CONGENITAL ANOMALIES OF THE VISCERA

Their Embryological Basis

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HARVARD UNIVERSITY PRESS • CAMBRIDGE

1957

Distributed in Great Britain by Oxford University Press, London

Library of Congress Catalog Card Number 56-13344

Designed by Burton J. Jones, Jr.

Photocomposition by Graphic Services, Inc., York, Pennsylvania

Printed in the United States of America
by The Murray Printing Co., Wakefield, Massachusetts

Bound by Stanhope Bindery, Inc., Boston, Massachusetts

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PREFACE

The courses in embryology commonly required for the medical degree stress especially the early stages of normal development, from the fertilization of the ovum to the origin and primary growth of the various organs and systems, and of the body as a whole. A working knowledge of these subjects is essential to the understanding of this present book. In these courses the accent is chiefly on the normal; in only a few textbooks on the subject are abnormal conditions considered. For the graduate in medicine who is starting an internship or residency in pediatrics, and for one already engaged in the practice of this branch of medicine, these courses leave much to be desired. Confronted by the various types of congenital malformations so often exhibited by the young patients, he feels strongly the need of further knowledge of the later fetal or prenatal or even postnatal growth, and of the abnormal possibilities as well as the normal sequences of developmental processes. To supply this need, at least in part, and to call attention to the delicate adjustments, both in time and in the relative positions of the various parts, by which normal development is achieved and without which anomalies are certain to occur, this book has been written.

Almost all of the known forms of recognized abnormalities in the various organs can be traced to some simple disturbances of the growth sequence. As expressed by Shaner, *Anat. Rec. 118,* 539–560 (1954), in writing of the heart, "In general, a simple arrest of development, followed by a halting resumption of growth, complicated by hydrodynamic forces and other minor but well known disorders, will explain the most complicated heart abnormalities." In other cases, the growth of a part may be accelerated instead of arrested, or the change of growth rate may be located at an unusual position, and these changes may result in an entirely different type of anomaly. The ultimate cause of these slight local changes of growth rate may be chemical or hormonal or thermal, the first two being transmitted to the embryo from some deficiency in the maternal diet [for example, J. Warkany, *Vitamins and Hormones 3,* 73–103 (1945); C. D. C. Baird, M. M. Nelson, I. W. Monte, and H. M. Evans, *Circulation Res. 2,* 544–564 (1954)], the thermal caused by intercurrent acute maternal disease. Chronic or hereditable maternal disease seems to be commonly reflected in a general debility of the ovum, rendering it unduly sensitive to adverse conditions, although cases showing the definite inheritance of specific abnormalities have been recorded; but the belief that systemic and multiple malformations are always due to heredity through changes in the germplasm is of doubtful validity. Whatever the inciting cause of the changes in growth rate, it is efficient for an organ only if active at a certain critical period of the initiation of that organ's development, in the early period of pregnancy. The resultant sequences leading to the development of the anomaly can usually be readily followed. From the knowledge of these developmental sequences new types of abnormality, either hitherto undescribed or published merely as rare and unexplained findings, can be understood and traced to their embryological sources. No attempt has been made to collect all or even the major part of these rare or new anomalies, but the number of them found in a large children's hospital is surprising.

Certain malformations of the central nervous system have been mentioned only as connected with or resulting from an anomaly of some other organ. The brain and spinal cord are too vast and too intricate a subject to be properly considered here.

To complete the story for each organ or system, the normal development is rapidly reviewed, and as aids for this review many of the simple drawings by Professor F. T. Lewis, which have served well in his and my former textbooks of histology, have been retained here. Others are from former papers of mine, and for many of these, as well as for several new drawings prepared for this book, I am glad to thank Miss E. Piotti, whose skill is already well known. Many other illustrations have been taken from these and from other published sources. For permission to use this material I am sincerely grateful. Also, I wish to acknowledge with many thanks the constant help and encouragement offered by my colleagues in this hospital, Drs. W. E. Ladd, T. W. Lanman, E. B. D. Neuhauser, R. E. Gross, J. Craig, and many others who, by supplying many illustrations for my use and much-needed advice for the text, have made this book possible. Finally, special thanks are due to Dr. Sidney Farber, for his great kindness in reading the manuscript for me and for his many helpful suggestions.

