## The Formation of the Front Part of the Neural Tube

The textbooks generally follow the earlier descriptions of the mode of formation of the front part of the neural tube. For instance, HIS[1] observed a rostral and a caudal region of this part of the neural tube, which VON KUPFFER[2] called archencephalon and deuteroencephalon respectively. The latter was not considered to be distinctly delimited caudally. The corresponding embryonic stage was called the 'two-vesicle-stage'.

As early as the 17th century a 'three-vesicle-stage' was observed in chick embryos, arising according to VON KUPFFER by division of the deuteroencephalon into a rostral dilation, the mesencephalon, and a caudal one, the rhombencephalon. The archencephalon or, as it is also called, the prosencephalon, remains on the other hand undivided.

The final stage in external morphogenesis was described as a cleavage of the prosencephalon into the telencephalon and the diencephalon of the rhombencephalon into the metencephalon and the myelencephalon. This is the 'five-vesicle-stage'. It is later transformed through cell migrations, cell differentiations, and so on. In principle, however, the division into five 'vesicles' is still used, even when adult stages are described.

VON KUPFFER[2] already observed a primary transverse banding before the closure of the neuropore and after that a secondary neuromery. HILL[3] found a distinct neuromery in, for example, living salmon embryos.

By examination of the ontogenesis of the neural tube in embryonic stages following close upon each other, by model construction on large scale, by graphic reconstructions, by section series cut in various directions and by comparative studies, confirmation of such neuromeries was provided by among others BERGQUIST[4-7], KÄLLÉN and LINDSKOG[8], SAETERSDAL[9], BERGQUIST and KÄLLÉN[10,11], KÄLLÉN[12-15]. Later these observations were confirmed by WEDIN[16,17], SVETLOF[18] and others. The transverse banding can be followed right to the caudal end of the neural tube. The neuromeres appear principally in a rostro-caudal sequence (JOHNSON[19], BERGQUIST[20], KÄLLÉN[21]). Besides VON KUPFFER's two different successive neuromery systems, a third neuromery system has been demonstrated, which appears after the other two. The three phases of neuromery have been called proneuromery, neuromery and postneuromery (BERGQUIST and KÄLLÉN[11]). They are separated by the interneuromeric phases I and II, during which the transverse banding appears less distinct or is even quite extinguished.

During the postneuromery a longitudinal grouping of the cell masses in the wall of the neural tube also appears. These are the so-called His-Herrick longitudinal cell columns. In this way a squared pattern arises. The single squares have been called 'Grundgebiete' by BERGQUIST[22] and 'migration areas' by BERGQUIST and KÄLLÉN[10,11]. These regions are later split and become more complicated. From them cell groups can migrate during the so-called successive migration phases I and II and by degrees give rise to cortical layers or cerebral nuclei at the same time as cell differentiation starts.

Contrary to the HERRICK[23] and KUHLENBECK[24-26] school, which analyses a theoretical 'Bauplan', BERGQUIST[22] and BERGQUIST and KÄLLÉN[11] have stressed the migration-area-pattern, which is based on experimental, mitotic-analytic and comprehensive morphogenetic examinations.

According to SAUER[27] mitotic activity is to be found only in the neural epithelium adjacent to the ventricular lumen. After a sufficient number of cells have been formed, they migrate laterally into the wall of the neural tube. A correlation between mitotic activity developing in this matrix layer, the neural epithelium and the form pattern of the neural tube was confirmed by COGHILL[28]. BERGQUIST[22] found that, during the migration-area phase, so-called proliferation furrows on the inside of the wall of the neural tube are correlated with an increased mitotic activity in the neural epithelium close to the neural tube lumen (the neurocoel). KÄLLÉN[21,29,30] pointed out that in neuromere bulges a higher mitotic frequency could also be established. The interneuromic phases showed a falling mitotic frequency (BERGQUIST and KÄLLÉN[11]). The successive migration also precludes an increase in the number

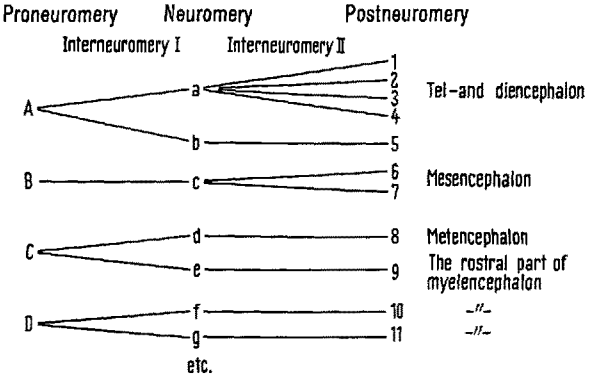


Fig. 1. Diagram of proneuromery, neuromery and postneuromery and of the interneuromere phases I and II between them.


