

THE DEVELOPMENT OF THE MUCOUS MEMBRANE OF THE ŒSOPHAGUS, STOMACH AND SMALL INTESTINE IN THE HUMAN EMBRYO

FRANKLIN P. JOHNSON

From the Department of Comparative Anatomy, Harvard Medical School

WITH TWENTY-FOUR FIGURES

SEVEN PLATES

The development of the mucous membrane of the digestive tract, although studied for many years by competent observers, still affords opportunity for further investigation. The present work was undertaken for the purpose of studying the development of the structures found in the digestive tract, and to obtain a comparable series of wax reconstructions illustrating the changes that take place in the form of the mucosa. Especial stress has been laid on the development of vacuoles and diverticula, villi, glands, and folds. It was originally intended to include the development of the mucous membrane of the vermiform process and the large intestine, but for lack of favorable material, this has been omitted in the present paper. This work was suggested by Dr. F. T. Lewis, and has been done in connection with his chapter on the digestive tract for Keibel's Text Book of Human Embryology. A more complete review of the literature than is here given, will be found in Dr. Lewis' chapter.

The material used was obtained from human embryos in the Harvard Collection. The earlier stages were already prepared in the embryological collection. The crown rump lengths and series numbers of these are as follows:

LENGTH IN MM.	SERIES No.	LENGTH IN MM.	SERIES No.
7.5.....	256	23.....	181
10.....	1000	24.....	24
16.....	1322	29.....	914
19.....	819	30.....	913
19.....	828	32.....	649
22.....	851	37.....	820
22.8.....	871	42.....	838
22.8.....	737	78 (incomplete series).....	723,724

The crown-rump lengths and numbers of the older embryos used are as follows:

LENGTH IN MM.	SERIES No.	LENGTH IN MM.	SERIES No.
55.....	249	120.....	203
73.....	116	134.....	30
78.....	142	145.....	131
91.....	224	187.....	315
99.....	340	240.....	186
120.....	342	Newborn.....	341

From the older embryos, the different parts of the digestive tract were separately removed, imbedded in paraffin, and cut in serial sections of 8 microns in thickness. The sections were stained by different methods, among which were Heidenhain's iron hæmatoxylin, Hansen's iron hæmatoxylin, and Mallory's aniline blue connective tissue stain. Both eosin and orange G were used as counter stains. From the preparations thus made, certain stages of development were selected, and a number of wax reconstructions made. The models have in most cases been made to the magnification of 145 diameters, so as to be easily compared. However, in some of the gland models, this magnification was doubled, and in others trebled.

ŒSOPHAGUS

Early Stages. In an embryo of 7.5 mm., the œsophagus is a cylindrical tube of epithelium extending from the pharynx to the stomach. The lumen is round and relatively large at its upper end, but tapers gradually until at its middle it is quite small. Passing downward from this region, the œsophagus gradually increases in size and at its lower end leads into the stomach, there

being no sharp line of demarcation between the two. The indistinctness of the cell boundaries makes it very difficult to determine definitely the number of cell layers in the epithelium. Because of this, different observers have not agreed upon the number of cell layers present in the early stages. It can, however, be said with reasonable certainty that the epithelium at 7.5 mm. is stratified and in the upper and lower thirds of the œsophagus shows three or four rows of nuclei, in the middle third, two or three rows. The basal cells are the more columnar and are characterized by having their nuclei in that end of the cell which is toward the lumen. Surrounding this central tube of epithelium is mesenchyma, which although undifferentiated is slightly condensed.

In an embryo of 16 mm. the œsophagus has increased in length and breadth. The upper end is both larger and more irregular in outline. The epithelium contains three or four rows of nuclei and lies on a very distinct basement membrane. Here again, the basal layer of cells is the more columnar and its rounded nuclei lie in the upper ends of the cells, that is, away from the basement membrane. In its lower portion, the œsophagus is smaller and oval in cross section. Throughout its entire extent the œsophageal epithelium is surrounded by mesenchyma which is limited externally by a narrow ring of deeply staining myoblasts, elongated in form, and so placed as to form the circular layer of the muscularis.

Vacuoles. The next stage examined was an embryo of 19 mm. (series 819). In this only about the lower half of the œsophagus was available for study. The epithelial tube is now irregular in outline, and presents within its walls numerous small cavities or vacuoles. Some of these are minute, others have a diameter 0.051 mm., which is greater than the diameter of the lumen itself, making it difficult to determine from cross sections which is lumen and which vacuole. In some places the vacuoles open directly into the lumen, in other places they are separated from it by a partition of epithelium. Fig. 1a is of a model of the œsophageal epithelium at this stage and shows its vacuolated structure. The portion of the œsophagus modelled was selected at a place just below the bifurcation of the trachea. In a second embryo

of 19 mm. (series 829) similar vacuoles are found, but are less numerous than in the above embryo of the same length. They are also more numerous in the lower portion of the œsophagus than in the upper.

At 22.8 mm. (series 871) the diameter of the œsophagus is nearly double that at 19 mm. The vacuoles are more numerous and, as shown in fig. 1b, communicate with one another and with the main lumen to a greater extent. In the upper part of the figure the œsophagus appears to have a double lumen. This appearance is due to the fusion of a number of vacuoles. The vacuoles are about the same size as those found in the preceding embryo but the lumen has increased in diameter. Although vacuoles also occur in the dorsal and ventral walls of the œsophagus, they are less numerous there than in the lateral walls. The few vacuoles found in the dorsal and ventral walls do not show in the figures; they are, however, of the same general character as those described.

In other embryos of 22 mm., 22.8 mm. (series 737) and 23 mm. the vacuoles are found to be less numerous in the upper half of the œsophagus than in the lower half. At 29 mm. and 30 mm. they have become very few; at 32 mm. only slight traces of them are found; at 37 mm. they have entirely disappeared.

Vacuoles of the nature described were noted by Schultz in 1897. Kreuter ('05) believed that they cause a temporary occlusion of the œsophagus, but Forssner ('07) showed by means of models that the main lumen is not obliterated. Schridde ('08) failed to find an occlusion at any stage and denied the presence of vacuoles but described epithelial bridges which arise by epithelial proliferation in circumscribed places. From a study of these structures by means of wax reconstructions, the writer is able to confirm the results of Forssner inasmuch as the lumen is not entirely occluded and vacuoles are present.

The exact cause and significance of the vacuoles are difficult to determine. Similar vacuoles are found in the œsophagus of pig, rat and rabbit embryos. They have been reported by Forssner in the hedgehog, where in a certain stage they lead to a complete occlusion. Vacuoles similar to those of the œsophagus are found in the walls of the stomach and the duodenum of human embryos.

Kreuter states that there is no reason to believe that the vacuoles are areas of degeneration for he was nowhere able to demonstrate evidences of a degeneration of cells followed by resorption. There can be seen, nevertheless, a few nuclei lying within certain vacuoles which stain less intensely and are more indistinct than the nuclei of the epithelium. It does not appear, however, that these occasional degenerating nuclei are responsible for the production of the vacuoles. It seems obvious from the arrangement and crowded condition of the surrounding nuclei that the vacuoles increase in size. As they become larger the epithelium between the vacuoles and the lumen, and between adjacent vacuoles becomes reduced to a thin partition. This partition eventually breaks through and makes the cavity of the vacuole and the lumen continuous.

Measurements of the thickness of the epithelial wall of the œsophagus are interesting in connection with the vacuoles. At a time when vacuoles begin to form, the epithelial wall of the œsophagus is composed of apparently three or four layers of low columnar cells. While vacuoles are present the number of cell layers varies from one to four. By a breaking through of the vacuoles into the lumen and a disappearance (or migration) of the more superficial cells, the epithelium is reduced in thickness. At 19 mm. and 22.8 mm. the epithelium averages .051 mm. while at 30 mm. only .030 mm. in thickness. This loss in thickness is soon compensated by a growth in the height of the individual cells, for at 42 mm. there are only two layers of cells, the average thickness of the epithelium being .043 mm. Two results of vacuolation are, therefore, a destruction of the more superficial layers of cells, and an increase in the size of the lumen of the œsophagus. This increase in the size of the lumen is proportionately great in the early stages but less in the older ones.

Folds. At an early stage the epithelium of the œsophagus becomes thrown into large longitudinal folds which are usually four in number. Later smaller folds develop at the bases of, or in between, the larger ones. These folds give to the œsophagus in cross section the appearance of a Maltese cross as was first noted by Koelliker ('61). Certain of the folds make their appearance

before others and show different stages of development in different regions of the same œsophagus. The exact time and order of the appearance of these structures was studied in a number of embryos with the following results.

As stated before, the epithelial tube of the œsophagus at 7.5 mm. is cylindrical in shape, very small at its mid-region, but gradually becoming larger when followed either up or down. In embryos of 10 mm. and 16 mm. the upper portion of the œsophagus is flattened ventro-dorsally, the middle region is circular but now more expanded, and the lower portion is flattened laterally. In the upper part of the œsophagus there is a slight infolding of the ventral wall of the epithelial tube.

In the upper part of the œsophagus at 22.8 mm. (series 871) there is a ventral infolding of the epithelium. This is the direct downward continuation of that fold of the pharynx which gives to the latter, when seen in cross section, its characteristic crescentic shape. Following downward this fold is soon lost and the œsophagus becomes rounded. Another fold appears in the mid-region of œsophagus, this being an infolding from the dorsal side. Still further caudally, as the stomach is neared, a third infolding is found, this being left lateral in position. This lateral fold in an older embryo is seen to be directly continuous with the dorsal fold above. The folds found in this embryo are, therefore, really two in number, a ventral one which appears in the upper third of the œsophagus, and a dorsal one which is seen in the middle third and again as a lateral fold in the lower third. Since the study of the order of the appearance of these folds was made by wax reconstructions in a series of embryos, it was necessary to secure for modelling approximately the same level of the œsophagus in each specimen. The region selected was that immediately below the bifurcation of the trachea.

The œsophagus at 37 mm. in the region of the bifurcation of the trachea (fig. 2) is somewhat crescentic in cross section. Dorsally, facing the dorsal aorta, there is a deep fold which continues upward and downward and passes directly onto the stomach. In the lower third, however, it deepens and changes its position by moving through an arc of about 90° to the right. At 42 mm.

in the same region as the above (fig. 3) there are two distinct folds, a dorsal and a ventral. These folds, which I have designated as the first pair of primary folds, are continued downwards onto the stomach, but before reaching it are twisted to the right and occupy positions on the left and right sides of the œsophagus respectively. In the figure a second pair of primary folds can be seen, which, although indistinct at this level, are well marked below. In the region modelled and below it, the fold on the left side is the more marked, but above the right fold alone is seen, and the ventral and dorsal folds approach one another on the left side, making a three sided figure. At the extreme upper end of the œsophagus these folds become irregular and are broken up by the formation of other smaller folds. All the folds shown in fig. 2 are twisted as the stomach is neared, each occupying a position of about 90° to the right of its original position.