J. L. Bremer

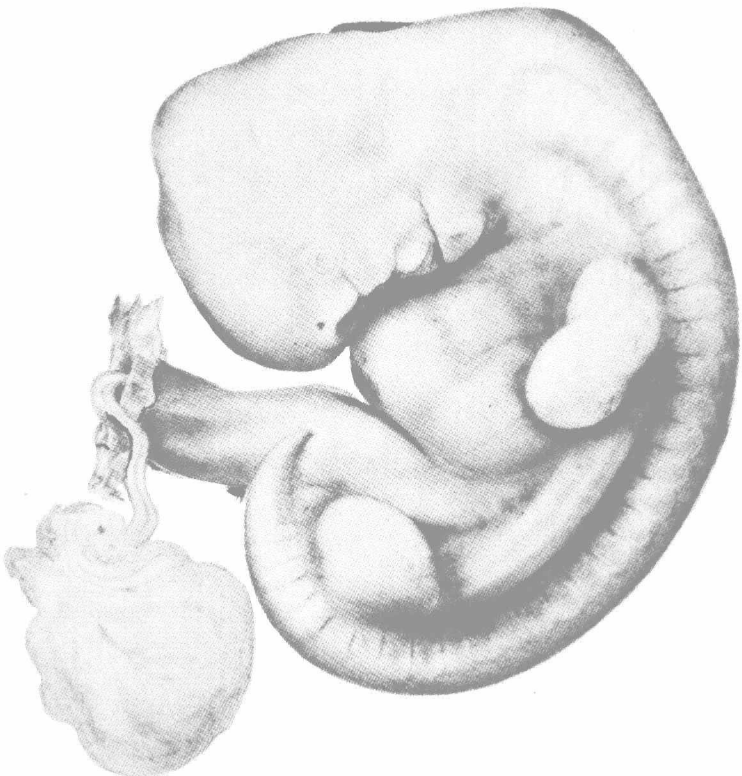

Fig. 1. Lateral view of human embryo early in the seventh week after fertilization.

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THE RESPIRATORY AND ALIMENTARY SYSTEMS

Nose, Mouth, and Face

The entrances both to the respiratory and to the alimentary systems form portions of the face.

The early embryo, during the differentiation of the germ layers, consists of a flattened sheet forming the common wall of the yolk sac and the amniotic cavity. The upper or dorsal layer of this sheet is of ectoderm continuous with the lining of the amnion; the bottom or ventral layer is a continuation of the yolk sac entoderm. On this flat disk a central darker spot, the primitive knot or Hensen's node, represents the rapid local multiplication of cells, and a less prominent lineal extension of the node, called the primitive streak, marks the future caudal end of the embryo. Cranially from the node extends the notochord, between the surface ectoderm and the underlying entoderm, and dorsal to the notochord the ectoderm thickens as the paired parallel medullary or neural plates, which are to form the spinal cord and brain. The plates and the notochord grow forward rapidly and soon dominate the diminishing primitive streak and node, until the latter appears as a minute terminal structure at the caudal end of the spinal cord. The neural plates soon outdistance the notochord in forward growth, and, once beyond it, their cranial tips bend abruptly ventrally, perhaps to conserve linear space.

