In Memory of the Embryologist Ronan O’Rahilly

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Ronan O’Rahilly, an outstanding embryologist who provided a new level of precision for human embryology, passed away on the 24th of June in 2018 at the age of 96 years. Ronan O’Rahilly defined international standards for human embryology, which are now recognized by embryologists, gynecologists, and doctors working in reproductive medicine. For cellular and molecular biologists as well as for stem cell researchers, his work is an important reference. Since it is impossible to evaluate all his scientific achievements in this short article, the focus is laid exclusively on the precise staging of developing human embryos.

Ronan O’Rahilly was born on the 13th of September in 1921 in Cork (Ireland). In 1937, at 16 years of age, he started his studies in chemistry and physics at the National University of Ireland in Cork and later continued in the basic disciplines of medicine, such as anatomy, physiology, zoology, and botany. In 1940, he was awarded the Charles Gold Medal in advanced anatomy and embryology. He finished his studies with a doctorate in medicine (MD) and a doctorate in science (DSc). In 1946, after various clinical positions, he became lecturer for anatomy at the University of Durham and at the University of Sheffield in 1948. In 1950, he became professor at the Wayne State University in Detroit and in 1962 he was appointed full professor of anatomy at the University of Saint Louis. In 1969, he followed a call to the Department of Embryology at the Carnegie Institution of Washington in Balti-

Ronan O’Rahilly and Fabiola Müller 1987 with a reconstruction of an embryonic human brain at stage 19 in the Carnegie Laboratories of Davis.

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more, where he began to work on the definition of stages of human development. In 1973, the Carnegie Collection was transferred from Baltimore to the University of California at Davis Medical School. In 1974, Ronan O’Rahilly was appointed director of this collection and at the same time full professor of human anatomy and neurology. In 1982, O’Rahilly was awarded the honorary doctorate (Dr hc) of the University of Montpellier (France). From 1981 until 1988, he served as Editor-in-Chief of *Acta Anatomica* [see editorial by Hans-Werner Denker, this volume]. After his retirement in 1990, O’Rahilly came as a guest professor to the Institute of Anatomy and Special Embryology, University of Fribourg, in Switzerland. At the University of Fribourg, he received a lectureship from 1995 until 2001 and still enjoyed teaching human embryology. Medical students highly appreciated his lectures (a more extensive biography is presented by Rager [2003]).

The scientific research on the development of human embryos saw a major advance in the second half of the 19th century by the work of Wilhelm His (1831–1904), who was “the founder of human embryology” [O’Rahilly and Müller, 2001, p. 4]. He invented a device to produce serial sections of embryos which had been fixed and embedded before. Using these serial sections, he was able to reconstruct, for the first time, the 3-dimensional form of human embryos. This technique of reconstruction was improved and refined during the following decades, in particular by Erich Blechschmidt (1904–1992), whose reconstructions are unique worldwide due to their precision, stability, size, and perfection [Blechschmidt, 1963, 1973]. Consequently, it became possible to follow up the embryonic development in three dimensions although this was fragmentary at the beginning. Wilhelm His presented his results in his main publication *Anatomie menschlicher Embryonen*, which appeared 1880–1885 in 3 volumes [His, 1880–1885]. The next important step was taken by Franz Julius Keibel and Franklin Paine Mall in their *Manual of Human Embryology* [Keibel and Mall, 1910–1912]. Mall also founded the Carnegie Embryological Collection in Baltimore, which became the most important collection of human embryos in the world with time. However, the determination of developmental stages of embryos was still rather imprecise. Their age was estimated roughly, primarily by their size. Mall was the first person to set up a preliminary staging system. George L. Streeter succeeded Mall as director of the Carnegie Collection. In his *Developmental Horizons in Human Embryos* [Streeter, 1942–1951], he laid down the basis for a determination of human embryo stages using morphological landmarks.

This is the historical point where Ronan O’Rahilly started his research and eventually pushed human embryology an important step forward. At the Carnegie Institution, O’Rahilly launched his work on the definition of the early human developmental stages. Since the information on age and size was unreliable, particularly at the early periods of development, he extended and refined Streeter’s approach to define features and criteria by which a given embryonic developmental age could exactly be identified. As a result, a complete system for the embryonic period proper consists of 23 stages: it starts with fertilization (stage 1) and ends with the completion of most internal and external features such as a rounded head with eyelids and ears (stage 23) in an embryo measuring about 3 mm at the end of the 8th developmental week.

The first description of these stages was published in 1973 [O’Rahilly, 1973]. A revised version appeared in 1987 [O’Rahilly and Müller, 1987], which was carried out in collaboration with his wife Fabiola Müller. The stages defined by O’Rahilly and Müller are now called Carnegie Stages because most of the embryos which were used for the definition of stages were located in the Carnegie Collection and because the staging of human embryos began at the Carnegie Institution of Washington.

At the Institute of Anatomy and Special Embryology of the University of Fribourg in Switzerland, O’Rahilly continued to work on the refinement of his description of various organ systems with regard to the Carnegie Stages and published a great number of original articles well into the 21st century. He had always been particularly concerned with the human nervous system. The 3rd edition of his textbook on human embryonic development (*Human Embryology & Teratology*), which is still highly appreciated all over the world, appeared in 2001 [O’Rahilly and Müller, 2001]. The textbook on *The Embryonic Human Brain* was published 2006 in the 3rd edition [O’Rahilly and Müller, 2006]. Both textbooks were written in collaboration with his wife Fabiola Müller.

Although O’Rahilly confined himself to purely scientific statements, important conclusions can be drawn from his results. One of these conclusions is that human development proceeds in a continuous manner, and there is no particular point in development in which a completely new event would happen. Seemingly new phenomena can always be described as a result from preceding processes. Each developmental stage, although defined by several concrete criteria, continues to the next stage without discretely definable steps of development. Even fertilization is not an event happening at a certain

point in time; according to O’Rahilly, it is a “procession of events that begins when a spermatozoon makes contact with a secondary oocyte or its investments, and ends with the intermingling of maternal and paternal chromosomes at metaphase of the first mitotic division of the zygote” [O’Rahilly and Müller, 2001, p. 31]. From the observation of the continuity of human development, he concluded that a human being begins to exist at fertilization and develops from thereon continuously.

Ronan O’Rahilly was a man with a sharp intellect, an excellent memory, and a great interest in cultural events. Friendship was very important for him. At the same time, he was distinguished by his modesty. He never put him-

self into the center of attention and never praised his achievements. Till the end of his life, he had a very clear mind, was interested in many things and events, and kept his sense of humor. All of a sudden and completely unexpected, he died on the 24th June last year due to an acute illness.

A complete list of his publications until 2003, handed over by Ronan O’Rahilly to the author, can be found in Rager [2003]. Another list can be found online at https://embryology.med.unsw.edu.au/embryology/index.php/Embryology_History_-_Ronan_O%27Rahilly. This list is less complete but also contains publications from 2003 to 2013.

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