At 55 mm., both pairs of primary folds are well developed (fig. 4) and give to the lumen of the œsophagus in cross section the appearance of a Greek cross. These folds are also seen in embryos of 30 mm. and 42 mm. in the lower parts of the œsophagus. As seen in fig. 5, at 134 mm., these primary folds are augmented by secondary folds which develop at the bases of the former. Three such folds are seen in fig. 4, one of which is quite large. The same folds are found in embryos of 187 mm., 240 mm., and at birth.

By way of summary concerning the development of folds of the mucous membrane of the œsophagus, it may be said that the dorsal one is the first to develop completely. This is followed closely by the ventral fold. The second pair of primary folds develop from below upwards and have reached to the bifurcation of the trachea in an embryo of 42 mm. The secondary folds are less constant structures. They begin as thickenings of the epithelium between the bases of adjacent primary folds. In the upper part of the œsophagus, especially in the older stages, folds are very irregular. The reader is referred to Table 1, page 532 for measurements of folds of the œsophagus in different stages of development.

The fact that the epithelial folds of the œsophagus rotate

through an angle of about 90 degrees and always in the direction of the hands of a clock, seems to have some significance. Just what the cause of this rotation may be is debatable. Kreuter discards the idea that the lower part of the œsophagus may share in the rotation of the stomach. However, this may be its cause. This view is supported by the arrangement of the branches of the vagus nerves. These branches are also twisted at the same level as the œsophageal folds. It would, therefore, not seem improbable that the lower part of the œsophagus had been twisted along with the nerves by the stomach. Since the twisting of the stomach takes place before the appearance of the folds, it would necessarily have to be assumed that the lines along which the first œsophageal folds develop are marked out before the actual appearance of the folds themselves.

Ciliated cells. The presence of ciliated cells in the œsophagus was noted in 1876 by Neumann, who observed them in embryos of from 18 to 32 weeks. He described the epithelium as stratified, the superficial layer being made up of patches of both ciliated columnar and squamous cells. Schaffer ('04), confirmed by Jahrmaerker ('06) and Schridde ('07), states that the ciliated cells may extend through the thickness of the epithelium down to the basement membrane. Jahrmaerker has recorded the presence of ciliated cells in the œsophagus of an embryo at 44 mm. In an embryo of 42 mm. no ciliated cells could be found, but the preservation of this embryo was poor and the staining unfavorable for the recognition of cilia. In a specimen of 55 mm. ciliated cells are abundant. Here the epithelium of the œsophagus is composed of from two to four layers of cells with distinct cell boundaries. The basal cells are columnar and have their oval nuclei away from the basement membrane. In those places where there are not more than two layers of cells, the superficial cells are columnar, very granular, and ciliated. Where there are three or four layers of cells, only the lower layer is columnar, the upper layers being composed of polygonal or flat cells.

In order to study the distribution and number of the ciliated cells, wax reconstructions were made, the areas of ciliated cells being carefully painted on each wax section before piling. Fig.

6, from an embryo of 55 mm., shows one half of a model viewed from its inner surface. The stippled areas represent those covered with cilia. As can be seen, the larger areas of ciliated cells are on the folds and these areas include but few islands of polygonal cells. Between the folds there is a preponderance of squamous cells, which are interrupted by a few small ciliated patches. In the upper part of the œsophagus the ciliated areas are slightly larger than in the region modelled. A similar reconstruction was made of the epithelium of the œsophagus at 99 mm. (fig. 7). It shows that the amount of ciliated surface has actually and relatively increased and there are now more islands of polygonal cells on the folds.

In embryos of 120 mm., 134 mm., and 187 mm., ciliated cells in the œsophagus are observed to be distributed in about the same proportions as at 99 mm. At eight months the upper part of the œsophagus shows only a few small patches of ciliated cells. In a specimen at birth the areas are abundant but proportionately smaller than in the earlier stages, and the islands are now more widely separated. The islands consist of distorted columnar ciliated cells, the distortion probably being due to the pressure of the rapidly increasing polygonal cells, which are seen crowded closely against the islands and in places partly undermining them. In a child of two weeks (7 months premature birth) no ciliated cells can be found in any part of the œsophagus. Jahrmaerker and Schridde were unable to find ciliated cells at birth.

Glands. In regard to the glands of the œsophagus, there are two distinct types to be considered; the true or deep œsophageal glands, and the cardiac or superficial œsophageal glands. The former are found in the adult all along the œsophagus, with the exception of the lower 2 to 4 mm. of its length; the latter in the lower 2 to 4 mm. and also (70 per cent of cases examined by Schaffer) in that portion of the upper part of the œsophagus which lies between the level of the cricoid cartilage and the 11th tracheal ring.

In an embryo of 78 mm. (incomplete series 723 and 724) small patches or islands of glandular epithelium are found in both the upper and lower ends of the œsophagus. Schaffer ('04) described

similar groups of cells in an embryo of four months, at the level of the third or fourth tracheal cartilage, and Schridde ('07) found a group in an embryo of 105–110 mm. (16 to 17 weeks) at the level of the cricoid cartilage. Areas of glandular cells are abundant in the lower part of the œsophagus at 120 mm. Some groups are arranged as islands, others are evaginated so as to form small pockets. From the bottoms of these pockets budding glands are seen. In the lower part of the œsophagus at 240 mm. the glandular cells are more conspicuous. On the sides of the large folds, but chiefly at their bases, patches of secreting cells are seen forming small isolated islands, pockets, and grooves. The glandular epithelium is high columnar and is everywhere surrounded by stratified squamous and ciliated cells. The pockets form the ampullæ of the cardiac glands, from which numerous small buds have grown out. A model of such a gland, found at the bottom of a fold at the lower end of the œsophagus, is shown in fig. 8. The surface which is ruled in the figure indicates the simple glandular epithelium; the unruled surface, the stratified squamous epithelium.

The presence of the deep œsophageal glands was first noted in an embryo of 240 mm. Their beginnings are seen as small outgrowths of the stratified epithelium. These buds are found at the bases of the primary folds and upon the outer surface of the secondary folds. They are lined by a stratified squamous epithelium similar to that lining the œsophagus. In a specimen from the upper part of the œsophagus at 8 months, a gland was found which extended through the muscularis mucosæ into the submucosa. Its walls were composed of one and two layers of cuboidal cells, but nowhere throughout its entire extent could secreting cells be seen.

At birth the œsophageal glands (fig. 9) have grown out through the muscularis mucosæ and lie in the inner part of the submucosa. The mouths of the glands are lined with a stratified squamous epithelium of three or four layers of cells which is directly continuous with the œsophageal epithelium. Gradually the stratified squamous epithelium passes into the double layer (in some places single), of low cuboidal cells which lines the excretory

duct. The excretory duct of the gland passes through the thick *muscularis mucosæ* at nearly right angles to the surface epithelium. On reaching the outer border of the *muscularis mucosæ*, it bends to either side. Instead of pointing toward the stomach, as has been described in the adult *œsophagus* (Goetsch), glands may extend either upward or downward. The distal terminations of most of the glands are expanded and lined by a simple glandular epithelium of low columnar cells. In the gland A (fig. 9) the end piece shows a number of bud-like processes which are the beginnings of branches. The end piece of gland B is a simple curved expanded tube, the expanded portion being for the most part glandular. In the gland C there is no end piece at all, the whole gland being lined by two layers of non-secreting low cuboidal cells. In a study of the *œsophageal* glands of the pig, Flint has described a similar early stage, in which the glands contain no secreting cells. However, glands of this type are rather rare in the human embryo at birth, there being a preponderance of those with secreting cells and beginning branches.

In summarizing the development of glands of the *œsophagus*, it may be said that the first evidence of the cardiac glands is the appearance of small patches of glandular cells in the surface epithelium. These patches occur at both the upper and lower ends of the *œsophagus* and are seen as early as the third month. Later, by evagination, small pockets are formed from these patches. This is followed by a subsequent budding from the outer surface. Thus are formed a number of branches which open into a single pocket or ampulla. Cardiac glands never extend through the *muscularis mucosæ*. The deep *œsophageal* glands, first seen in an embryo of 240 mm., are outgrowths of the stratified squamous epithelium, which after piercing the *muscularis mucosæ*, bend to either side, and lie in the submucosa close to the *muscularis mucosæ*. The secreting cells do not appear until after the gland is well formed, and are found only near its distal termination. Here at birth a number of budding processes, lined with a secretory epithelium, are seen arising from the end pieces. Thus the cardiac glands and the *œsophageal* glands differ in that, in case of the cardiac glands the secretory epithelium appears before the

gland formation begins, while in the oesophageal glands it does not appear until after the excretory ducts are formed.

TABLE 1
OESOPHAGEAL EPITHELIUM. (MID REGION)

EMBRYO	THICKNESS ¹ OF SURFACE EPITHELIUM		DIAMETER OF EPITHELIAL TUBE	PRIMARY FOLDS		SECONDARY FOLDS	
Length In mm.	In Cell Layers	In mm. ²	In mm.	Number	Height ² in mm.	Number	Height ² in mm.
7.5	3-4 (?)	.020	.043	0			
16.	3-4 (?)	.043	.148	0			
19.	1-4*	.051*	.163	0			
22.8	1-4*	.051*	.228	1	.010		
30	2-3	.030	.306	2	.056		
42	2-3	.043	.398	3-(4)	.089		
55	2-4	.051	.51	4	.094	1	.012
99	3-4	.051	1.01	4	.31	4	.081
120	4-5	.043	.90	4	.29	4	.054
187	4-5	.051	1.63	4	.47	3	.091
240			1.81	4	.58	4	.127
Birth	5-6	.056	2.26	4	.68	3-4	.163

¹ On tops of folds when present.

² Average of a number of measurements.

* Vacuolated stages.

STOMACH

For this portion of the present paper only the fundus region of the stomach has been studied, the development of the gastric pits (foveolae gastricae) and the gastric or peptic glands (glandulae gastricae propriae) being given chief attention. Koelliker ('61 and '79) regarded the gastric pits and glands as hollow epithelial processes which grow downward into the mesenchyma. Laskowsky ('68) confirmed by Schenk ('74) and Brand ('77), described glands as epithelial in origin, but believed that an upward growth of the underlying mesenchyma was the active factor in their production. Sewall ('79), working on sheep embryos, concluded that the first chief and parietal cells were epithelial in origin, but were later replaced by others of mesenchymal origin.