The face of the embryo begins to take form after the completion of the first or head bend of the projecting head fold, as a result of which the forebrain region lies at right angles to the rest of the body. The foregut has grown forward from the yolk sac to meet a shallow surface depression, the stomodaeum, at the still intact oral plate or oral membrane, composed of the fused surface ectoderm and foregut entoderm. Along the sides of the head are developing three pairs of sense organs (or integral parts of sense organs), the paired olfactory and otic organs and the lens for each eye. They first appear as rounded or oval areas of thickened surface ectoderm, called placodes, which, as development proceeds, sink into the underlying mesenchyma as depressed cups or pits open to the surface. In this condition the olfactory organs remain permanently; the placodes for lens and for inner ear sink deeper, lose connection with the surface epithelium, and remain as closed vesicles surrounded by mesenchyma, awaiting further differentiation (Fig. 2). In many ways this development resembles that of the central nervous system, in that the latter also is initiated by the formation along the back of the embryo of two parallel linear thickenings of surface ectoderm, the neural plates, which then become depressed as the neural groove, close over as the neural tube, and sink below the surface.

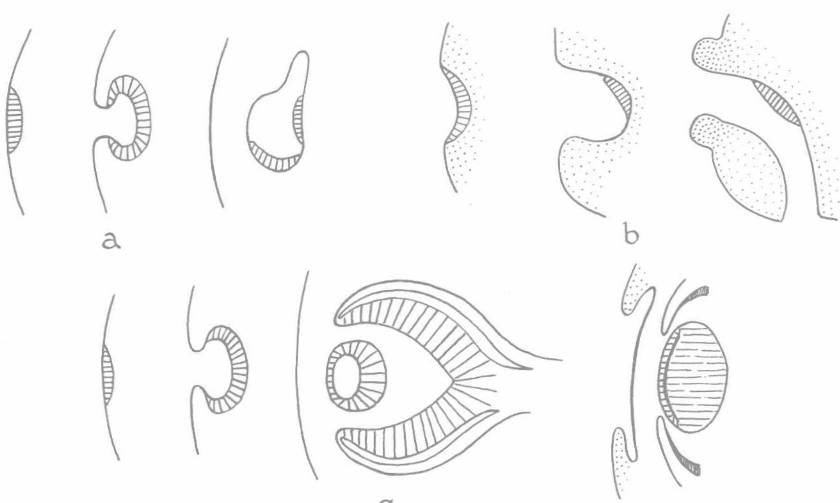

Fig. 2. Diagrams to show placodes and development of (*a*) ear, (*b*) nose, and (*c*) lens.

The first placodes to appear, in point of time, are those for the inner ears. At 19 days, in the seven-somite embryo, the otic placodes can be detected as rounded areas of thickened ectoderm, one on each side of the head over the hindbrain. Soon they pass through the open-cup stage to become closed vesicles, the otocysts (Fig. 2, *a*), which later differentiate into the epithelial cochlea, the semicircular canals, and the entire ectodermal inner ear. Each otocyst sinks deep in the surrounding tissues and between it and its parent skin ectoderm develops the first or most anterior of a series of branchial pouches from the pharynx and corresponding branchial clefts or grooves on the side of the head, to be described in the next chapter. Each cleft runs from over the otocyst ventrally toward its fellow of the opposite side, and may be considered as the boundary line between face and neck. The otic placodes themselves are important at present only as a guide to the position of the clefts. The first clefts are important landmarks in face development.

The olfactory placodes are situated in the skin ectoderm at the morphologically cranial end of the head, ventrolateral to the forebrain. Appearing during the fourth week, they soon form deep open depressions, the olfactory pits, but, instead of closing off as vesicles, these pits remain open, grow deeper, curve, and finally open to the surface again at a point that is later to be included within the mouth (Fig. 2, *b*). The pits actually form the nasal passages, within which a small area only is modified as the olfactory organ.[1] Also, on the median wall of each nasal passage an additional minor pit develops to lodge the vomeronasal, or Jacobson's organ. This is apparently an independent sense organ, possibly for underwater olfaction in lower forms.[2] In man it remains vestigial. Around the opening of each olfactory pit a broad raised rim develops, incomplete on the lower side (Fig. 1, frontispiece), where a groove is directed morphologically ventrally toward the stomodaeum.

