



Endocrinology of Yesteryear

From playwright to professor: the story of Charles Brown-Séquard

Charles Edouard Brown-Séquard was born on April 8 1817 on Ile France, a Caribbean island later conquered by the British and called Ile Mauritius. Although a British subject, his French origins meant that, culturally, he remained very much attached to France and, as a young man of great intellectual promise, his fame as a successful playwright brought him to Paris. However, he soon realized that fierce competition and the lack of any political support meant that there was little opportunity for him to succeed, so he turned to the study of medicine in an attempt to assure himself a living.

Medicine was then at the dawn of a remarkable period of growth. In 1815 there were no more than 10 physiological laboratories in the world, but by 1890 that number had grown to between 100 and 250.

Experimental physiology was still in its infancy and most prominent doctors or faculty professors, such as Claude Bernard, the famous French physiologist, ran private research laboratories. They financed these by teaching physiology students, many of whom came from wealthy families and paid fees. The brilliantly inquisitive Brown-Séquard became fascinated by the physiology of the neural system and was taken on as an assistant by Dr Martin-Magron and Professor Magendie. The pay was so low that he was forced to live in an unheated room and often had to prepare his meagre meals from the remains of his experimental laboratory animals! He slept very little, and usually spent 18-19 hours per day in the laboratory or reading and writing. Today we can only admire this young man's perseverance and diligence, which is typical of the 19th century's medical giants.

Brown-Séquard's dream was to become an established professor in Paris but, although his scientific work clearly deserved recognition, he found that prejudice against his non-French origins prevented it. This fact is illustrated by the words of the famous French neurologist, Paul Broca, when he recommended Brown-Séquard to the University of Pennsylvania in 1852: "For eight years Brown-Séquard has exhausted his resources and imposed upon himself incredible sacrifices in order to carry out expensive research into experimental physiology... Also acknowledged to be possessed of eminent talent, he has nevertheless been unable to attain any official position simply because he is a foreigner." In 1851, 4 years after Claude Bernard became Professor of Physiology at the Collège de France, this prejudice, combined with a nervous breakdown and political change, led him to interrupt his career in Paris and travel to the United States, where he accepted appointments at the University of

Philadelphia, Harvard University and in New York. Such abrupt changes in his career would be a hallmark of his entire scientific life. At that time, however, experimental research in American universities was still limited, whereas conditions in France began to improve, particularly at the Collège de France. Consequently, he spent 6 years of his life crossing the Atlantic. It is said that he continued to do research on the ships using the sailors as subjects!

In the years leading up to 1856, Brown-Séquard conducted his most outstanding experimental research and this included his work on the spinal cord. As with so many of the so-called established theories of the 19th century, the dogma that sensitive fibres occurred only in the dorsal columns of the spinal cord was based on strong opinion rather than on fact. Based on animal experimentation and studies of one patient with a traumatic spinal cord lesion, Brown-Séquard contradicted this theory and postulated that the ventral columns of

Editorial

With this second issue of *EFES News*, we launch a series of articles remembering famous physicians who have contributed to endocrinology. Many of early modern medicine's towering figures have contributed to the history of endocrinology and this issue's article celebrates a 19th-century physician and scientist whose creative approach to research and hard-won successes continue to inspire us today.

As well as looking back, this issue also looks forward and provides an overview of some recent discoveries in endocrinology and their exciting therapeutic potential. Also coming up in the future is the 5th European Congress of Endocrinology in Turin in 2001 and Ebo Nieschlag's article gives us a glimpse of the delights in store for us at this meeting and the hard work that has been done and continues to be done behind the scenes.

I hope you enjoy this issue and look forward to your feedback.

ALBERT BURGER, EDITOR

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the spinal cord were also sensitive conducting fibres. Later, he established that these fibres crossed over from the dorsal to the ventral part of the spinal cord. The term, Brown-Séquard's syndrome, has remained in the literature as a hallmark of neurological discovery.

In 1869 Brown-Séquard suddenly left his position as Professor of Physiology at Harvard in the hope of securing a prominent position in Paris, only to be offered the lowly position of a 'chargé de cours' despite his celebrity status as a neurologist and physiologist. In 1878 he was finally called to a position that matched his expertise: the chair of the late Claude Bernard, Professor of Medicine at the Collège de France.