Toldt ('81) in a noteworthy study of the histogenesis of the gas-

tric mucosa in cat, pig, and human embryos, concluded that the glands are formed exclusively by downgrowths from the epithelium. Minot ('02) likewise describes an epithelial origin for the glands. Later, Strecker ('08) returned to the old idea of a mesenchymal origin for the gland cells. The results of the present work are largely in accord with those of Toldt. However the present study deals mainly with the form of the mucous membrane and is based upon a series of wax reconstructions, while Toldt was concerned chiefly with detailed histogenesis.

Early Stages. In an embryo of 7.5 mm. the stomach is a well marked, spindle-shaped swelling, about .132 mm. in transverse diameter. It is placed with its long axis parallel to the long axis of the body of the embryo. Its epithelium is about .046 mm. in thickness and at the extremities of the stomach is composed of two or three layers of low columnar cells, at the mid region of higher columnar cells. As in the œsophagus, the basal layer of cells is the tallest, and the nuclei are placed at the upper ends of the cells. In an embryo of 8 mm., described by Jahrmærker, the nuclei of this strata were found in the basal ends of the cells, and this he pointed out as a distinction between œsophagus and stomach at this stage. The epithelium of the stomach is surrounded by loose mesenchyma which is limited, except at its mesenteric attachments, by the mesothelial lining of the coelom.

In an embryo of 10 mm. the stomach is more pyriform in shape and is now undergoing rotation to the right on its long axis. The lumen has greatly increased in diameter but the epithelial wall is of about the same thickness, measuring .048 mm. The number of strata of cells varies from two to three. Both the basal and the superficial layers of cells are distinctly columnar the latter showing distinct top plates. The nuclei of the basal layer are again in the upper ends of the cells, those of the superficial layer at the lower ends. The surrounding mesenchyma is slightly condensed, and a basement membrane is distinct in some places.

Gastric Pits. At 16 mm. the stomach is lined by an epithelium of high columnar cells of two or three layers, the entire thickness of the wall measuring .054 mm. The nuclei of the basal layer of

cells are again in their upper ends. The epithelium on the side toward the bursa omentalis shows several irregularities. These are vacuoles and pit-like depressions. The vacuoles are similar to those found in the oesophagus, but are smaller and far less numerous. The pit-like depressions are surrounded on their sides by the columnar cells of the epithelium. The nuclei of the cells which line the pits are rounded and are quite regularly placed around the lumen, so that the whole structure has somewhat the appearance of a taste bud. The pits measure about .009 mm. in width and about .028 mm. in depth. There are no corresponding outbulgings of the basement membrane made by these pits on the mesenchymal surface of the epithelium.

In an embryo of 19 mm. the epithelium of the stomach is of the same type as in the preceding embryo, having two or three layers of cells and a thickness of .048 mm. It contains a few small vacuoles. The pits are more numerous than before and some are elongated so that now they form short grooves. These are most numerous in the lower end of the stomach. Again there is nothing on the mesenchymal side of the epithelium to correspond to these depressions. In this embryo the beginning of the tunica muscularis is first seen.

The epithelium of the stomach at 22.8 mm. measures on the average .055 mm. in thickness. A few vacuoles, similar to those found in the oesophagus of this embryo, were observed. They were, however, much smaller than those in the oesophagus. The pits are more numerous and distinct than in the preceding embryo. Again some are rounded and some groove-like in form, but still they produce no swellings on the under side of the epithelium. At 42 mm. the pits are abundant. The epithelium measures .055 mm. in thickness and shows for the first time slight bulgings into the mesenchyma.

In an embryo of 55 mm. the epithelium of the stomach shows well defined pits and furrows on its inner surface. A surface view of a portion of the epithelium of the fundus of the stomach at this stage is shown in fig. 10. The cylindrical pits are irregularly scattered about, and the grooves are placed parallel to the long axis of the stomach. The epithelium, which was previously

stratified, is now becoming one-layered. This change is brought about by a readjustment of the cells, caused—first, by the development of the pits; second, by the development of somewhat similar pits or furrows on the outer surface of the epithelium. These latter structures are found alternating with the pits of the inner surface and are in different stages of development. Some appear as mere slits in the epithelium, others are already broader than many of the gastric pits themselves. Whether these pits are formed by an ingrowth of the mesenchyma, or whether they are formed independently of mesenchyma by a readjustment of the epithelial cells, is difficult to determine. In the specimens studied, the mesenchyma had shrunk away from the epithelium, but from their extreme depth and narrowness it is hardly probable that the mesenchyma could have extended into the narrowest of these furrows. However formed, these furrows cause the epithelium to be transformed into a simple epithelium. The cells of the surface epithelium and those about the pits give off slender basal processes. These cells have been described by Baginsky ('82) at 7 months, and by Fischl ('91) at birth. The cells have distinct cell boundaries, rounded nuclei, are granular, and show distinct top plates.

At 91 mm. the grooves on the mesenchymal side of the epithelium are well developed. In a model of the epithelium at this stage (not figured) these mesenchymal grooves have about the same appearance as the gastric pits, so that one can hardly determine which is the internal and which the external surface. The epithelium is composed of a single layer of cells. The cells are now higher, with more elongated nuclei, and have long basal processes. Some of the cells are clearer than others and seem to be filled with mucous secretion.

At 120 mm. the gastric pits have increased in number and in size, and are slightly more separated from one another than before. The growth of the epithelium has taken place both by an enlargement of the pits already formed and by the addition of other pits. A wax reconstruction of the epithelium of the fundus of the stomach at this stage (fig. 11) compared with fig. 10 (55 mm.) will give a clearer idea of the growth of the pits. The arrangement

of the parallel grooves is beginning to be lost, and the whole surface of the mucous membrane appears to be cut up by the network of anastomosing pits. The areas marked off by this network are slight elevations (much higher in the pyloric region), and have been considered by Brand as villi. Those of the fundus, however, are much broader and more irregular at their bases than the intestinal villi. Moreover, they have an entirely different developmental history. It is doubtful, therefore, whether these structures of the fundus can be considered as villi. The tunica propria, composed of developing reticular tissue, extends up between the pits to the surface epithelium. The surface epithelium is composed of a single layer of columnar cells, which are filled with mucous and contain at their lower ends oval or irregular elongated nuclei. The basal processes are not so elongated as in the preceding stage. At the bottom of the pits the cells are cuboidal.

Gastric Glands. A view of the under surface of the epithelium at 120 mm. (fig. 12), shows the beginnings of the gastric glands. They appear as knob-like outgrowths from the bottoms of the gastric pits. As many as three glands are sometimes seen arising from a pit at the same level. The small buds are for the most part as yet simple glands, although several were seen which had begun to branch. They are of different lengths, the longest being about .048 mm., and their diameters at the necks measure about .036 mm. The glands show small but well defined lumina and are lined by a simple cuboidal epithelium. The parietal (de-lomorphous) and the chief (adelomorphous) are easily distinguishable. The parietal cells stain more intensely with eosin than do the chief cells, and their protoplasm is slightly more granular.

Cross sections through the middle of the stomach at 187 mm. show the mucous membrane to be thrown into a number of large folds. The gastric pits are of about the same character as described for the 120 mm. embryo but they have increased in size. Some of the largest now measure about .089 mm. in depth. The surface epithelium is higher than in the preceding embryo and is composed of cylindrical cells which are mucous in character. The cells contain oval nuclei which lie in the lower halves of the cells

but not against their bases. At the bottoms of the pits the glands are seen. These are now longer and more branched, the longest measuring about .12 mm. The diameters at the neck vary somewhat, but most are about .038 mm. The diameters of the branches are smaller than the main stem of the gland. The glands are lined by a simple epithelium of irregular or polyhedral cells. Both the chief and the parietal cells are abundant. The bases of the glands lie close to the muscularis mucosae, which at this stage is well developed and consists of several distinct strands of smooth muscle fibres.

The changes that take place in the stomach epithelium from the 187 mm. stage are merely those in the increase in numbers and growth of the structures already formed. At 240 mm. the gastric pits measure from .102 to .158. mm., and the glands about .85 mm. to .136 mm. in length. From this it can be seen that the growth of the glands has been more rapid than that of the pits, some of the glands now being longer than some pits. In a model of the epithelium of the fundus of the stomach at 240 mm. (not figured), gastric pits are more irregular in form but are broader across their tops than those of the 120 mm. stage. They are, moreover, further apart than before. Fig. 13 shows gastric glands modelled under higher magnification. Two types of glands are seen, the smaller simple ones and the larger branched. In the compound glands the branching is not confined to any particular level, but branches are given off at the neck or any level below it. The cells lining the pits are like those found in the preceding stages, the chief and parietal cells being more numerous than before.

At birth the structure of the mucosa of the stomach is very similar to that found in the adult. The gastric pits are only slightly deeper than at 240 mm. The surface epithelium is composed of high cylindrical mucous cells with oval nuclei and basal processes. At the bottoms of the pits the cells are lower but are still distinct. As seen in fig. 14 the glands are longer and more branched than before. They have small lumina which are lined with chief and parietal cells.

The growth of the mucous membrane of the stomach is perhaps best shown in table 2. From the earliest stage up to 42 mm. there is but a slight increase in the thickness of the epithelial wall. At 16 mm. the pits begin to form, and rapidly increase in number and in size. At 55 mm., due to the presence of pits on the inner surface and alternating grooves on the outer (mesenchymal) surface, as described above, the epithelium becomes reduced to a single layer of low cells. When measured as in the preceding stages, the epithelium averages .057 mm. in thickness. When determined as in the following stages, *i.e.*, the epithelium which surrounds the individual pit, it measures .012 mm. Thus by the readjustment of the cells which is completed at this stage, the epithelium is reduced in thickness from .057 mm. to .012 mm. At 91 mm. the surface epithelium is much thicker because of the extremely long basal processes of its cells. At 120 mm. the basal processes are shorter, but from this stage up to birth there is a gradual increase in the thickness of the epithelium. The gastric pits rapidly increase in depth but there is a more gradual and variable increase in their width and the distance between adjacent pits. The glands also increase rapidly in length, but slowly in diameter.

