# **REVIEW ARTICLE**

# Early human development and the chief sources of information on staged human embryos

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In a brief historical survey, the importance of Wilhelm His, senior, to human embryology is emphasized. He provided the impetus to Mall to establish the Carnegie Embryological Collection, which serves as a 'Bureau of Standards' for early human development. The Carnegie system of 23 stages for the embryonic period proper (first 8 postovulatory wk) is outlined, and some common misusages are noted. Finally, because of the difficulty in tracking down data based on staged human embryos, an annotated list of more than 40 key references is provided.

embryonic period; embryonic stages; developmental 'horizons'; Carnegie Collection; Wilhelm His, senior

"The norm should be established; embryos should be arranged in stages" (Franklin P. Mall)

### Introduction and historical aspects

Although the study of prenatal life dates back to antiquity, little progress was made in human embryology until the systematic studies of Wilhelm His, senior, on "Anatomie menschlicher Embryonen", undertaken and published during the latter half of the 19th century. The combined use of fixation, sectioning with a microtome, and reconstructions from the resultant sections (according to Born's wax plate method) enabled His to begin to elucidate the anatomy of individual human embryos. His had great influence on both Keibel and Mall (Fig. 1), and he "provided the incentive for Keibel's *Normentafeln* ... and [for my (the future Carnegie) collection] of human embryos" (Mall, 1913).

An important landmark, and still the most detailed account available, was the "Manual of Human Embryology" by Keibel and Mall (1910, 1912), published simultaneously in English and German. For the first time an attempt was made to provide "an account of the development of the human body, based throughout on human material". The account of early human development, however, was incomplete ("The formation of the germ layers, like the processes of segmentation, has not yet been observed in the human species") because, although a monograph on an early human embryo had been published as early as 1899 by Peters, the details of early human development had to await the founding of the Carnegie Department of Embryology by Franklin P. Mall



Fig. 1. A scheme to show the influence of Robert Remak and Johannes Müller on Wilhelm His, senior, and the influence of His on Franz Keibel and Franklin P. Mall in providing the impetus for their important work on human embryology. Researchers on human development and placentation during the Streeter era included G.W. Bartelmez, G.W. Corner, A.T. Hertig, C.H. Heuser and E.M. Ramsey.

in 1914, as well as the collection of very early specimens by Hertig and Rock in the 1940s and 1950s. Only recently has a synthesis of the appropriate data become available (O'Rahilly, 1973). The Carnegie Collection, which was transferred from Baltimore to Davis in 1973, still serves, in the judicious words of George W. Corner, "as a kind of Bureau of Standards" for primate embryology.

#### The embryonic period

It is customary and convenient to divide prenatal life into (1) the embryonic period proper, which comprises the first 8 postovulatory wk (i.e., timed from the last ovulation), and (2) the fetal period, which extends to birth. The embryonic period, which has been studied in much greater detail, is particularly important because, during that time, the vast majority of the named parts of the body become identifiable: from the chorda tympani to the stapedius, from the intercostal vessels to the atrioventricular bundle, from the abductor digiti minimi to the sustentaculum tali. Moreover, the majority of congenital anomalies develop during the embryonic period proper.

At the end of the embryonic period proper, i.e., at 8 postovulatory wk, the embryo measures approximately 30 mm in crown-rump length and weighs approximately 2–2.7 g. It is quite remarkable that an embryo less than half the length of an adult thumb already possesses probably more than 90% of the more than 4500 named structures of the adult body. There need be scant wonder that the preformationists so long held sway!

#### **Embryonic staging**

A series of embryos cannot be arranged in perfect sequence, because any given specimen may be advanced in one respect while being retarded in another. Moreover, neither the length of an embryo nor the height of a child is an adequate guide to developmental status. Hence, stages based on the morphological state of development have been devised for many species. (Basically, embryonic stages resemble those later devised for the newborn infant, e.g. by Dubowitz et al., 1970.) Staging was first applied to human embryology by Mall in 1914, and his successor, George L. Streeter, provided the definitive classification of human embryos into stages. Subsequently, the first 9 stages had to be redefined, and the Carnegie system, in the form in which it is currently used (O'Rahilly, 1973), is given in Table I.

