CONSTANTIN VON ECONOMO'S THEORY OF PRIMARY CONTROL OF SLEEP BY THE CENTRAL NERVOUS SYSTEM

C.S. Constantinescu, Consultant, Division of Neurology, University Hospital, Queen's Medical Centre, Nottingham and H. Gröger, Lecturer, Institute for the History of Medicine, University of Vienna, Austria

Constantin von Economo[1,2] (1876–1931) was a complex personality: a man of great culture, an avid reader, an expert in music, a poet of talent. He was fluent in five or six languages, well-trained in engineering, and a skilled pilot. His work, for example, on progressive cerebration, a theory according to which humankind can exceed its current maximal potential of knowledge and intelligence, extends beyond brain research, revealing a philosopher of learning. Von Economo made several major scientific contributions to the fields of neuroanatomy, neurophysiology, neurohistology, neuropathology, clinical neurology, and psychiatry; a combination of strong knowledge of neuroanatomy and astute clinical observations and clinicopathological correlations in the disease that bears his name, von Economo's encephalitis lethargica led to a better understanding of the phenomena and mechanisms of sleep.

BIOGRAPHICAL NOTE AND OVERVIEW OF ECONOMO'S WORK

Constantin Baron Economo von San Serff was born of an aristocratic Macedonian Greek parentage in Braila, Romania. He was brought up in Trieste, where he studied at the Austrian gymnasium, from which he graduated with high honours in 1893. At the age of 14, inspired by Cesare Lombroso's writings, he decided to study medicine, but was dissuaded from this by his father who desired that he studied machine engineering in Vienna in 1893. He developed a genuine interest in technical and engineering problems and was later to consider these two years as by no means wasted. In 1895 he began the study of medicine at the University of Vienna and was appointed as a student demonstrator in the Histological Institute of Victor von Ebner where he completed his first published work on the development of the hypophysis in birds. During this period he also worked in Siegmund Exner's Physiological Institute. After graduation in 1901 he spent one year in medicine with Nothnagel, then the chief of the Vienna Medical Clinic, who had a keen interest in neurological diseases, and later received extensive clinical neurological and psychiatric training in several of the other great centres of European neurology and psychiatry. In Paris, he worked for one year under Pierre Marie (neurology) and Magnan (psychiatry). In Nancy, he learned Bernheim's techniques of hypnosis and suggestion therapy. In Berlin, he worked with Ziehen (psychiatry) and Oppenheim (neurology) and as a visiting doctor and scientist in the department of Bethe in Strasbourg, and later in the clinic of Kraepelin in Munich where he wrote a paper on the normal anatomy of the nerve cell. He declined Kraepelin's offer of a permanent post and returned to Vienna in 1906, as assistant to the psychiatric clinic of Julius Wagner von Jauregg (1857–1940) where in addition to clinical duties, he continued to pursue laboratory research in neuroanatomy and neuropathology. His early investigations were in the anatomy and physiology of the midbrain and diencephalon and he published on pontine tumours, brainstem trigeminal pathways and the anatomical pathways for chewing and swallowing. With Karplus, he performed animal experiments in an attempt to induce movement disorders by artificially damaging areas of the brainstem.[3] Together these studies created a solid background of anatomical and physiological knowledge, making possible the observations that led to his description of encephalitis lethargica, and his localising the sleep centres to the regions of the midbrain-diencephalic junction. He reported the discovery of encephalitis lethargica on 17 April 1917, and throughout his career devoted 27 papers and two monographs to research related to this condition.[4]

His other major contributions in neurology were the unequalled study of the cytoarchitectonics of the cerebral cortex ('Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen', with G Koskinas, 1925),[5] studies on Wilson's disease, and the theory of progressive cerebration.[6] As a neurological clinician, beyond his expertise in encephalitis lethargica and its sequelae, his advice was frequently requested in patients suffering from brain tumours or injuries. As a psychiatrist, he described 'paranoia querulens' and was one of the first to emphasise the role of family studies in psychiatric disorders.[7,8] In 1928, when his life-long mentor, the 1927 Nobel laureate Wagner von Jauregg, retired, he was urged to take over the chair of psychiatry, but declined as he intended to dedicate more time to his research. In 1931, Economo became director of a Brain Research Institute created especially for him. He died of heart failure later that year.

BRIEF OVERVIEW OF SLEEP THEORIES IN ECONOMO'S TIME

Economo was well aware of the main contemporary theories (and variants thereof) expressed in several published reviews on the subject of sleep.[9–11] A detailed discussion of these theories, in the light of present day knowledge, can be found in Finger's book;[12] this is very similar to that published by Economo. According to Finger, the theories could be divided into three major groups, each with multiple variants. The blood flow / anaemia theories, whose advocates were, among others, Fleming, Durham, and Mosso, placed the major emphasis on cerebral circulatory changes during sleep.[12] Chemical theories postulated that sleep is induced by changes in the chemical composition of blood, such substances as oxygen, carbon dioxide, lactic acid, and others postulated, designated 'hypnotoxins' by Legendre and Piéron.[12] The deafferentation theory proposed that sleep was due to a temporary dissociation between higher nervous centres and their sensory input, whether due to an inhibitory reflex or off / on switching mechanism produced by either neurons or glia: this theory implied that defined nervous system centres regulate sleep.