Folds. Folds of the mucous membrane of the stomach are more variable in number than in the cesophagus. In an embryo of 10 mm. the epithelial wall of the stomach is perfectly smooth throughout. At 16 mm. there are two or three slight folds on the side of the greater curvature, and indications of about the same number of the side of the lesser curvature. At 19 mm. there are 2-3 large longitudinal folds on the side of the greater curvature, while the opposite wall is rounded, with no indications of folds. At 22.8 mm. there are 7-10 folds, including both walls; at 42 mm. 10-12; at 55 mm. about the same number but they are not as high. At 120 mm. and 187 mm. large folds are found, while at 240 mm. and at birth the folds are very much higher. In the last four cases, the number of the folds was not obtained. From these and other observations it would seem that the folds are rather inconstant structures, their number and size depending on the state of contraction of the muscular walls. Brand ('77) found

12-15 longitudinal folds of the stomach mucosa in an embryo of two months. Koelliker ('69) found in an embryo of four months, 3-4 folds; in another embryo of four months, 11-12; at three months, 5-6. He therefore regarded their number as variable. Toldt ('81), in a study of cat embryos, considered the folds of the stomach as unimportant, being formed by the contraction of the musculature.

TABLE 2
STOMACH EPITHELIUM (FUNDUS)

EMBRYO	THICKNESS OF SURFACE EPITHELIUM		GASTRIC PITS			GLANDS		FOLDS	
Length in mm.	In Cell Layers	In mm.	Depth ¹ in mm.	Width (at tops) in mm.	Distance apart in mm.	Length ¹ in mm.	Diameter ¹ (a neck) in mm.	Number	Height ¹ in mm.
7.5	2-3	.046							
10	2-3	.048							
16	2-3	.054	.028	.009	‡			5-6	.042
19	2-3	.048	.031	.009	‡			2-3	.067
22.8	2-3	.055	.048	.012	‡			7-10	.18
42	1-3	.055	.041	.012-.017	.036-.04			10-12	.25
55	1	.057							
		or							
		.012	.048	.007-.012	.024-.03			10-12	.11
91	1	.048	.072	.012-.030	.048-.08				
120	1	.029	.084	.019-.036	.054-.10	.048	.036		.36
187	1	.036	.089	.019-.038	.068-.17	.120	.038		.88
240	1	.038	.106	.019-.038	.102-.23	.136	.040		.88
Birth	1	.048	.108	.02-.048	.102-.17	.255	.048		.70

¹ Average of a number of measurements.

‡ Irregularly placed.

SMALL INTESTINE

Vacuoles and Diverticula. In the following section of the present paper the development of the intestinal villi and glands has been given especial attention. The vacuoles of the solid stage of the duodenum and intestinal diverticula are briefly described, particularly, because of a probable relation which they bear to the vacuoles found in the oesophagus and the stomach, and because they are closely associated with the development of villi.

The small intestine in the early stages of development of the human embryo is lined with an epithelium which is similar to that of the oesophagus and the stomach. This epithelium is composed of from two to four layers of cells surrounding the central lumen, which in the earlier stages is pervious throughout. The portion of the small intestine which is to become the duodenum begins to grow more rapidly than the lower portion, and in any single embryo may be seen to have attained a higher degree of development. In an embryo of 7.5 mm. the diameter of the epithelial tube of the duodenum is about twice that of the ileum, and its epithelial wall is much thicker. In the older stages, however, this advance in growth of the duodenum is not retained.

In an embryo of 10 mm. the posterior wall of the duodenum is thicker than the anterior and contains for a short distance both above and below the entrance of the ductus choledochus, numerous small vacuoles. Beyond this opening the lumen of the duodenum becomes extremely small, and only a few vacuoles are present. The remainder of the intestine is smaller than the duodenum at this stage, and is more regular and round. Its epithelium, which is composed of three to four layers of cells and is about half the thickness of the duodenum, does not contain vacuoles.

Tandler ('00) described similar vacuoles in the duodenum of embryos of from 30 to 60 days. He found that their formation in some cases led to a complete occlusion of the duodenal lumen, and believed that failure of the lumen to open again caused the well-known anomaly of duodenal atresia. Minot ('00) described a like condition in the large intestine of the chick. It is evident from his drawings (figs. 3-5) that the lumen of the large intestine of the chick is more completely occluded than that of the human duodenum. Forssner ('07) found similar vacuoles and duodenal occlusions in human embryos of about 20 mm. and also in the duodenum of rat embryos.

At 16 mm. the epithelium throughout the entire extent of the duodenum is filled with vacuoles which are larger and more numerous than in the former stage. Immediately below the openings of the ducts, the vacuoles are most numerous and the

lumen of the duodenum is totally occluded. Below this region the vacuoles are fewer and the lumen from this point on is open.

A few vacuoles are present in the upper part of the jejunum at this stage (16 mm.) but these are not as large or as distinct as those found in the duodenum. The lumen of the jejunum and ileum, unlike that of the duodenum, is pervious throughout its entire extent, although in the ileum it is much smaller. There have developed in the epithelial wall at this stage a number of outgrowths, which have been described as "intestinal diverticula." These rounded, bud-like structures are constricted at their necks, and extend into the surrounding mesenchyma. They are found in different stages of development and are variable in size. The smallest have diameters of .043 mm., the largest of about .072 mm., which is about $\frac{1}{3}$ that of the small intestine itself. The older pockets are well marked and are six in number, the younger ones are not as distinct and a few are doubtful. These were 11 in number, making a total of 17 pockets in the small intestine of this embryo.

Keibel ('05) noted the presence of similar pockets in embryos of man, Tarsius, pig, and deer, and considered it strange that these structures were not mentioned by Voigt ('99) and Berry ('02). Lewis and Thyng ('08) described diverticula which they found along the small intestine in human, pig, and rabbit embryos. In a human embryo of 23 mm. they counted 33 pockets; at 22 mm. (H. E. C. series 851), 48 pockets. Elze ('09) found in various mammalian embryos, rounded and elongated intestinal pockets similar to those described by Lewis and Thyng. He observed that the pockets are always on the wall of the intestine away from the mesentery, and that those pockets which were elongated and extended along the intestine for a short distance, invariably pointed down the intestine (ab-orally). In the human embryos of the Harvard Collection, so far as they have been examined, the diverticula present the same characteristics. Because of differences in their arrangement and position, Elze puts the diverticula of the duodenum in a separate class from those of the jejunum and ileum.

At 19 mm. (series 819) the vacuoles in the duodenum are larger than those at 16 mm. The lumen is continuous throughout and

is larger both in actual measurement and in proportion to the size of the vacuoles. In the lower part of the duodenum, these vacuoles are somewhat different from those found in the upper part and from those found in the œsophagus. Many of them have corresponding outbulgings of the epithelium on the mesenchymal surface. Some of these are constricted at their necks and form small side pockets, but for the most part they do not open into the main lumen of the duodenum. These "duodenal pockets," if such they may be called, are presumably different from those referred to by Lewis and Thyng, which give rise to an occasional accessory pancreas. They differ also from the intestinal pockets in their position on the walls of the duodenum, their constrictions are not always so well marked, and their cavities only occasionally open into the main lumen. However, so far as size and general appearance are concerned, they resemble the pockets of the jejunum and the ileum. Besides distinct pockets, all gradations between the simple vacuole of the interior and constricted side pockets are found in the walls of the duodenum. These pockets of the duodenum, therefore, probably represent transition forms between the vacuoles of the upper part of the digestive tube and the intestinal pockets of the lower part.

In the jejunum and the ileum at 19 mm., there are 41 diverticula. These have the same general character as those of the 16 mm. stage, but some, and especially those in the lower part of the ileum, are much larger. They are not equally distributed throughout the whole gut but are more numerous in the ileum. None are present in the upper part of the jejunum.

In the duodenum of an embryo of 22.8 mm. the vacuoles are few above the opening of the ductus choledochus. Below this level, fig. 16, they are numerous and larger in proportion to the size of the tube than at 19 mm. Moreover, they do not form duodenal pockets as in the 19 mm. stage. They cause the whole lumen to be broken up, and, as shown by modelling, the lumen in this region is occluded. This stage, therefore, as far as the vacuoles are concerned, resembles the condition found at 16 mm. more than that found at 19 mm. In the jejunum and ileum 33 pockets were counted. Again they vary in size, the largest meas-

uring .084 mm. Three of these pockets are seen in fig. 17. The first one (lettered *a*) is constricted from the intestine on all sides. The other two (*b* and *c*) are elongated forms, and are not entirely constricted at their necks, *b* being a surface view, and *c* an end view. The two latter extend along the intestine and their free ends point ab-orally.

At 24 mm. the vacuoles have disappeared from the upper half of the duodenum, but they are still present in the lower half. In the upper half, well formed villi are present; in the lower half, villi are seen which are fused together at their apices, but spaces are seen between adjacent villi. These spaces are the above described vacuoles. It is evident from this that the disappearance of the vacuoles is associated with the formation of villi. The exact part played by the vacuoles in the formation of villi will be dealt with in connection with the latter structures. In the duodenum of an embryo of 30 mm. the vacuoles have entirely disappeared.

Because of the development of villi, the intestinal diverticula are difficult to count at 24 mm. It is due to these beginning villi that the pockets disappear. Villi arise around the mouth of a pocket, and by their subsequent growth and enlargement, the pocket is gradually lost by being absorbed in their walls. Some pockets are more elongated than others, and on either side of these short longitudinal folds are seen. By a growth of these folds, pockets are likewise obliterated. As the villi develop from above downward, the pockets disappear in the same order. Consequently, in embryos of 29 mm., 30 mm., 32 mm., and 42 mm., the number of intestinal diverticula becomes smaller and smaller. Those in the ileum attain the highest development. As they increase in size their outer surfaces become flattened and later may even become concave. At 30 mm., the diameter of one of the largest pockets measures .108 mm; at 37 mm. .176 mm.

The significance and fate of the diverticula have been discussed by Lewis and Thyng. They conclude that some elongated forms, which are usually found in the duodenum, are the source of an occasional accessory pancreas. The more rounded intestinal pockets usually degenerate, but some may remain to form cysts

and nodules. It has been my fortune to find, in the mid region of an embryo of 134 mm., a large persistent intestinal diverticulum, fig. 23. It resembles in shape the pockets found in the lower part of the ileum in the 30 mm. and 37 mm. stages. It is connected to the intestinal epithelium by a constricted neck. At its widest place it measured .50 mm. in transverse diameter, and at its neck .21 mm. Extending outward from its somewhat concave outer wall are a number of intestinal glands which are similar to those found in other parts of the intestine. Extending into its cavity from the internal surface of the outer wall are a few villi, one of which is large and extends through the neck of the pocket into the lumen of the intestine.