The lens placodes appear, at about 5 weeks, at the sides of the head, also over the forebrain, but caudal to the olfactory pits, and pass through the open-cup stage to become sunken vesicles (Fig. 2, *c*). In certain of the molluscs (e.g., Limax, a naked snail) vision is received by the placode itself; the cells of the deep layer of the vesicle elongate as visual receptors and transmit the visual sensation to dendrites of nerve cells in the proper sensory ganglion. A chitinous lens is provided by the overlying surface ectoderm. In the vertebrates, as acute vision becomes more important for active life, the placode eye is reduced to a subsidiary role, acting merely as a much more plastic optic lens, while the sensory visual receptors are transferred to the retinal layer of the *optic vesicle,* a structure that by its origin as a hollow outgrowth from the outer edge of the alar plate of the still open forebrain (i.e., the most cranial portion of the neural crest), by its distinctive pattern of growth close to the side of the brain in a morphologically ventral direction, and by its terminal expansion and slender connection with the parent brain, can be likened to a sensory ganglion and considered as the most cranial member of the long line of dorsal root ganglia, which also show primarily a slight cleftlike cavity.[3] The optic vesicle expands dorsally, close to the side of the brain, and then is indented to form the two-layered optic cup, the inner layer of which serves as the retina. Yet, although they no longer are to serve as visual receptors, the cells of the deeper wall of the lens vesicle still elongate and to such an extent that they soon fill the vesicular cavity and transform the lens vesicle into a solid body, which is taken into the open mouth of the optic cup and there permanently attached. The eye is thus formed by the combination of two entities, the brain wall and the overlying skin ectoderm each supplying a share. Together they produce on the side of the head a rounded mound surrounded by a curving groove which continues as a straight open furrow or sulcus to the ventral surface of the head and there opens into the stomodaeum in common with the groove from the nasal placode (Fig. 3, *a*).

In the later development of the eye, at about 7 weeks, the protruding mound of the eyeball and its surrounding groove are progressively buried by the growth of two folds of ectoderm and supporting mesoderm, derived from the outer rim of the circular groove. These are the eyelids, and they are oriented in the face as definitely upper and lower, without regard to the orientation of the retina or of the eyeball itself. For the greater part of fetal life the lids are shut and fused, enclosing the conjunctival sac, from the lateral angle of which the lacrimal glands grow out as a group of primarily solid epithelial buds. From near the medial angle two other epithelial buds grow out and soon join as a single rod, which then lengthens and joins the adjacent nasal cavity as the forerunner