[1] W. HIS, Arch. Anat. Physiol., Anat. Abt. *17*, 172 (1893).
[2] C. VON KUPFFER, *Handbuch der vergleichenden experimentellen Entwicklungslehre der Wirbeltiere* (Hrsg. O. Hertwig, Jena 1906), vol. II, p. 3.
[3] CH. HILL, Zool. Jahrb. Abt. Anat. Ontog. Tiere *13*, 393 (1900).
[4] H. BERGQUIST, Acta zool. *33*, 117 (1952).
[5] H. BERGQUIST, Kungl. Fysiogr. Sällsk. Lund Handl. *63*, 1 (1952).
[6] H. BERGQUIST, Anat. Anz. *102*, 449 (1956).
[7] H. BERGQUIST, *Studii si cercetari Stiinte medicale* (Academia R.P.R. Baza, Timisoara 1963), no. 1, p. 7.
[8] B. KÄLLÉN and B. LINDSKOG, Acta anat. *18*, 273 (1953).
[9] T. A. S. SAETERSDAL, Univ. Bergen Årbok Naturvit. *5*, 1 (1953).
[10] H. BERGQUIST and B. KÄLLÉN, Acta anat. *4*, 353 (1953).
[11] H. BERGQUIST and B. KÄLLÉN, J. comp. Neurol. *100*, 627 (1954).
[12] B. KÄLLÉN, Kungl. Fysiogr. Sällsk. Lund Handl. *62*, 1 (1951).
[13] B. KÄLLÉN, Kungl. Fysiogr. Sällsk. Lund Handl. *64*, 1 (1953).
[14] B. KÄLLÉN, J. Embryol. exp. Morph. *1*, 387 (1953).
[15] B. KÄLLÉN, Kungl. Fysiogr. Sällsk. Lund Förhandl. *25*, 1 (1955).
[16] B. WEDIN, Acta anat. *21*, 59 (1954).
[17] B. WEDIN, *Embryonic Segmentations in the Head*, Diss. Malmö (1955).
[18] P. G. SVETLOF, Arch. Anat. Embr. *34*, 1 (1957).
[19] F. P. JOHNSON, Contrib. Embryol. *6*, 125 (1917).
[20] H. BERGQUIST, Acta Soc. med. Upsal. *42*, 23 (1952).
[21] B. KÄLLÉN, *Progress in Neurobiology* (1956), p. 353.
[22] H. BERGQUIST, Acta zool. *13*, 57 (1932).
[23] C. J. HERRICK, *The Brain of the Tiger Salamander* (Chicago 1948).
[24] H. KUHLENBECK, Folia anat. Japon. *4*, 111 (1926).
[25] H. KUHLENBECK, Anat. Anz. *75*, 305 (1933).
[26] H. KUHLENBECK, Anat. Rec. *124*, 417 (1956).
[27] F. C. SAUER, J. comp. Neurol. *62*, 377 (1935).
[28] G. E. COGHILL, J. comp. Neurol. *37*, 71 (1924).
[29] B. KÄLLÉN, Acta Soc. med. Upsal. *57*, 87 (1952)..
[30] B. KÄLLÉN, Kungl. Fysiogr. Sällsk. Lund Handl *26*, 1 (1956).

of mitoses in the neural epithelium (BERGQUIST[31]). Compare HAMBURGER[32], HARKMARK[33], SAETERSDAL[9], HUGOSSON[34] and RÜDEBERG[35].

By exposing chick and mouse embryos to colchicin KÄLLÉN[36,37] obtained embryos with mitotic cells arrested in metaphase on the ventricular surface of the neural tube. Simultaneously a marked deepening of the neuromeric folds and of the proliferation furrows was obtained —probably due to the accumulation of cells at the ventricular surface.

By time-lapse filming (MENKES[38], BERGQUIST[39]) both neuromere phases and interneuromere phases have been observed in living chick embryos.

By the studies on proliferation patterns, the colchicine experiments, and the time-lapse filming the purely morphologic results concerning neuromeries, interneuromere phases, migration areas and successive migrations have been partially or entirely substantiated. The cause of the different sequences of proliferation patterns is probably of inductive nature but its detailed cause is unknown.

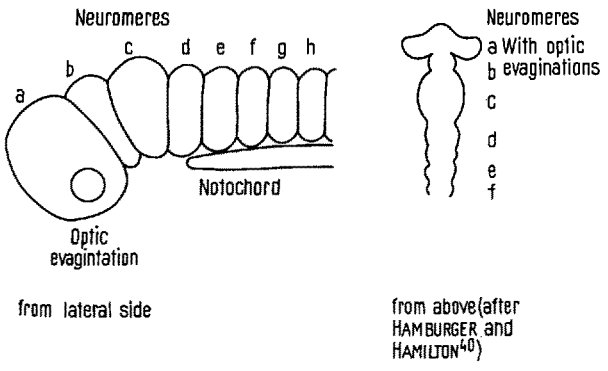


Fig. 2. Neuromeres.