In the duodenum at 134 mm., several epithelial cysts were found, which are entirely cut off from the epithelium of the duodenum. They are spherical in shape, and each has several glands extending from its external surface. The flattened cells which line these cysts give evidence of an internal pressure. In what manner these cysts are formed, I will not venture to say. There is, however, the probability of their having developed by the persistence of the early duodenal vacuoles or pockets.

Development of Villi. Koelliker ('61 and '79) states that at the end of the second month and in the third, the beginnings of separate villi appear. Barth ('68) and Brand ('77) confirmed this view. Voigt ('99), working on pig embryos, describes an irregular breaking up of the heretofore smooth inner surface of the gut wall by means of depressions and furrows. These furrows increase in numbers and run together to form a net-work of canals. From the fields thus marked off arise slight elevations, the first traces of the villi. Berry ('00), studying pig and human embryos, writes:

"The summary given by Oppel shows beautifully the comparative anatomy of the villi and their evolution. In vertebrates of low order, the intestine is smooth, no villi being present. Then appear longitudinal folds, and then all gradations between folds and villi, and finally villi. It is interesting to note that in those intestines in which folds of the mucous membrane are present, they are more numerous and prominent in the upper part than in the lower

part of the intestine. As villi are developed they again appear in the upper part of the intestine first, so stages are found with villi in the duodenum, and only folds in the ileum. Furthermore, when villi alone are present, they are more numerous in the duodenum than lower down. The most striking result in the following out the development of the villi in the human intestine is that they repeat all the stages found from the standpoint of comparative anatomy."

He concludes, "The villi appear first as longitudinal folds. These folds grow larger and then break up into villi."

Forssner ('07) in a study of oesophageal and intestinal atresiae, while not mainly concerned with the development of villi, confirms the work of Berry in that the villi of the human small intestine appear first as longitudinal folds.

In the human embryos I have studied, only in the lower part of the small intestine was I able to find distinct longitudinal folds preceding the formation of villi. In the upper two thirds of the small intestine, villi are found developing as knob-like invaginations of the epithelium.

The first evidences of villi found are in an embryo of 19 mm. Immediately below the pyloric end of the stomach, the duodenal epithelium shows, besides its vacuoles, other irregularities. These are thickenings of the epithelium and invaginations of the epithelium into the lumen of the intestine, and represent different stages in the development of villi. The thickenings vary in size and height, some being twice as thick as the epithelium of the intestine in other places. The invaginations are slight rounded elevations of epithelium, and have developed from the thickenings by a pushing in of the mesenchyma, which now forms the cores of these small villi. That these are villi and not folds is evident because they can be followed through only four to six $23\ \mu$ sections and in breadth at their bases they measure from .10 to .14 mm. From these measurements the bases of these elevations are seen to be approximately circular in cross section. Villi are of all gradations in height, one of the tallest measuring .09 mm. (The height of a villus has in every case been measured on the mesenchymal surface, *i.e.*, the depth of the hole which is filled with mes-

enchyma.) Although the villi are somewhat more numerous in the duodenum, where the diameter of the epithelial tube is large, they are also found in the greater part of the jejunum. Following down the jejunum, the larger villi become fewer and fewer until a region is reached which shows only thickenings. Below this point the lumen of the intestine is smaller and rounded and remains this way until the large intestine is reached.

At 22.8 mm. the villi are larger and more numerous than at 19 mm. They are, as shown in fig. 15, irregularly shaped processes. Below the openings of the ducts, villi—if it can be assumed that they are present—are not recognizable from an inner view of the gut cavity. This is due to the occlusion of the duodenal lumen and to the occurrence of the large vacuoles. However, the outer surface of the epithelium of this region is marked with pits filled with mesenchyma. These pits are similar to those forming the cores of distinct villi found in the other parts of the intestine. It can be inferred from this, therefore, that the formation of villi is taking place while the vacuoles are present in the epithelium, but the individual villi are not distinguishable during the solid stage of the duodenum.

Just below the vacuolated region of the duodenum, true villi are found at this stage (22.8 mm.). They extend into the first loop of the jejunum, but the villi of the duodenum, having developed first, are the larger. As the jejunum is followed down, the villi become smaller and smaller, until a level is reached in which villi are absent. The villi developing in this lower portion of the small intestine are as young as any in the whole gut. In order to make an accurate study of their development, a wax reconstruction was carefully made of this region. Fig. 18 shows half of the model, *a*, looking at the outer surface of the epithelium; *b*, at its inner surface. An examination of the inner surface shows the presence of a number of rounded, knob-like structures, the beginnings of the villi. These are only seen in the upper part of the model. Thickenings of the epithelium are seen in a region below the villi, but at the extreme end of the tube there are no evidences of villi at all. By comparing the external surface of the epithelium, *a*, with the internal surface, *b*, it is seen that there are depressions on

the outer surface to correspond with the villi. The thickenings of the epithelium may or may not have corresponding slight depressions. This model indicates that each villus originates as a thickening of the epithelium, and that later this thickening is invaginated. Still later the epithelium of the invagination becomes thinner and is reduced to a single layer of cells. Below the region of thickenings, the lumen of the intestine becomes smaller and rounded. In no place could longitudinal folds of the epithelium be found.

The idea that villi formation goes on simultaneously in that portion of the small intestine (duodenum) which is vacuolated and in that portion which is not, is further supported by the condition found in the duodenum at 24 mm. In this embryo, only the lower portion of the duodenum shows vacuoles. In the upper part of that region which was previously occupied by vacuoles, villi are easily recognized. Further down there is a region in which are seen a number of villi which are fused together at their apices, that is, end to end. In some places this fusion has the form of thin membranes extending from villus to villus. The formation of the villi seems to be taking place by a pulling apart of preformed villi, and in this process the vacuoles are lost by becoming a part of the lumen. The process of separation of the villi progresses from above downward.

In the mid region of the small intestine at 24 mm. (fig. 19), the villi are seen as separate knob-like elevations of various shapes and sizes. For the most part they have nearly circular bases, but some are elongated. Their apices are rounded. The average of a number of measurement shows the breadth of a villus to be about .11 mm. The tallest villi found in this region measured .12 mm. The epithelium on the tops of the villi is single layered, although in places it appears pseudo-stratified, and is .020 to .025 mm. in thickness. Between the villi are epithelial thickenings which measure .064 mm. in thickness and are composed of from 3 to 5 layers of cells. An examination of the whole of the model (half of which is seen in fig. 19) shows that the villi are arranged in five longitudinal rows. In the lower part of the intestine the villi are smaller; still lower down only epithelial thickenings occur.

Some of these are more elongated than the thickenings found above and form slight irregular ridges. These ridges have as yet no corresponding depressions of the mesenchyma. Below this, there is a diminution in the size of the intestine, and the ridges—2-4 in number—are irregular and changeable in position. Before the large intestine is reached, the ridges are lost and the lumen of the small intestine assumes a more rounded appearance.

The vacuoles have entirely disappeared from the epithelium of the duodenum at 30 mm. and the lumen is pervious throughout. The villi are even more numerous than at 24 mm. and vary in size, the tallest now measuring about .211 mm. The diameters of their bases vary within the limits of .089 and .146 mm. The villi are very irregular in shape, some flattened at their bases, others rounded. The arrangement of villi in rows is more pronounced than at 24 mm. Additional villi have developed either in between the villi of the rows already present, or by forming additional rows. In some places the rows of villi have the appearance of irregular longitudinal folds, suggesting a fusion of adjacent villi. This appearance is perhaps due to the rapid development of new villi between the older ones.

In the jejunum at this stage a similar arrangement of villi is found, but in its lower part the developing villi are further separated. Following down the ileum, they become smaller and smaller. Then comes a region in which there are only a very few villi and thickenings, these being more scattered than before. Following this, there is a region in which the diameter of the tube diminishes, and in this portion longitudinal folds are present. Further down it widens out again and the folds are lost; this is followed by another diminution. Several of these narrowed places are found in this part of the small intestine, and between them the tube regains its former diameter. In the narrowed portions, rather irregular folds are found, varying from 2 to 4 in number. In the widened portions, very young villi are present, but no folds. Fig. 20 is of a wax reconstruction of a portion of the epithelium at a place where there is a diminution in the diameter of the ileum. In the widened portion, the beginnings of a few villi are seen;

in the narrowed portion, two distinct folds, the tops of which are irregular in height, are present.

In the jejunum at 37 mm., the villi are similar to those at 30 mm., but are now regular in shape. They appear to be fused to a greater extent, and there are more longitudinal rows. In shape the villi vary from small low swellings to rounded or elongated processes, some of which are .214 mm. in height. They are only a little taller in the duodenum than below. Further down, at the entrance of a persistent yolk stalk, the intestine becomes wide. In this widened portion both villi and thickenings are seen. Below this region the diameter of the epithelial tube becomes smaller and irregular longitudinal folds are found. Still further down only low ridges are found which have no corresponding depressions for the mesenchyma. These ridges extend as far as the ileo-caecal valve. Practically the same conditions are found in an embryo of 42 mm., there being a few folds in the lower part of the ileum where the lumen is narrow. Where it is wide, villi are found.

In the mid region of the small intestine at 55 mm. (fig. 21), the villi have greatly increased in size and in number. They are, for the most part, rounded conical processes but a few are irregular and blunted. A most striking fact is that the villi are all very near the same size. Since additional villi develop as separate invaginations, one would expect to always find a greater number of small villi than large ones. But the small villi have always been found to be less numerous. It follows, therefore, that their growth must be more rapid than that of the older villi. Additional rows of villi have developed between those already present. At 55 mm. there are about 13 rows in the mid region of the small intestine. The villi of the new rows are as tall as those of the older ones, in fact, the later developed rows cannot be distinguished from the earlier ones. The arrangement of the villi in rows is best seen in a view of the external wall of the epithelium (fig. 22). In the extreme lower end of the ileum at this stage (55 mm.) two or three slight folds are found.

Regarding the further development of villi, there is but little of interest. They gradually increase in number and in size throughout stages from 73 mm. to birth (Tables 3 and 4). In the later

stages they present a variety of different shapes in different parts of the intestine. The villi of the duodenum at 78 mm. are cylindrical, with rounded ends, averaging .23 mm. in height. In the upper part of the jejunum they are blunter and measure .20 mm; in the mid region elongated and slender, .25 mm. in height; while in the lower part of the ileum they are swollen at their apices and measure about .28 mm. In the mid region at 134 mm. (fig. 23), the villi are pointed processes; at 187 mm. and 240 mm., they are more elongated. In the mid region at seven months (premature birth) irregular villi are found, some of which are foliate in shape and grooved on their sides. At birth, the villi of the mid region are likewise very irregular in shape.

