fatigue to neurasthenia to war neurosis. Over-enthusiasm blighted the early years of endocrinology when what was needed was, as Leonard Rowntree (a clinician) wrote in 1922, “well planned and carefully executed clinical and experimental investigations, accompanied by analytic and critical judgement”.<sup>117</sup> Physicians were beguiled by the contrast between the physiological actions of adrenaline and the symptoms of Addison’s disease which appeared to be the exact opposite. Ergo Addison’s disease was adrenaline deficiency. It also seemed logical to assume that there must be minor degrees of Addison’s disease. Thus was born the concept of hypoadrenia, which several physiologists claimed was one of the reasons for the disrepute into which endocrinology fell in the 1920s when Harvey Cushing suggested that many clinicians were “credulous” and had lost their bearings and embarked “glandward ho!”.<sup>118</sup> Roy Hoskins’ final verdict on the clinical construct of hypoadrenia was that:

A host of sick people swallowed dried adrenal gland substance and recovered from a host of diseases. *Post hoc, propter hoc*—the adrenal material cured the disease and hypoadrenia was vindicated.<sup>119</sup>

<sup>115</sup> W W Swingle, J K J Pfiffner, ‘Adrenal cortical hormone’, *Medicine*, 1932, **11**: 371–43. These extracts were weak and expensive to make. Each cat needed 5 cc per day and to keep one alive for 100 days cost \$500.

<sup>116</sup> W N Berkeley, *The principles and practice of endocrine medicine*, London, Henry Kimpton, 1926, p. 217.

<sup>117</sup> Leonard G Rowntree, ‘Discussion on internal secretions’, *J. Am. Med. Assoc.*, 1922, **79**: 107.

<sup>118</sup> Harvey Cushing, ‘Disorders of the pituitary gland: retrospective and prophetic’, *J. Am. Med. Assoc.*, 1921, **76**: 1721–6.

<sup>119</sup> R G Hoskins, *The tides of life: the endocrine glands in bodily adjustment*, London, Kegan Paul, Trench Trubner, 1933, p. 52.