Brown-Séquard made two remarkable contributions to the field of endocrinology. During the 1850's Addison elegantly described the now well-known Addison's disease and Brown-Séquard immediately performed experimental work showing that the ablation of the suprarenal bodies was not compatible with life. This experiment was not fully valued at the time, but has since been recognised as a cornerstone in endocrinology. However, Brown-Séquard is much more famous for his second observation which has remained, until

today, very controversial: As a 72-year-old man he noticed a great decline in his physical and spiritual capacity to work and took to taking watery extract of ground-up dog and guinea pig testicles! The following is an extract from his report on its effect: "Before the experiments which now occupy me, I had to sit down after standing for an hour working in the laboratory. (sic) Was left exhausted. Today and since the second day and above all the third day after the first injection all that has changed, and I have regained at least all the force which I possessed a number of years ago. I can also now without difficulty and even without thinking about it go up and downstairs almost running, the thing which I always did before the age of 60." As a good scientist he even documented his regaining strength with a dynamometer, an instrument he had been using to monitor his loss of strength since the age of 62. He never discussed the effect of his extract on impotence and libido as these topics were still taboo. The news, announced before the Société de Biologie on June 1 1889, provoked a major controversy.

Brown-Séquard's liquid was then applied to all kinds of diseases, including syphilis and tuberculosis. It is to his credit that he and his assistant made no attempt to profit financially from their discovery and continued to produce the extract free of charge to anyone who wished to conduct experiments with it. When, at last, Brown-Séquard's laboratory could no longer satisfy demand, the methodology was published and huge financial exploitation followed.

To my knowledge we still don't know how rich in testosterone and related androgens this extract was. It is likely, however, that it did contain androgens, and today's body builders and athletes would not deny the usefulness of such a drug. Perhaps more importantly, Brown-Séquard's new type of therapy, later named ophotherapy, was extensively used over the following years with extracts of all kinds of glands. The main success of this type of therapy was introduced shortly afterwards: thyroid extracts taken orally have been credited with saving many thousands of lives.

Unfortunately, the extract did not prevent the aging of this remarkable man who died less than a year and a half later. His story reminds us that the early giants of physiological research relied on genius and sheer hard work to achieve their goals and went through the most unbelievable sacrifices in the process. It is also important to note the frustrating economic and social climate in which these scientists were forced to work. How would it have been if a united Europe had already existed and the only barrier to success was language? It is the aim of EFES to ensure that any vestiges of the unfavourable economic and social climate that existed in the nineteenth century are removed and that language becomes an ever-diminishing hurdle in the endocrinological Europe of the future.

References

- Aminoff M J 1993 *Brown-Séquard, a visionary of science*. New York: Raven Press.
Olmsted J M D 1946 *Charles Edouard Brown-Séquard*. Baltimore: The John Hopkins Press.

Geoffrey Harris Prize

We have pleasure in announcing a new EFES prize generously sponsored by the Beaufour Ipsen Group. This important prize, worth 12 000 Euros, is designed for established researchers in the field of neuroendocrinology and is the first of its kind in Europe. Please contact the EFES secretary: Dr M Forest, INSERM U-329, Hôpital Debrousse, 29 rue Soeur Bouvier, 69322 Lyon CEDEX 05, France (Fax: + 33 478 25 61 68; Email: forest@lyon151.inserm.fr) for full details. The deadline for entries is 31 December 1999 and the award will be presented at the European Workshop for Pituitary Adenomas in Oxford, UK which takes place from 10 to 13 September 2000.

The KIMS UK National Advisory Board,
sponsored by Pharmacia & Upjohn

will be holding a

Satellite Symposium

prior to the 19th Joint Meeting
of the British Endocrine Societies with EFES

Entitled: 'Novel Aspects of
Hormone Replacement Therapy'

Monday 13 March 2000

at 1400 h, Hall 1, International Convention
Centre, Birmingham, UK

A buffet lunch will be served from 1330 h in Hall 11

For further information please contact:
Helen Gregson, British Endocrine Societies
on +44 1454 619347

Endocrinology Tomorrow

New relevance for the PPAR gamma receptor in human disease

The peroxisome proliferating activating receptors (PPAR) alpha, beta and gamma were discovered in the 1990's and belonged then to the large class of orphan receptors. Soon the ability of PPAR alpha to bind hypolipidemic fibrates and PPAR gamma to specifically bind the newly developed drug, thiazolidione, which decreases insulin resistance and blood glucose levels, was discovered. As a result, a multitude of functions in lipid metabolism, inflammation and atherosclerosis were postulated.