In briefly summarizing the development of villi, it may be said that the general tendency throughout the whole of the small intestine is for villi to develop as separate invaginations of the epithelium. Owing, however, to the occurrence of transitory structures (vacuoles, diverticula, and folds) their development is manifested differently in different parts of the intestine. In the duodenum the early growth of the villi is closely associated with and concealed by the vacuolated condition of the epithelium. While the vacuoles are present, the apices of the villi of one wall seem fused with those of the opposite wall. They become distinct when this fusion breaks down. At the same time the vacuoles are lost by entering into the formation of the lumen. Throughout the upper two thirds of the jejuno-ileum, villi are first seen as separate thickenings of the epithelium. These thickenings become invaginated, and the thickened plate of epithelium becomes reduced to a single layer of cells. In the lower third of the small intestine, longitudinal folds precede the formation of villi. However, since the folds are present only in those regions of the intestine which are not expanded, they are probably formed because the outer coats of the intestine have not grown as rapidly as the epithelium. The irregularities seen along the tops of the folds, which are of about the same size as the slight swellings in the expanded portions of the gut, are probably developing villi. The folds may later disappear by a general expansion of the epithelial tube, or by being absorbed by the rapidly growing villi. I find

no evidence that there is a mechanical cutting up of the folds into villi, such as has been described.

The villi of all parts of the intestine later become arranged in more or less regular longitudinal rows. Additional villi develop as separate growths by forming new rows, and also in between the villi of the older rows. In some places their development has gone on so rapidly that the villi of a single row are not entirely separate, and give the appearance of short, irregular longitudinal folds. This appearance is lost in the later stages.

In any single embryo, the larger villi, which are all approximately the same size, are always found to be more numerous than the smaller ones. This indicates that the growth of the younger villi is more rapid than that of the older ones. After they have attained the size of the older ones, however, they develop at a corresponding rate.

The growth of the villi in the duodenum and mid region of the small intestine is shown in Tables 3 and 4. The villi of the duodenum, having developed first, are the taller in the earlier stages. At 55 mm. the villi in the mid region have attained the height of those in the duodenum and from this stage on are larger. The bases of the villi remain approximately constant in size but show a slight initial increase and later a diminution in their diameters. The epithelium on the tops of the villi, which is at first stratified, then simple columnar, and finally simple cuboidal, is much reduced in thickness.

Intestinal Glands. According to Koelliker ('61 and '79) the intestinal glands (Lieberkühn's crypts) arise as hollow outgrowths of the epithelium which push their way into the mesoderm. Barth ('68) did not accept this view of the origin of the glands, but believed that they are formed by the spaces left in between the villi. Brand ('77) believed that an upward growth of the mesenchyma was the active factor in the development of the glands. Minot ('92) and Kollman ('98) agree with Koelliker. Voigt ('99) studied the development of the intestinal glands in the pig embryo, and likewise concluded that they originate as hollow outgrowths of the epithelium which are given off between

the bases of the villi and extend into the mesenchyma. This view was later accepted by Hilton ('02).

So far as can be observed from sections, the results of the present work are in accord with those of Voigt and Hilton. In a wax reconstruction of the intestinal epithelium at 37 mm. (not figured) no evidences could be seen of the glands from an external view of the epithelium. At 55 mm. (fig. 22) the exterior of the epithelium in the mid region of the small intestine shows small knoblike outgrowths. These I have considered to be the very first appearances of the intestinal glands. The cells of these knoblike processes are very granular, distinctly different from the clearer cells on the tops and sides of the villi. In amongst the granular cells can be seen a few scattered goblet or beaker cells. The protoplasm of the goblet cells is clear, their flattened or crescentic nuclei staining deeply. In the duodenum of this stage (55 mm.), the beginning glands are somewhat more pronounced. In embryos of 73 mm., 91 mm., and 120 mm., the glands gradually become more distinct and longer, and the goblet cells which line both the glands and the villi become more numerous. The intestinal glands at 134 mm. (mid region of the small intestine) are shown in fig. 23, and at 240 mm. (duodenum) in fig. 24. Throughout the older stages, the glands increase in length and in number. They are usually simple tubular in form, but some are branched. Measurements of the glands in different stages of development are given in Tables 3 and 4.

Duodenal Glands. Regarding duodenal (Brunner's) glands Koelliker states that their formation begins in the fourth month and that they are originally the Lieberkühn glands. Later they send branches into the submucosa, which, at the end of the sixth month, reach to the muscular layer. Barth found that in the rabbit the duodenal glands sprout off from the Lieberkühn glands as a double outgrowth. Brand ('77) observed Brunner's glands first in a human embryo of three and one half months.

In the duodenum of an embryo of 55 mm. no traces of the duodenal glands could be found, while at 78 mm. (Embryo 142)—three months—a few could be seen in the upper third of the duodenum. They arise from the bottoms of the intestinal glands,

as described by Barth, but may or may not be forked at their origins. They can be distinguished from the intestinal glands by the clearer protoplasm of their cells, by their branching, and by the greater distance that they extend into the mesenchyma. As the muscularis mucosae has not developed, there is as yet no line of division between the mucosa and the submucosa.

In the middle third of the duodenum at 91 mm., no duodenal glands are present. At 120 mm. they are present in the whole of the duodenum. They are more numerous in the upper third than lower down, and branching has gone on to a greater extent. In the upper third of the duodenum at 187 mm. the glands are much larger and the branches of each gland are arranged in groups. At the base, toward the muscularis, there is a slight condensation of the mesenchyma, which appears to have been caused by the downward growth of the gland. Only a few glands are found in the middle third of the duodenum at this stage (187 mm.). Fig. 24, from a wax reconstruction, shows the structure of the duodenal glands at 240 mm. The intestinal glands are the short tubular ones arising from around the bases of the villi; the duodenal glands are larger and more branched. The fewness of the primary sprouts in the area modelled is striking, there being only four for the entire number of branches shown, two of which are quite small. The branches of each gland are arranged in groups, lettered in the figure *A*, *B*, *C*, and *D*.

Folds. As stated before, irregular longitudinal folds of the mucous membrane are found in the ileum in stages ranging from 24 mm. to 55 mm. These folds, however, are only transient, and are in no way related to the folds found in the later stages and in the adult. They have practically disappeared at 55 mm.

Circular folds, which have been studied from longitudinal sections, are found in the small intestines of the older embryos. Whether these folds are formed by the contraction of the musculature, or whether they are the non-effacable plicae circulares (valvulae conniventes) could not be positively determined from cut sections, but from their regularity and constancy, I have considered that they are the latter structures. Their presence was first noted in the mid region of the small intestine at 73 mm., but

here they are rather indefinite and uncertain. In the upper third of the duodenum and in the uppermost part of the jejunum at 78 mm. no evidences of the circular folds could be found, but they are distinct in the mid region of the small intestine. They are quite regularly placed, averaging .78 mm. distant from each other. In height they vary from .17 mm. to .23 mm. At the extreme lower end of the ileum at this stage, no folds are present. None were found in the duodenum at 120 mm. (embryo 203). Slight folds are present in the lower end of the ileum at 134 mm. In a distended portion of the small intestine at 145 mm. (mid region), circular folds were found which measure .06 mm. in height, and at an average distance of 1.87 mm. apart. In the duodenum at 240 mm. two circular folds were found at distances of 4.7 mm. and 7.1 mm. below the pyloric orifice. In the mid region of the small intestine at this stage, folds were found which vary from .25 mm. to .51 mm. in height, and at a distance averaging 1.3 mm. apart.

TABLE 3
DUODENAL EPITHELIUM (UPPER THIRD)

EMBRYO	THICKNESS ¹ OF SURFACE EPITHELIUM		DIAMETER OF EPITHELIAL TUBE	VILLI		INTESTINAL GLANDS		DUODENAL GLANDS	
Length in mm.	In Cell Layers	In mm. ³	In mm.	Height ² in mm.	Diameter ³ (at bases) in mm.	Length ⁴ in mm.	Diameter ³ in mm.	Length ⁵ in mm.	Diameter ³ in mm.
7.5	2-3	.036	.077						
16.	*	*	.176						
19.	2-4	.043	.194	.088	.11				
22.8	1-2	.019	.299	.123	.12				
24	1	.024	.36	.193	.11				
30	?	?	.44	.211	.13				
37	1	.024	.53	.23	.13				
42	1	.021	.65	.25	.13				
55	1	.019	.95	.26	.12	.048	.06		
78	1	.016	1.03	.29	.11	.088	.04	.07	.033
120	1	.015	1.11	.31	.11	.09	.06	.12	.031
187	1	.015	2.7	.47	.09	.14	.05	.22	.031
240	1	.015	3.5	.35	.11	.12	.05	.35	.036

¹ On tops of villi when present.

² Tallest.

³ Average of a number of measurements.

⁴ Longest.

⁵ Vertical distance below bottoms of intestinal glands.

* Vacuolated stage.

TABLE 4

EPITHELIUM OF SMALL INTESTINE (MID REGION)

EMBRYO	THICKNESS ¹ OF SURFACE EPITHELIUM		DIAMETER OF EPITHELIAL TUBE	VILLI		INTESTINAL GLANDS	
Length in mm.	In Cell Layers	In mm. ³	In mm.	Height ² in mm.	Diameter ³ (at bases) in mm.	Length ⁴ in mm.	Diameter ³ in mm.
7.5	2-3	.024	.052				
16	2	.024	.101				
19	3-4	.052	.141				
22.8	3-5	.052	.158				
24	1	.024	.35	.12	.11		
30	?	?	.28	.18	.11		
37	1	.024	.39	.20	.14		
42	1	.021	.44	.18	.13		
55	1	.020	.75	.26	.13	.036	.06
73	1	.019	1.09	.35	.15	.048	.06
91	1	.024	1.28	.37	.14	.050	.06
120	1	.015	1.40	.56	.11	.060	.06
134	1	.015	2.0	.63	.11	.065	.06
187	1	.015	2.5	.70	.11	.088	.06
240	1	.012	3.2	.70	.07	.10	.04
Birth	1	.012	4.9	.70	.11	.12	.04

¹ On top of villi when present.² Tallest.³ Average of a number of measurements.⁴ Longest.

CONCLUSIONS

Esophagus

1. The oesophagus is at first a simple epithelial tube, the walls of which contain three or four rows of nuclei.

2. In embryos of about 20 mm., vacuoles form in the epithelium but the lumen remains pervious throughout. These vacuoles disappear by breaking into the lumen. This causes the epithelium to become thinner and the lumen to increase in size. The cause of the formation of vacuoles has not yet been determined.