The following points, frequently "more honoured in the breach than the observance", need to be emphasized: (1) Streeter's term "horizon" is no longer used, having been replaced by the better term "stage"; (2) Roman numerals, as used by Streeter, have been replaced by Arabic numerals to designate what are now referred to as Carnegie stages; (3) the most useful single measurement of an embryo or a fetus is the crown-rump length (Mall, 1907), which should always be expressed in mm; (4) the crown-rump lengths used by embryologists agree closely with those determined ultrasonically (Drumm and O'Rahilly, 1977); (5) the length of an embryo is not a stage, and expressions such as "at the 15 mm stage" should be replaced by "at 15 mm"; (6) ages are

# R. O'Rahilly: Staged human embryos



Figs. 2 and 3. Right lateral and anterior views of a human embryo at the end of the embryonic period proper, 8 postovulatory wk. The embryo, which belongs to Carnegie stage 23, measures 30.7 mm in crown-rump length. From a study of the internal development, it is known to be a male embryo. (Sex cannot be determined from the external appearance before 50 mm.) The umbilical cord contains the normal hernia, which is usually reduced at about 40 mm. The palms of the hands face the abdomen, whereas the soles of the feet face each other ("praying feet"). This important stage of development is at the junction of the embryonic and fetal periods, prior to which most named structures of the body have made their debut, and most congenital anomalies would already have become manifest.

expressed (at least within the embryonic period) as postovulatory weeks or days, and little or no attention is now paid in embryology to menstrual data (menstrual "age" is a misnomer); (7) Streeter's ages, which were based on the macaque, are now known to be incorrect for the human, and hence have been abandoned; (8) the 23 stages refer to the embryonic period only, i.e. the first 8 postovulatory wk, no successful system of staging having yet been devised for the fetal period.

## Sources of information since 1960

A considerable amount of information concerning staged human embryos is available, and is necessary in order to assess the precise timing and sequence of events in the development of the various organs and systems of the body. Because these data are widely scattered in the scientific literature and are difficult to track down even for specialists in the field, the following annotated list of the chief sources of recent

Carnegie stage	Pairs of somites	Length (mm)	Age (days) <sup>1</sup>	Age (days) <sup>2</sup>	Features
1				1	Fertilization.
2			1.5-3	2-3	From 2 to about 16 cells.
3			4	4-5	Free blastocyst.
4			5 - 6	5-6	Attaching blastocyst.
5		0.1 - 0.2	7 -12	7-12	Implanted although previllous.
(5a		0.1	7 - 8		Solid trophoblast.
{5b		0.1	9		Trophoblastic lacunae.
l5c		0.15-0.2	11 -12		Lacunar vascular circle.
6		0.2	13	13-15	Chorionic villi; primitive streak may appear.
(6a					Chorionic villi.
16ь					Primitive streak.
7		0.4	16	15-17	Notochordal process.
8		1.0 - 1.5	18	17-19	Primitive pit; notochordal and neurenteric canals.
9	1-3	1.5 - 2.5	20	19-21	Somites first appear.
10	4-12	2 - 3.5	22	22-23	Neural folds begin to fuse; 2 pharyngeal bars; optic sulcus.
11	13-20	2.5 - 4.5	24	23-26	Rostral neuropore closes; optic vesicle.
12	21-29	3 – 5	26	26-30	Caudal neuropore closes; 3 pharyngeal bars; upper limb buds appearing.
13	30-?	4 – 6	28	28-32	Four limb buds; lens disc; otic vesicle.
14		5 – 7	32	31-35	Lens pit and optic cup; endolymphatic appendage distinct.
15		7 – 9	33	35-38	Lens vesicle; nasal pit; antitragus beginning; hand plate; trunk relatively wider; cerebral vesicles distinct.
16		8 -11	37	37-42	Nasal pit faces ventrally; retinal pigment visible in intact embryo; auricular hillocks beginning; foot plate.
17		11 -14	41	42–44	Head relatively larger; trunk straighter; nasofrontal groove distinct: auricular hillocks distinct; finger rays
18		13 –17	44	44-48	Body more cuboidal; elbow region and toe rays appearing; eyelids beginning; tip of nose distinct; nipples appear; ossification may begin.
19		16 -18	47.5	48-51	Trunk elongating and straightening.
20		18 -22	50.5	51-53	Upper limbs longer and bent at elbows.
21		22 –24	52	53-54	Fingers longer; hands approach each other, feet likewise.
22		23 -28	54	54-56	Eyelids and external ear more developed.
23		27 -31	56.5	56-60	Head more rounded; limbs longer and more developed.