The concept of the existence of a localised sleep regulatory centre was not accepted by many of Economo's

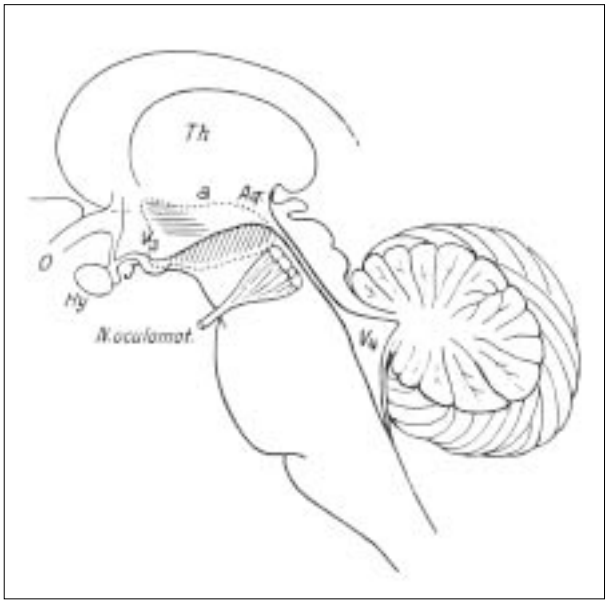

FIGURE 1
Drawing (1925) representing the anatomical location of the sleep regulatory centre proposed by Constantin von Economo (see reference 10). Putative localisation of the sleep regulatory centre represented by the dotted line *a* at the junction of the diencephalon and mesencephalon. *Aq*, aqueduct; *Hy*, hypophysis (pituitary); *I*, infundibulum; *O*, optic chiasm; *Th*, thalamus; V_3 and V_4, third and fourth ventricle; diagonal stripes: region in which damage induces sleep; horizontal stripes: region in which damage induces insomnia.

scientific colleagues in his day, yet the discovery and the description of the localised pathology of encephalitis lethargica was interpreted by Economo as being in favour of this concept. He called his hypothesis 'the theory of lack of stimuli', although he did not agree with the concept that a lack of stimuli was a primary cause for sleep, and he used clinical examples to disprove it.

An important earlier contribution to which Economo gives much credit had been made by another Viennese, the great neuroscientist and ophthalmologist, Ludwig Mauthner (1840–94),[13] who localised the pathology of Wernicke's encephalopathy associated with pathological sleep and abnormal eye movements to the periaqueductal grey matter and oculomotor nuclei.[14] Economo's presumed sleep centres, therefore, were in close vicinity to these structures, immediately adjacent to, but not including, eye movement centres of the oculomotor nuclei, because forms of pathological sleepiness do not necessarily involve eye movement abnormalities.

ENCEPHALITIS LETHARGICA AND THE CONCEPT OF SLEEP LOCALISATION

Economo's acute sense of clinical observation allowed him to recognise important common features in a disease with heterogenous manifestations, and thus to describe for the first time encephalitis lethargica as an entity in 1917. His knowledge of the anatomy and physiology of the midbrain and diencephalon allowed the localisation of pathology to these areas. He reviewed contemporary medical and lay literature, as well as reported verbal accounts of the condition from Italy, and he identified similarities of this condition with the Nona epidemic in Italy in 1890, and the Tübingen sleeping sickness (*Schlafkrankheit*) of 1712. He appreciated that there was a distinction between the disease he described and another form of encephalitis associated with lethargy described around the same time by Cruchet[15] which he indicated was a different condition or a more heterogenous group of conditions;[16] this was confirmed by comparative neuropathological studies.[1]

Economo's first report on encephalitis lethargica already defined its essentials: a spectrum of clinical manifestations, of an inflammatory-infectious (presumed viral) nature (he was later to perform animal transfer experiments in attempts to prove the infectious etiology), and a tropism for the grey matter of the midbrain.

He distinguished two categories of patients: the majority with hypersomnia and eye movement abnormalities; and a second group with insomnia and a hyperkinetic movement disorder. Neuropathological examination revealed involvement of the midbrain periaqueductal grey matter in the former variant, and the basal ganglia, particularly the anterior caudate, in the latter. Economo concluded that the rostral-most area of the brainstem at the midbrain-thalamic junction contains a centre for sleep control (Figure 1).[9–11]

Von Economo also distingushed between a cerebral and a bodily form of sleep, showing that the synchrony between the two can be lost in pathological conditions.[9–11] In support of this dichotomy, he used clinical examples of patients with encephalitis lethargica who were awake but paralysed, a phenomenon called 'sleep paralysis' which may be one of the features of narcolepsy. Indeed, he predicted that pathological alterations associated with narcolepsy are also localised to the sleep regulatory area at the midbrain-thalamus junction.

Economo's theory brought further support to Mauthner's concept of midbrain-thalamic junction localisation of sleep regulatory functions. These findings were in agreement with work by Walter R. Hess in Zürich[17] (later a Nobel laureate), and Marinesco in Bucharest, who induced sleep experimentally by stimulating the midbrain periaqueductal grey matter.[18]

Subsequent observations strongly stimulated by his pioneering studies, using newer techniques, have shown that the neural areas regulating sleep have a more widespread distribution.[19] Economo always emphasised the potential clinical applicability of his research, suggesting that the exact localisation of brain centres for sleep could help with the treatment of sleep disorders.

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