This year at Endo 99, O'Rahilly *et al.* reported evidence for the first time, of the relevance of the PPAR gamma receptor in human disease. They described a female patient and her son with severe insulin resistance, diabetes mellitus and hypertension and showed that these patients possessed a heterozygous mutation that inhibits the function of the normal allele in a dominant negative manner - a new clinical syndrome is born.

O'Rahilly *et al.* 1999 *Endo '99 Hot topics* 3(Abstr.).

B2036-PEG, a new drug for the treatment of acromegaly?

The treatment of acromegalic patients can be unsatisfactory since tumour resection does not lead to the normalization of growth hormone (GH) secretion. The use of long-acting somatostatin analogues and dopaminergic compounds has improved this situation markedly and now there is hope for another effective drug, B2036-PEG, a GH analogue preventing GH receptor dimerization. It was tested in 112 patients in 16 centres and preliminary data indicate its effectiveness in lowering IGF-1 values while, as expected, increasing serum GH levels (Trainer *et al.* 1999).

GH plays an important role in the development of diabetic retinopathy, nephropathy and insulin resistance, so it is likely that drugs acting in this way may become very useful in experimental clinical medicine.

Trainer *et al.* 1999 *Endo '99 Hot Topics* 4(Abstr.).

New evidence that T3 can act independently of its receptors

Since the phenotypic, clinical and biochemical manifestations of hypothyroidism are well defined, predicting the phenotype of mice deficient in thyroid hormone (T3) alpha and beta receptors should have been easy. However, Gøthe *et al.* (1999) discovered that such mice only display a small proportion of classical hypothyroidism phenotypes but exhibit an extremely hyperactive pituitary-thyroid axis, poor female fertility and growth and bone retardation. This implies that T3 may have pathways of action additional to those mediated by T3 receptors, a hypothesis confirmed by Johansson *et al.* (1999) who showed that it is the cardiac T3 alpha receptor that is responsible for elevated heart rate in hyperthyroid animals, whilst mice deficient in this receptor are bradycardic.

The successful functioning of complex nuclear machinery depends on T3 receptors and its heterodimers, co-activators and repressors, so one should not be surprised that receptor deficiency is not identical with hormone deficiency. Pharmacological manipulation of the different receptor subtypes could lead to the elucidation of their different roles (see paragraph on GC-1 below).

Gøthe *et al.* 1999 *Genes and Development* **13** 1329-1341.

Johansson *et al.* 1999 *American Journal of Physiology* **276** H2006-H2012.

GC-1 - shedding new light on the physiological roles of T3 receptor isoforms

The recent crystallization of the rat alpha and human beta T3 receptors has enabled researchers to show that T3 binds to its receptor by forming part of its hydrophobic core; the receptor then engulfs the ligand like a carnivorous plant (Ribeiro *et al.* 1998). This discovery has led to the design of GC-1, a new thyroid hormone analogue with an affinity for beta T3 receptor fifty times greater than that for alpha T3 receptor (Chiellini *et al.* 1998). The development of further high affinity subtype-selective ligands could revolutionize our understanding of the T3 receptor and hence clinical thyroidology, an area that has not changed its therapeutic arsenal in 50 years!

Chiellini *et al.* 1998 *Chemistry and Biology* **5** 299-306.

Ribeiro *et al.* 1998. *Journal of Steroid Biochemistry and Molecular Biology* **65** 133-141.

Could a fungus from Congo hold the answer to diabetics?

By screening 50 000 natural compounds, a group of researchers have discovered a central African fungus with insulin-like action. The active compound, now called L-783,281, activates a tyrosine kinase cascade and ISR-1 following insulin receptor activation and seems to be specific for the insulin pathway, since it does not activate the pathway of the IGF-1 receptor or other receptor tyrosine kinases. Neither does it compete with insulin for its receptor suggesting therefore that it probably acts beyond the receptor. It is likely to be active orally and has already been shown to reduce serum glucose levels in insulin-resistant mice (ob/ob), mimicking the action of insulin. Thanks to this molecule, a new spectrum of orally active compounds will be developed which might revolutionize the treatment of diabetic patients.