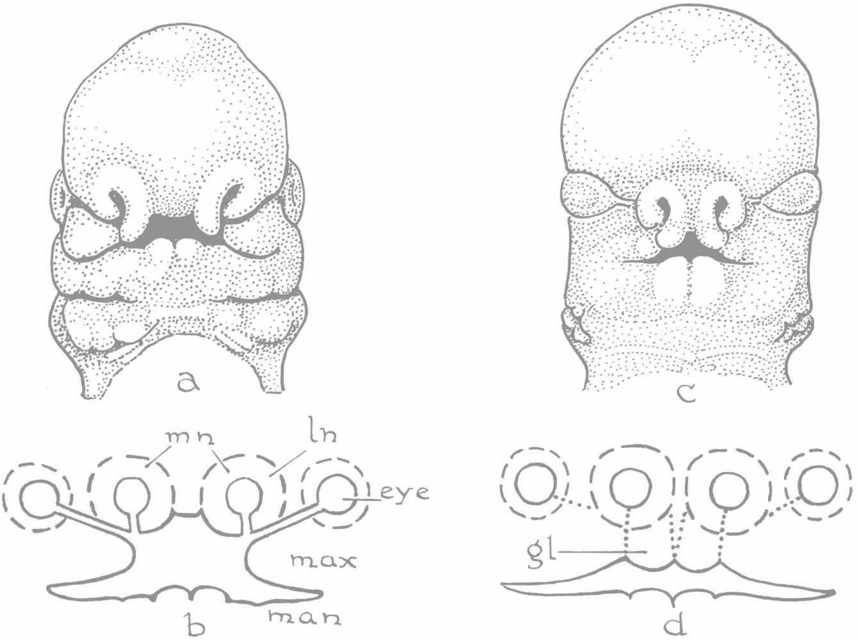

Fig. 3. Frontal aspect of faces of human embryos of (*a*) 9 mm and (*c*) 12 mm (after Patten); (*b, d*), diagrams to show relation of face to nasal and lens placodes and to mouth; *lm, mn*, lateral and mesial nasal processes; *max, man*, maxillary and mandibular processes; *gl*, globular process.

of the nasolacrimal duct,[4] later canalized. Other authors [5, 6] derive this duct from the deeper cells of the open furrow from the eyeball, reoriented in a slightly different direction and joining the two outgrowths from the inner canthus at one end and the nasal cavity at the other. The original groove from eyeball to stomodaeum is ultimately closed.

In relation with each placode, then, there is at one time a ventrally directed groove. Still another pair of lateral head grooves develops as the result of the head bend, which causes a crease around the ventral surface of the head in the region of the midbrain, continued for a certain distance on the lateral surfaces. Each lateral crease is provided with a branch running caudally, and these paired branches determine the location of the future mouth. With the continued rapid forward growth of the brain and the retarded growth of the ventral part of the head, these branches are carried to a relatively more caudal position between the eyes and the first branchial clefts.

The four grooves at the side of the head—nose, eye, mouth, ear—divide this region into four "processes." Beginning at the morphological tip of the head, the first of these are the median and lateral nasal processes (I and II), separated by the nares and nasal grooves; the lateral nasal process is limited by the optic groove, and thus includes both the raised rim of the nasal passage and the flat surface between that and the groove running ventrally from the eyeball. Between the optic groove and the mouth is the maxillary process (III), and between the mouth and the first branchial cleft lies the mandibular process (IV). At the front of the head, between the upper parts of the two median nasal processes, is the unpaired median nasal field or frontonasal process. Because of the head bend the nasal processes point in a direction at right angles to the maxillary and mandibular processes; by their future growth and union the various processes form the face.

Formation of the face. The two median nasal processes grow downward and fuse with each other below and with the median nasal field above (Fig. 3). The tip of each process, below the external naris, becomes rounded and is known as the processus globularis. The lateral nasal processes, on the other hand, remain short and allow the maxillary processes, finding vacant space below them, to grow across their lower ends and meet the sides of the globular processes, thereby closing the optic and olfactory grooves and shutting out the lateral nasal processes from any participation in the upper lips. The mandibular processes, longest of them all, meet in the midline, and by themselves form the whole of the lower jaw. Each fuses superficially along the side, for a varying distance, with the maxillary process to make the cheek; the extent of this fusion determines the size of the mouth, too long a fusion causing an abnormally small mouth, microstomia, too little fusion resulting in macrostomia. In the latter case the red of the lips may be of normal proportions, not reaching to the border of the opening.

The protruding nose develops during the fourth month by the forward growth of a single cartilaginous septum, derived from the unpaired nasal field, and of several paired median and alar cartilages, derived from the median and lateral nasal processes. The paired nature of the tip of the nose can always be felt and often seen. The globular processes do not contribute to this late growth, but remain at the former level to serve as the lips. The external nares, which at 2 months still remain in the plane of the face, are turned down to a more horizontal position by this late growth of the cartilaginous septum. The new space thus formed is the vestibulum nasi. The attachment of the alae nasi to the face shows that only the rim around the olfactory pit is concerned in this growth, in other words, that the lateral nasal process extending laterally to the optic groove is actually divisible into the rim portion and a flat portion, and that these two portions may act individually. This fact will help to explain the relations seen in certain anomalies.