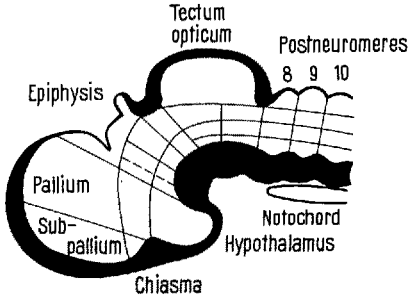


Fig. 3. Migration area pattern.

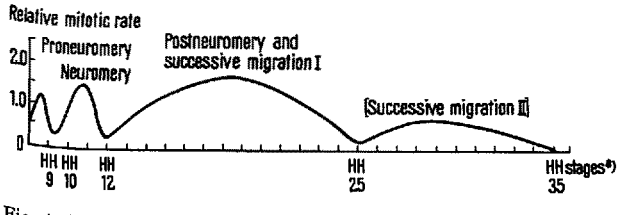


Fig. 4. Diagram of the dynamics of the proliferation during early CNS ontogenesis. [a]) HAMBURGER and HAMILTON[40].

The course of morphogenesis seems to proceed as follows: (1) Through induction from the chordamesoderm a neural placode is formed. The placode forms a neural groove, which, when it folds up, is divided into transverse bands (proneuromeres), which can be followed right into the caudal part of the neural groove. (2) The proneuromery is succeeded by interneuromeric phase I of very short duration, during which the transverse banding appears less pronounced or is totally obliterated. (3) The interneuromeric phase I is succeeded by the most pronounced transverse banding, the *neuromery*, which also remains longest in the neural tube and like the proneuromery extends mainly in a rostrocaudal sequence. (4) Interneuromeric phase II then occurs in a similar way to interneuromeric phase I. This phase also passes quite rapidly. (5) The third phase of transverse banding, the *postneuromery*, which arises after the interneuromeric phase II, develops in a rostro-caudal sequence, but stops in the caudal part of the brain. (6) At about the same time as the postneuromery the His-Herrick cell columns arise in the longitudinal direction. They cross the postneuromeres, giving rise to a squared pattern, the squares of which frequently soon divide into smaller regions. They have been called *migration areas*. (7) At the stage of CNS development when postneuromeres or migration areas are observed, vigorous cell migrations may take place in the neural tube. The *first migration* (migration I) coincides with these morphologic events. Later a *second cell migration* (migration II) can start independently in some particular parts of the embryonic brain. (8) Afterwards the cell masses are arranged in cortical and nuclear structures of the brain at the same time as cell differentiation advances. (9) The embryonic events from proneuromery through the successive migrations are correlated with a changing mitotic activity. (10) Secondary vesicles also arise in the proneuromere stage as eye dilatations. Later further evaginations arise as the hypothalamic sac, the hemispheres, the epiphysis, the optic evagination, the tectum and so on.

A description of early brain morphogenesis based on the so-called brain vesicle stages does not appear to be justified.

*Zusammenfassung.* Die Ontogenese des Zentralnervensystems durchläuft drei frühe Entwicklungsphasen: Proneuromerie, Neuromerie und Postneuromerie. Danach folgen: distale Zellmigrationen in die Neuralrohrwand. Sämtliche Phasen sind mit der Mitosenaktivität korreliert.

H. BERGQUIST

*Institutes of Anatomy and Zoology, University of Gothenburg (Sweden), September 12, 1963.*

[31] H. BERGQUIST, Exper. *13*, 84 (1957).
[32] V. HAMBURGER, J. comp. Neurol. *88*, 221 (1948).
[33] W. HARKMARK, J. comp. Neurol. *100*, 115 (1954).
[34] R. HUGOSSON, Diss. Lund (1957).
[35] S. RÜDEBERG, Diss. Lund (1961).
[36] B. KÄLLÉN, Acta anat. *27*, 351 (1956).
[37] B. KÄLLÉN, Z. anat. Entw.-gesch. *123*, 309 (1962).
[38] B. MENKES, *Cercetari de embryologie experimentala*. I. (Timisoara 1958).
[39] H. BERGQUIST, Kungl. Fysiogr. Sällsk. Lund Förhandl. *27*, 1 (1957).
[40] V. HAMBURGER and H. L. HAMILTON, J. Morph. *88*, 49 (1951).