3. Longitudinal folds of the mucosa are constant structures in the oesophagus. In the upper third of the oesophagus the folds are irregular and variable. In the middle and lower thirds there

are four large primary folds. Of these the dorsal and ventral (left and right respectively in the lower part of the œsophagus) develop first; the left and right (ventral and dorsal below) develop soon afterward. Smaller secondary folds, variable in number, appear later at the bases of the primary folds. In the lower part of the œsophagus both primary and secondary folds are twisted through an arc of about 90 degrees in the direction of the hands of a clock. It is probable that this twisting is due to the early rotation of the stomach.

4. Areas of ciliated cells are found in the epithelium of the œsophagus in embryos ranging from 55 mm. to birth. There is both an actual and a relative increase in the amount of surface covered by ciliated cells in embryos up to 187 mm. At birth these areas are relatively smaller. Ciliated cells are absent in the œsophagus of a child of 14 days (seven months premature birth).

5. Cardiac glands are found in both the upper and lower ends of the œsophagus. They begin as small areas of glandular cells, which were first seen in an embryo of 78 mm. Later these areas evaginate, forming small pockets and grooves. Later, a number of tubular glands grow out from these pockets.

6. Œsophageal glands were first observed in an embryo of 240 mm. They grow out from the epithelium through the muscularis mucosae and lie in the submucosa. In contradistinction to the cardiac glands, their glandular epithelium does not develop until after the excretory ducts are formed. At birth the end pieces of the glands have begun to branch.

Stomach

1. A few vacuoles, similar to those of the œsophagus, are found in corresponding stages in the stomach.

2. At 16 mm., the heretofore smooth epithelium shows a number of pit-like depressions, the first appearances of the gastric pits. These rapidly increase in number and many become elongated to form grooves.

3. At first the basal surface of the epithelium shows no irregularities due to the gastric pits. Then appear slight swellings into the mesenchyma. Still later depressions or furrows, alternating with the gastric pits, extend inward into the epithelium from the mesenchymal surface. This brings about a readjustment of the cells, and causes the heretofore 2 to 3 layered epithelium to become single layered.

4. The groove-like pits anastomose with one another to form a network. This network marks out irregular areas of the surface epithelium, which have been described as villi.

5. Growth of the mucous membrane is accompanied by an increase in the number of pits and by an increase in their size. The additional pits develop in between those already formed.

6. Glands, first seen at 120 mm., bud out from the bottoms of the pits. These rapidly increase in number and give off branches. Parietal cells are first distinct at 120 mm.

7. Large longitudinal folds of the mucous membrane occur in the stomach, but are variable in position, number, and size. Their occurrence is probably due to the contraction of the muscularis.

Small intestine

1. Vacuoles occur in the epithelium of the duodenum of embryos ranging from 10 mm. to 24 mm. In embryos of 16 mm. and 22.8 mm. the vacuoles were found to lead to a complete occlusion of the duodenal lumen. In an embryo of 19 mm. some of the vacuoles were found to be arranged so as to form small "duodenal pockets." These resemble the intestinal pockets of the jejunum and the ileum. It is probable that these duodenal pockets are transition forms between the vacuoles of the upper part of the digestive tube and the intestinal pockets of the lower part. In the duodenum at 134 mm. several small epithelial cysts were found. It is possible that these are vacuoles or duodenal pockets which have persisted.

2. In the jejunum and ileum intestinal pockets, similar to those described by Keibel, Lewis and Thyng, and Elze, were found.

Most of these disappear by becoming incorporated in the walls of the developing villi, but some may persist. A large persistent diverticulum was found in an embryo of 134 mm.

3. The vacuoles of the oesophagus, stomach and duodenum, and the pockets of the duodenum, jejunum, and the ileum are related structures. They are all the result of a similar process of growth, which for some undetermined reason, manifests itself differently in different parts of the digestive tube.

5. In the upper part of the duodenum, in the jejunum, and in the upper part of the ileum, the villi originate singly as thickenings of the epithelium which are not preceded by longitudinal folds. These thickened plates of epithelium are invaginated, and later reduced to a single layer of cells.

5. In the remainder of the duodenum (approximately the lower two-thirds) the villi are developing while vacuoles are present, but are not recognizable because of the "solid" condition of the duodenum. The apices of the villi of one wall are adherent to those of the opposite wall. The spaces in between the adjacent fused villi are the vacuoles. By a separation of the apices, the individual villi appear, and the vacuoles become confluent with one another to form a continuous lumen.

6. In the lower part of the ileum low longitudinal folds occur. These folds, varying from two to five in number, are irregular in height and position. Their presence is probably due to the fact that the outer coats of the gut do not grow as rapidly as the epithelium. The irregularities along the tops of the folds are developing villi. Later the folds disappear by an expansion of the epithelial tube or by being absorbed by the rapidly growing villi.

7. As the villi develop they become arranged in longitudinal rows of varying regularity.

8. Additional villi develop as separate growths, either forming new rows between those already present, or arising in the older rows.

9. The growth of the younger villi, up to the size of the largest, is more rapid than that of the older ones.

10. Intestinal glands develop as separate hollow outgrowths of the epithelium. They were first seen in an embryo of 55 mm.

11. Duodenal glands originate as outgrowths from the intestinal glands. They branch repeatedly and the branches of each become arranged in groups. They were first observed in an embryo of 78 mm.

12. Circular folds of the mucous membrane make their appearance in the mid region of the small intestine at 73–78 mm. They become more numerous, more regularly placed, and taller in the older stages.

BIBLIOGRAPHY

- BAGINSKY. Untersuchungen über den Darmkanal des menschlichen Kindes.
1882 *Arch. für path. Anat.*, Bd. 89, p. 64-94.
- BARTH. Beiträge zur Entwicklung der Darmwand. *Sitzungsber. d. Wien. Akad. d. Wiss.*, Bd. 58, p. 128-136.
- BERRY. On the development of villi in the human intestine. *Anat. Anz.*, Bd. 1900 17, p. 242-249.
- BRAND. Beiträge zur Entwicklung der Magen- und Darmwand. *Verh. der phys. med. Gessellsch. zu Würz.*, Bd. 9, p. 243-256.
- ELZE. Beitrag zur Histologie des embryonalen Säugetierdarmes. *Inaug. Diss.* 1909 Freiburg.
- FISCHL. Beiträge zur normalen und pathologischen Histologie des Säuglingsmagens. *Zeit. für Heilkunde*, Bd. 12, p. 395-446.
- FLINT. Organogenesis of the œsophagus. *Anat. Anz.*, Bd. 30, p. 442-451.
1907
- FORSSNER. Die angeborenen Darm und Oesophagusatresien. *Anat. Hefte*, 1907 Abt. 1, Bd. 34, p. 1-163.
- GOETSCH. Structure of the mammalian œsophagus. *Am. Jour. Anat.*, 10, p. 1-40.
1910
- HILTON. The morphology and development of intestinal folds and villi in vertebrates. *Am. Jour. Anat.*, 1, p. 459-504.
- JAHARMAERKER. Ueber die Entwicklung des Speiseröhrenepithels beim Menschen. 1906 *Inaug. Diss.*, Marburg.
- KEIBEL. Zur Embryologie des Menschen, der Affen, und der Halbaffen. *Verh. d. anat. Gesellsch.*, p. 39-50.
1905
- KOELLIKER. Entwicklungsgeschichte des Menschen und der höheren Thiere. 1861 Leipzig.
1879 *Ibid.* Aufl. 2.
- KOLLMANN. Lehrbuch der Entwicklungsgeschichte des Menschen. Jena. 1898
- KREUTER. Die angeborenen Verschlüssungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte. *Deutsche Zeitschr. f. Chir.*, Bd. 79, p. 1-89.
1905
- LASKOWSKY. Ueber die Entwicklung der Magenwand. *Sitz. d. Wien. Akad. d. Wiss.*, Bd. 58, p. 137-143.
1868
- LEWIS AND THYNG. The regular occurrence of intestinal diverticula in embryos of the pig, rabbit, and man. *Amer. Jour. Anat.*, 7, p. 505-519.
1908

- MINOT. Text-book of human embryology. New York.
1892
1900 On the solid stage of the large intestine in the chick. *Jour. of the Boston Soc. Med. Sci.*, 4, p. 153-164.
- NEUMANN. Flimmerepithel im Oesophagus menschlicher Embryonen. *Arch. f. mikr. Anat.*, Bd. 12, 570-574.
1876
- SCHAFER. Die oberen cardialen Oesophagusdrüsen und ihre Entstehung. *Arch. f. path. Anat.*, Bd. 177, p. 181-205.
1904
- SCHENK. Lehrbuch der vergleichenden Embryologie der Wirbelthiere. Wien.
1874 p. 1-198
- SCHRIDDE. Ueber Magenschleimhautinseln im obersten Oesophagusabschnitte.
1904. *Arch. f. path. Anat.*, Bd. 175, p. 1-16.
1905 Weiteres zur Histologie der Magenschleimhautinseln in obersten Oesophagusabschnitte. *Ibid.*, Bd. 179, 562-566.
- SCHRIDDE. Die Entwicklungsgeschichte des menschlichen Speiseröhrenepithels und ihre Bedeutung für die Metaplasielehre. Wiesbaden. 101 pp.
1907
1908 Ueber die Epithelproliferation in der embryonalen menschlichen Speiseröhre. *Arch. f. path. Anat.*, Bd. 191, p. 128-192.
- SCHULTZE. Grundriss der Entwicklungsgeschichte des Menschen und der Säugethiere. Leipzig.
1899
- SEWALL. The development and regeneration of the gastric glandular epithelium during foetal life and after birth. *Journ. of Physiol.*, 1, p. 321-334.
1879
- TANDLER. Zur Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien. *Morph. Jahrb.*, Bd. 29, p. 187-216.
1900
- TOLDT. Die Entwicklung und Ausbildung der Drüsen des Magens. *Sitz. Ber. Wien. Akad. Wiss.*, 82 Abth. 3. p. 57-128.
1881
- VOIGT. Beitrag zur Entwicklung der Darmschleimhaut. *Anat. Hefte*, Abth. 1, Bd. 12, p. 49-70.
1899

PLATE I

EXPLANATION OF FIGURES

1. Wax reconstruction of epithelium of œsophagus, showing vacuoles. *a*, human embryo of 19 mm., series 819. *b*, embryo of 22.8 mm., series 871. $\times 89$.
- 2 Wax reconstruction of epithelium of œsophagus (region immediately below bifurcation of trachea). Human embryo of 37 mm., series 820. Showing single dorsal fold. $\times 89$.
3. Same, human embryo of 42 mm., series 838. Showing dorsal and ventral folds and beginnings of lateral folds. $\times 89$.
4. Same, human embryo of 55 mm., embryo 249. Showing Greek cross stage. $\times 89$.
5. Same, human embryo of 120 mm., embryo 342. Showing four primary and four secondary folds. Maltese cross stage. $\times 89$.