The palate. Within the mouth, from the oral surface of each globular process and of the anterior half of each maxillary process, a shelflike projection grows inward toward its fellow from the opposite side. These are called respectively the median, or premaxillary, and the lateral palate processes. It will be remembered that the nasal pits open posteriorly into the top of the oral cavity. The continued growth and final fusion of the palate processes from all four sources (the incisive foramen marks the extent of the premaxillary contribution) form the permanent palate, shutting off the upper part of the oral cavity. The various forms of cleft palate can be recognized as being due to the failure of certain elements to attain their normal growth. The nasal septum joins the palate from above. These several fusions serve to extend the nasal passages at the expense of the upper part of the oral cavity, and to move the choanae to the posterior end of the hard palate. Below the palate shelves a deep groove, the labial fossa, running transversely along the ends of the globular processes and the lower edges of the maxillary processes, serves to separate the upper lip from the gingival ridge along which the teeth are to develop, and a similar groove on the upper surface of the mandibular processes does the same for the lower jaw.

Normally the meeting surfaces of the various processes which form the face should have fused at the end of the second month. The fusion of the rounded globular processes causes a broad groove with raised edges, called the philtrum, in the center of the upper lip, which, with the two mandibular processes and two maxillary processes, divides the oral rim into five distinct areas and gives to the infantile mouth its pentagonal shape.[7] The other clefts between the various processes should close without a trace; failure to close properly is the cause of most facial anomalies.

Anomalies of the face. By far the most common of these is harelip (Fig. 4), caused by nonunion of the globular and maxillary processes, with cleft from mouth to nostril.[8] This condition may be single (i.e., on one side only) or double, and may be superficial, affecting the lip only, or deep, including the gingival ridge and the palate, but cleft palate may exist without harelip. The globular process normally carries the median and lateral incisor teeth, but in certain cases of harelip the line of cleavage runs between them. In fact, the congenital absence of one lateral incisor may represent a minor form of harelip.

As a rare variation the globular and maxillary processes may meet at one point only and then withdraw, leaving a bridge of

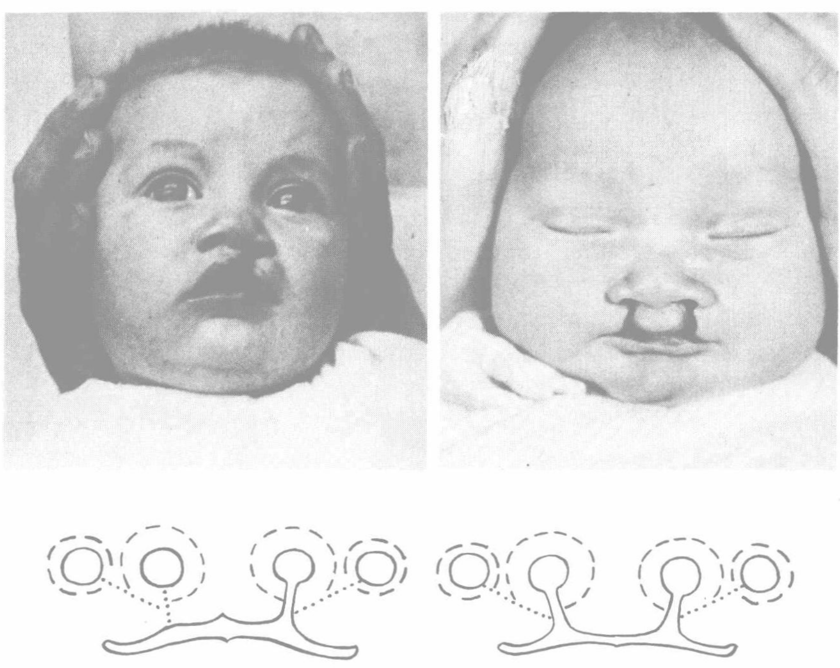

Fig. 4. Harelip, single and double (Ladd), with explanatory diagrams.