 TABLE I
 Developmental stages in human embryos

<sup>1</sup> Olivier and Pineau (1962) for stages 11-23; miscellaneous sources for stages 1-10. <sup>2</sup> Jirásek (1971).

information (together with Streeter's earlier papers) is provided. Articles on the reproductive system, the endocrine system, the vertebrae and the skull are in preparation.

## General

Stages 1-23, illustrated mostly by particularly fine views of reconstructions, many in color. Also some illustrations of fetuses.

Drumm, J.E. and O'Rahilly, R. (1977): The assessment of prenatal age from the crown-rump length determined ultrasonically. *Amer. J. Anat.*, 148, 555-560.

Good agreement is found between embryological data and those obtained ultrasonically.

Gasser, R.F. (1975): Atlas of Human Embryos. Har-

Blechschmidt, E. (1973): Die Pränatalen Organsysteme des Menschen. Hippokrates, Stuttgart.

per and Row, Hagerstown, Md.

Representative black-and-white photomicrographs (with labels) of 12 embryos from stage 2 to stage 23.

O'Rahilly, R. (1975): A Color Atlas of Human Embryology. Saunders, Philadelphia. A collection of 293 35 mm slides, most of which are in color and are of staged embryos (stages 1-23).

# Stages 1–9

Luckett, W.P. (1978): Origin and differentiation of the yolk sac and extraembryonic mesoderm in presomite human and rhesus monkey embryos. *Amer. J. Anat.*, 152, 59–97.

Well-illustrated account of special aspects of stages 5-8.

O'Rahilly, R. (1970): The manifestation of the axes of the human embryo. Z. Anat. Entwickl.-Gesch., 132, 50-57.

The recognition of dorsoventral (stage 3) and rostrocaudal (stage 6) axes.

O'Rahilly, R. (1973): Developmental Stages in Human Embryos, Including a Survey of the Carnegie Collection. Part A: Embryos of the First Three Weeks (Stages 1 to 9). Carnegie Institution of Washington, Wash., D.C.

Definition, description, measurements, illustrations, tables, and bibliography of stages 1-9.

# Stages 10-23 (to be revised by R. O'Rahilly)

- Heuser, C.H. and Corner, G.W. (1957): Developmental horizons in human embryos. Description of age group X, 4 to 12 somites. *Contr. Embryol. Carneg. Instn, 36*, 29–39.
- Streeter, G.L. (1942): Developmental horizons in human embryos. Description of age group XI, 13 to 20 somites, and age group XII, 21 to 29 somites. Contr. Embryol. Carneg. Instn, 30, 211-245.
- Streeter, G.L. (1945): Developmental horizons in human embryos. Description of age group XIII, embryos about 4 or 5 millimeters long, and age group XIV, period of indentation of the lens

vesicle. Contr. Embryol. Carneg. Instn, 31, 27-63.

- Streeter, G.L. (1948): Developmental horizons in human embryos. Description of age groups XV, XVI, XVII, and XVIII, being the third issue of a survey of the Carnegie Collection. Contr. Embryol. Carneg. Instn, 32, 133-203.
- Streeter, G.L. (1951): Developmental horizons in human embryos. Description of age groups XIX, XX, XXI, XXII, and XXIII, being the fifth issue of a survey of the Carnegie Collection. Contr. Embryol. Carneg. Instn, 34, 165-196.

