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[Department of Anatomy, University College, London, England]

Fiber pathways of the premamillary hypothalamus and of the mamillary bodies were described on the basis of axonal degeneration stained by the Nauta method. [The *SCI*® indicates that this paper has been cited in over 270 publications.]

R.W. Guillery
Department of Human Anatomy
University of Oxford
Oxford OX1 3QX
England

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When I undertook this study I had met W.J.H. Nauta only once; however, he influenced the work more than anyone else. In 1946 he published a beautifully organized account of hypothalamic lesions that alter sleep patterns.[1] The study was done in what must have been seriously constrained wartime conditions in Holland. In addition to the fascinating but undocumented statement that vegetables could sleep, this paper contained an analysis of pathways cut by lesions producing altered sleep rhythms. The anatomical analysis was limited because these pathways consist of thin fibers having little or no myelin coating, and the method then available relied on the myelin degeneration produced by a cut.

At the time, the hypothalamus was seen as a region concerned with an array of functions loosely grouped together as "visceral," ranging from blood pressure and gut motility to overt expressions of rage and sleep-wake rhythms. The anatomy of the region, summarized in 1938 by W.E. Le Gros Clark,[2] showed some surprisingly well-defined cell groups, most bearing no direct relation to known hypothalamic functions, and two distinct types of fiber system. One consisted of well-defined fiber bundles (the fornix and mamillothalamic tract) that linked the mamillary bodies to parts of the "limbic system." The second was composed of less clearly defined systems, including the medial forebrain bundle and periventricular system, that appeared to link the premamillary hypothalamus to the midbrain, the septum, and the dorsal thalamus. It was reasonable to believe that understanding these pathways would show how hypothalamic functions are organized and related to other brain parts.

After completing his 1946 study, Nauta moved to Zürich, where R. Hess was studying the effects of hypothalamic stimulation in conscious, freely moving cats. There, over a period of several years, Nauta developed a method for differentially staining degenerating nerve fibers, including some of the thinnest. This method[3] was to revolutionize and dominate neuroanatomy for almost two decades.

In 1953, as a part of my PhD work at University College, London, I had shown that the fornix loses many fibers as it approaches the mamillary bodies, but I could not trace these very thin, scattered fibers. About then, Bill Hayhow came to University College, obtained an early typed copy of the Nauta method, and traced optic fibers to the lateral geniculate nucleus, defining major layers in this nucleus by their inputs. I used this typed copy and traced the premamillary fornix fibers. From there it was a small step to look at other hypothalamic connections.

In the 1957 paper I described the mamillary pathways in the first part and the medial forebrain bundle and periventricular fibers in the second part. Had I made two papers from the single set of lesions, as I was strongly advised to do, each paper would probably have received only half the citations, and the work would not now be written about as a *Classic*.

Unfortunately, even the powerful new Nauta method did not, it seemed to me, provide any profound insights into hypothalamic organization. I turned to studies of axonal degeneration and later to a system where such degeneration can be studied most readily, the visual system and the lateral geniculate nucleus.

Today my view of contemporary hypothalamic anatomy is limited. Recently, P.G.M. Luiten and coauthors[4] summarized the past 20 years of autoradiographic and immunohistochemical studies, discussing in particular the links between the hypothalamus and the "limbic system." Unfortunately, the mamillary bodies are excluded. Perhaps their connections are so well defined that they are thought to be dull; however, before long their relation to the premamillary hypothalamus will have to be reconsidered.

1. Nauta W J H. Hypothalamic regulation of sleep in rats. An experimental study. *J. Neurophysiology* 9:285-316, 1946. (Cited 140 times since 1955.)
2. Le Gros Clark W E. Morphological aspects of the hypothalamus. (Le Gros Clark W E, Beattie J, Riddoch G & Dott N M, eds.) *The hypothalamus: morphological, functional, clinical and surgical aspects*. Edinburgh: Oliver and Boyd, 1938. p. 1-68.
3. Nauta W J H & Gygax P A. Silver impregnation of degenerating axons in the central nervous system: a modified technique. *Stain Technol.* 29:91-3, 1954. (Cited 690 times since 1955.)
4. Luiten P G M, ter Horst G J & Steffens A B. The hypothalamus: intrinsic connections and outflow pathways to the endocrine system in relation to the control of feeding and metabolism. *Prog. Neurobiol.* 28:1-54, 1987.

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