Zhang *et al.* 1999 *Science* **284** 974-977.

Preparation for the 5th ECE in Torino

June 9 - 13, 2001

Due to the success of the previous four European Congresses of Endocrinology (ECES) and the continuous strengthening of ties between European endocrinologists, it was decided during the EFES General Assembly in 1998 in Sevilla that the ECEs should take place more frequently. Therefore, the 5th ECE will be held in Torino in 2001 after a 3-year interval (instead of the previous 4-year interval) and will be hosted by the Italian Society of Endocrinology (President: Prof M Serio).

The venue will be the former Fiat factory in Torino which is an architectural masterpiece and has been converted into a marvellous Congress Center with all required amenities. The baroque city of Torino, situated between the Alps and the Barolo hills will provide an excellent setting for the meeting.

The Local Organising Committee (LOC) is headed by Prof F Camanni and Prof E Ghigo. In early 1999 the EFES Executive Committee (EC) established a 14-person Scientific Programme Organising Committee (POC) and chose the following members in order to ensure good geographical and scientific representation: E Nieschlag, (Chairman) (Germany), A Aranda (Spain), P Beck-Peccoz (Italy), JP Bourguignon (Belgium), JS Christiansen (Denmark), N Dekel (Israel), A Enjalbert (France), E Ghigo (Italy), V Popovic (Yugoslavia), G Schütz (Germany), J Toppari (Finland), A Uitterlinden (The Netherlands), JAH Wass (UK) and WM Wiersinga (The Netherlands).

In order to provide continuity and a consistent congress format the POC is backed by the EFES Standing Committee on Congresses, headed by Prof JAH Wass (UK). The POC initiated its activities by collecting suggestions for Plenary Lectures, Symposia, Meet-the-Professor Sessions and Technical Sessions from full and affiliated EFES Member Societies. The POC is confident that, by the beginning of 2000, it will have established an attractive programme for endocrinologists of all colours.

The 5th ECE should be especially attractive for young endocrinologists who will receive financial assistance with the registration fee, accommodation and travel. There will also be a prize for the 'Best Poster' submitted by an endocrinologist over the age of 65.

The efforts of the EFES EC, the POC and the LOC notwithstanding, the success of the 5th ECE depends on input from all societies and individual endocrinologists. All readers of this announcement should make an effort to draw the attention of fellow endocrinologists to this première event in European endocrinology.

E NIESCHLAG, POC CHAIRMAN

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Forthcoming Meetings and Courses

19th Joint Meeting of British Endocrine Societies jointly with EFES

Birmingham, UK, 13-16 March 2000
Contact: Helen Gregson (Tel: +44 1454 619347; Fax: +44 1454 616071; Email: info@endocrinology.org; Web: <http://www.endocrinology.org>).

Regional Course in Clinical Endocrinology

Varna, Bulgaria, 13-15 April 2000
Contact: Prof. Dragomir Koev (Fax: +359-2 874145).

4th Postgraduate Course in Molecular and Cellular Endocrinology

Como, Italy, 24-27 May 2000
Contact: Dr Anna Spada (Fax: +39 02 5519 5438; Email: endosci@imiucca.csi.unimi.it).

39th Annual Meeting of the European Society of Paediatric Endocrinology

Brussels, Belgium, 17-19 September 2000.
Contact: A Segers (Scientific Secretariat) (Tel: +32 2 764 1370; Fax: +32 2 764 8910) or Conference Secretariat, Congrex Sweden AB (Tel: +46 8 459 66 00; Fax: +46 8 661 91 25).

7th Postgraduate Course in Clinical Endocrinology

Delphi, Greece, 12-15 October 2000
Contact: Prof. G Koukoulis & Dr S Tsagarakis, (Fax: +30 1 7711289; Email: prc@compulink.gr).

5th European Congress of Endocrinology

Turin, Italy, 9-13 June 2001
Contact: CCI Centro Congressi Internazionale, (Tel: +39 011 434 7900; Fax: +39 011 434 7808; Email: efes2001@ibow.com; Web: <http://www.ibow.com/efes2001>).

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