# Nervous system

- Bartelmez, G.W. and Dekaban, A.S. (1962): The early development of the human brain. Contr. Embryol. Carneg. Instn, 37, 13-32.
  A well-illustrated account of the brain from stage 10 to stage 22.
- Gardner, E. and O'Rahilly, R. (1976): Neural crest, limb development, and Thalidomide embryopathy. *Lancet*, 1, 635-637.

Contains graphs showing the first appearance of the neural crest, and the limbs and their innervation (stages 10-19).

Lemire, R.J., Loeser, J.D., Leech, R.W. and Alvord, E.C. (1975): Normal and Abnormal Development of the Human Nervous System. Harper and Row, Hagerstown, Md.

A useful book with much information on neuroteratology. Unfortunately the authors use Roman numerals for stages, whereas they should be reserved for the now obsolete "horizons".

O'Rahilly, R. (1965): The optic, vestibulocochlear, and terminal-vomeronasal neural crest in staged human embryos. In: Second Symposium on Eye Structure, pp. 557-564. Editor: J.W. Rohen. Schattauer, Stuttgart.

A description of the subdivisions of the neural crest in the human (stages 10-18).

O'Rahilly, R. and Gardner, E. (1971): The timing and sequence of events in the development of the human nervous system. Z. Anat. Entwickl.-Gesch., 134, 1-12.

A synthesis of staged data (stages 8-23).

O'Rahilly, R. and Gardner, E. (1977): The developmental anatomy and histology of the human central nervous system. In: *Handbook of Clini*cal Neurology. Editors: P.J. Vinken and G.W. Bruyn. Congenital Malformations of the Brain and Skull, Vol. 30, Part I, pp. 15-40. Editor: N.C. Myrianthopoulos. North-Holland, Amsterdam.

A general account of the development of the human nervous system, with particular reference to stages 8-23.

O'Rahilly, R. and Gardner, E. (1979): The initial development of the human brain. Acta anat., 104, in press.

The brain from stage 8 to stage 16, with particular reference to the neuropores, neuromeres and telencephalon medium.

# Eye

O'Rahilly, R. (1966): The early development of the eye in staged human embryos. Contr. Embryol. Carneg. Instn, 38, 1-42.

A well-illustrated and detailed account of the eye from stage 10 to stage 23.

- O'Rahilly, R. (1975): The prenatal development of the human eye. *Exp. Eye Res.*, 21, 93-112. A shorter account that includes references to the recent literature.
- O'Rahilly, R. and Bossy, J. (1972): The growth of the eye. Part 1: in utero. An. Desarrollo, 16, 31-51. Contains many tables and graphs (stages 14-23).

# Ear

O'Rahilly, R. (1963): The early development of the otic vesicle in staged human embryos. J. Embryol. exp. Morph., 11, 741-755. The otocyst from stage 9 to stage 18.

#### Cardiovascular system

Asami, I. (1969): Beitrag zur Entwicklung des Kammerseptums im menschlichen Herzen mit besonderer Berücksichtigung der sogenannten Bulbusdrehung. Z. Anat. Entwickl.-Gesch., 128, 1-17. The interventricular and bulbar septa from stage 14 to stage 20.

Asami, I. (1972): Beitrag zur Entwicklungsgeschichte des Vorhofseptums im menschlichen Herzen, eine lupenpräparatorisch-photographische Darstellung, Z. Anat. Entwickl.-Gesch., 139, 55– 70.

The partitioning of the atrium and of the atrioventricular canal from stage 14 to stage 23.

Cooper, M.H. and O'Rahilly, R. (1971): The human heart at seven postovulatory weeks. Acta anat., 79, 280-299.

The heart from stage 19 to stage 21.

- deVries, P.A. and Saunders, J.B.deC.M. (1962): Development of the ventricles and spiral outflow tract in the human heart. Contr. Embryol. Carneg. Instn, 37, 87-114.
  An important article on the heart from stage 9 to stage 15.
- Gardner, E. and O'Rahilly, R. (1976): The nerve supply and conducting system of the human heart at the end of the embryonic period proper. J. Anat. (Lond.), 121, 571-587.

A very detailed account of certain aspects at stage 23.

Goor, D.A. and Lillehei, C.W. (1975): Congenital Malformations of the Heart. Grune and Stratton, New York.

A useful book with some new descriptions and also much information on congenital cardiac anomalies. Unfortunately, the authors still write of "horizons" and do not employ internationally accepted anatomical terminology.

O'Rahilly, R. (1971): The timing and sequence of events in human cardiogenesis. Acta anat., 79, 70-75.

A synthesis of staged data (stages 8-23).

Sissman, N.J. (1970): Developmental landmarks in cardiac morphogenesis: comparative chronology. Amer. J. Cardiol., 25, 141–148. Contains tables comparing cardiac development in staged human (stages 10–23), chick, and frog

embryos, and in unstaged pig, rabbit, rat, and mouse embryos.

# **Digestive system**

O'Rahilly, R. (1978): The timing and sequence of events in the development of the human digestive system and associated structures during the embryonic period proper. *Anat. Embryol.*, 153, 123-136.

A synthesis of staged data (stages 5-23).

### **Respiratory system**

O'Rahilly, R. and Boyden, E.A. (1973): The timing and sequence of events in the development of the human respiratory system during the embryonic period proper. Z. Anat. Entwickl.-Gesch., 141, 237-250.

A synthesis of staged data (stages 8-23).

O'Rahilly, R. and Tucker, J.A. (1973): The early development of the larynx in staged human embryos. Part A: Embryos of the first five weeks (to stage 15). Ann. Otol. (St. Louis), 82 (Suppl. 7), 1-27.

A well-illustrated account from stage 9 to stage 15.

# Urinary system

O'Rahilly, R. and Muecke, E.C. (1972): The timing and sequence of events in the development of the human urinary system during the embryonic period proper. Z. Anat. Entwickl.-Gesch., 138, 99-109.

A synthesis of staged data (stages 10-23).

#### **Reproductive system**

O'Rahilly, R. (1973): The embryology and anatomy of the uterus. In: *The Uterus by 23 Authors*, pp. 17-39. Editors: H.J. Norris, A.T. Hertig and M.R. Abell. Williams and Wilkins, Baltimore, Md.

Includes a table of staged data.

O'Rahilly, R. Prenatal human development. In: Biology of the Uterus, pp. 35-57. Editor: R.M. Wynn. Plenum, New York, 2nd edn.

Includes a table of staged data.

O'Rahilly, R. (1977): The development of the vagina in the human. In: Morphogenesis and Malformation of the Genital System. Birth Defects: Original Article Series, Vol. 13, Part 2, pp. 123-136. Editors: R.J. Blandau and D. Bergsma. Liss, New York. Includes some staged information.

## **Skeletal system**

- O'Rahilly, R. and Gardner, E. (1972): The initial appearance of ossification in staged human embryos. *Amer. J. Anat.*, 134, 291–307. Ossification from stage 18 to stage 23.
- O'Rahilly, R. and Gardner, E. (1975): The timing and sequence of events in the development of the limbs in the human embryo. *Anat. Embryol.*, 148, 1-23.

A synthesis of staged data (stages 12–23).

O'Rahilly, R. and Gardner, E. (1976): The embryology of bone and bones. In: *Bones and Joints by* 24 Authors, pp. 1–15. Editors: L.V. Ackerman, H.J. Spjut and M.R. Abell. Williams and Wilkins, Baltimore, Md.

Contains some staged information and some summarizing graphs of the limbs (stages 16-23).

O'Rahilly, R. and Gardner, E. (1978): The embryology of movable joints. In: *The Joints and Synovial Fluid, Vol. 1*, pp. 49–103. Editor: L. Sokoloff. Academic Press, New York. Contains summarizing graphs of the major joints

of the limbs (stages 16-23), and an extensive bibliography.

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