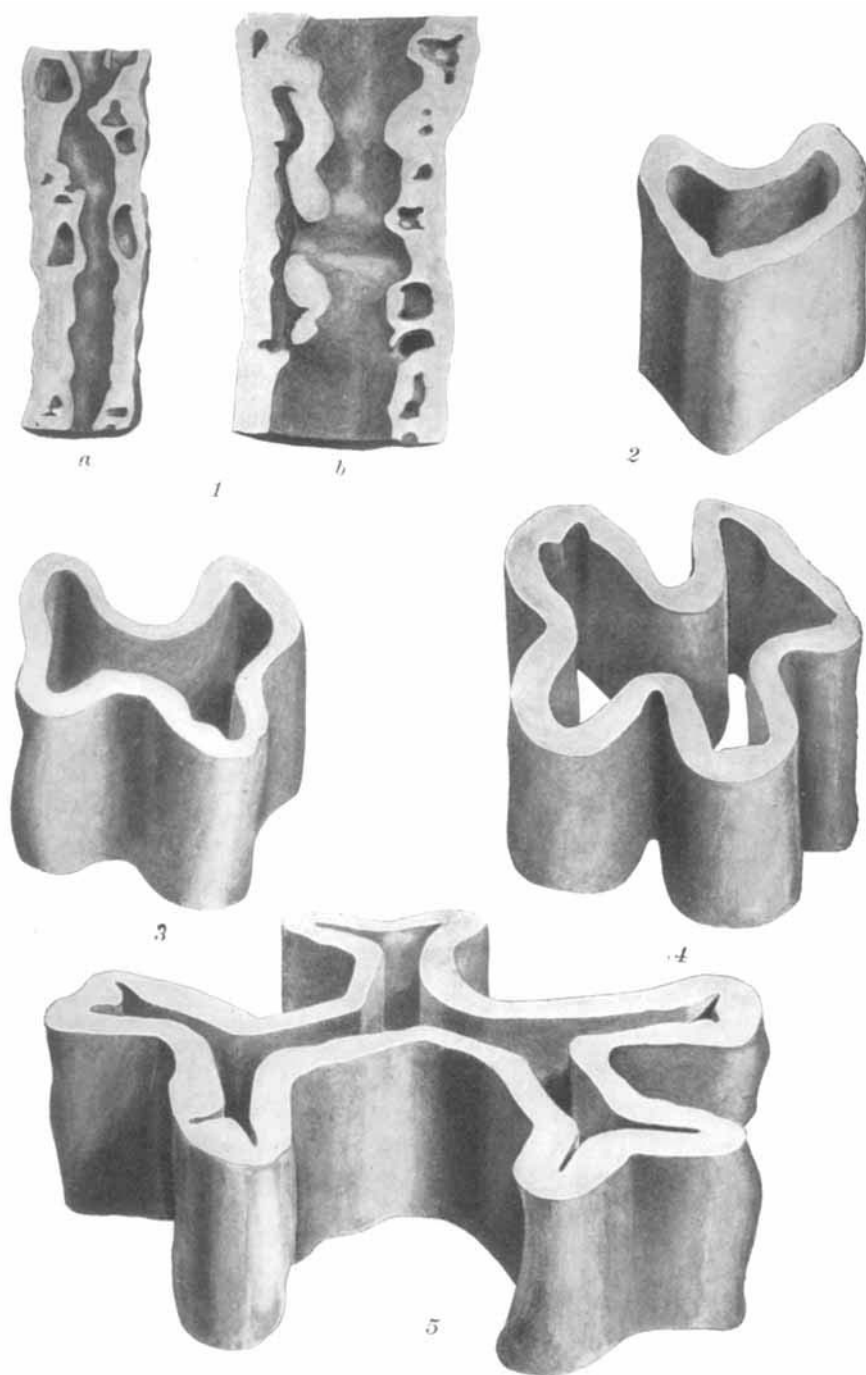


PLATE II

EXPLANATION OF FIGURES

6. Wax reconstruction of epithelium of œsophagus at level of bifurcation of trachea. Human embryo of 55 mm., embryo 249. Stippled areas represent those covered with ciliated cells; non-stippled areas, those covered with squamous cells. $\times 89$.

7. Same, human embryo of 91 mm., embryo 224. $\times 89$.

8. Wax reconstruction of a cardiac gland from lower end of œsophagus. Human embryo of 240 mm., embryo 186. Ruled surfaces represent those covered with glandular cells; non-ruled, those covered with squamous cells. $\times 89$.

9. Wax reconstruction of single fold of epithelium of the œsophagus, viewed from the exterior. Human at birth, embryo 341. Showing œsophageal glands. $\times 89$.



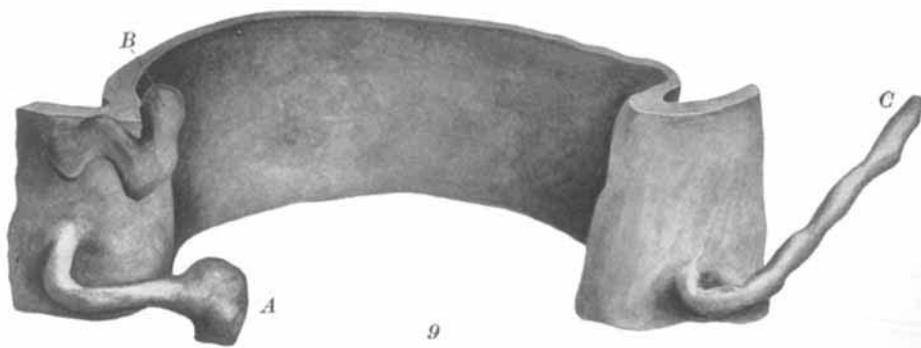
6



7



8

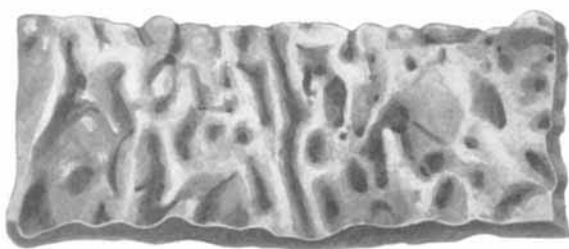


9

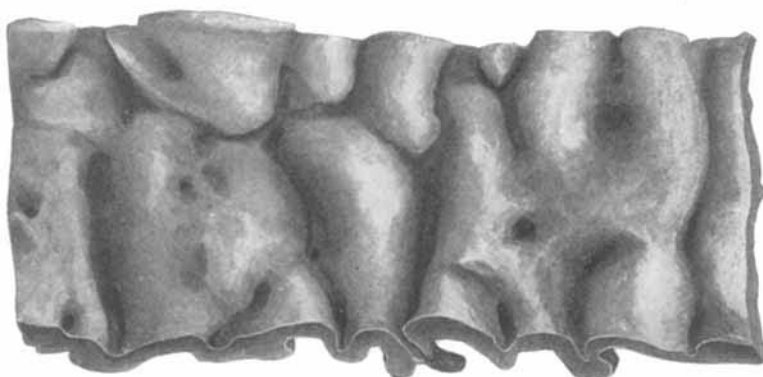
PLATE III

EXPLANATION OF FIGURES

10. Wax reconstruction of epithelium of fundus of stomach. Human embryo of 55 mm., embryo 249. View of internal surface. $\times 119$.
11. Same, human embryo of 120 mm., embryo 342. $\times 119$.
12. View of external surface of same model as shown in fig. 11. Showing gland formation. $\times 119$.



10



11



12

PLATE IV

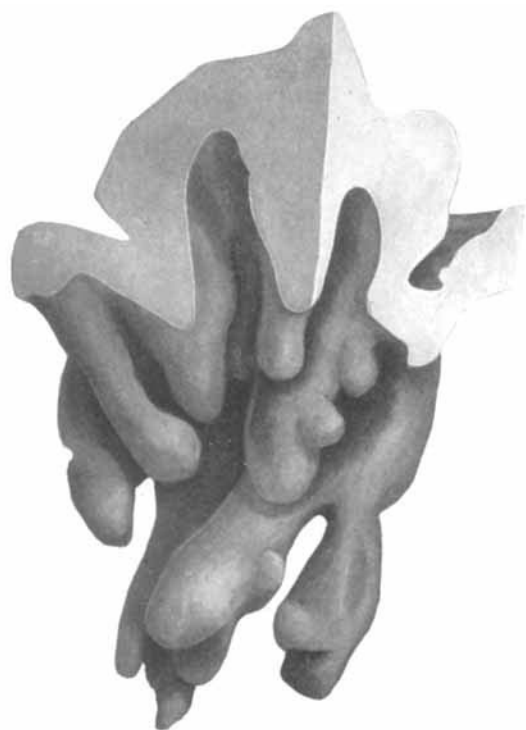
EXPLANATION OF FIGURES

13. Wax reconstruction of gastric glands of stomach. Human embryo of 240 mm., embryo 186. $\times 267$.

14. Same at birth, embryo 341. $\times 267$.

15. Wax reconstruction of epithelium of upper part of duodenum. Human embryo of 22.8 mm., series 871. Showing beginning villi and duct of the dorsal pancreas. $\times 89$.

16. Wax reconstruction of epithelium of lower part of duodenum. Human embryo of 22.8 mm., series 871. Showing vacuoles and occlusion of lumen. $\times 89$.



13



14



15



16

PLATE V

EXPLANATION OF FIGURES

17. *a, b, and c.* Wax reconstructions of intestinal pockets. Human embryo of 22.8 mm., series 871. $\times 89$.

18. Wax reconstruction of epithelium of jejunum (first loop in umbilical cord). Human embryo of 22.8 mm., series 871. Showing developing villi. *a*, external view; *b*, internal view. $\times 89$.

19. Wax reconstruction of epithelium of small intestine (mid-region). Human embryo of 24 mm., series 24. $\times 89$.

20. Wax reconstruction of epithelium of ileum. Human embryo of 30 mm., series 913. Showing low longitudinal folds. $\times 89$.

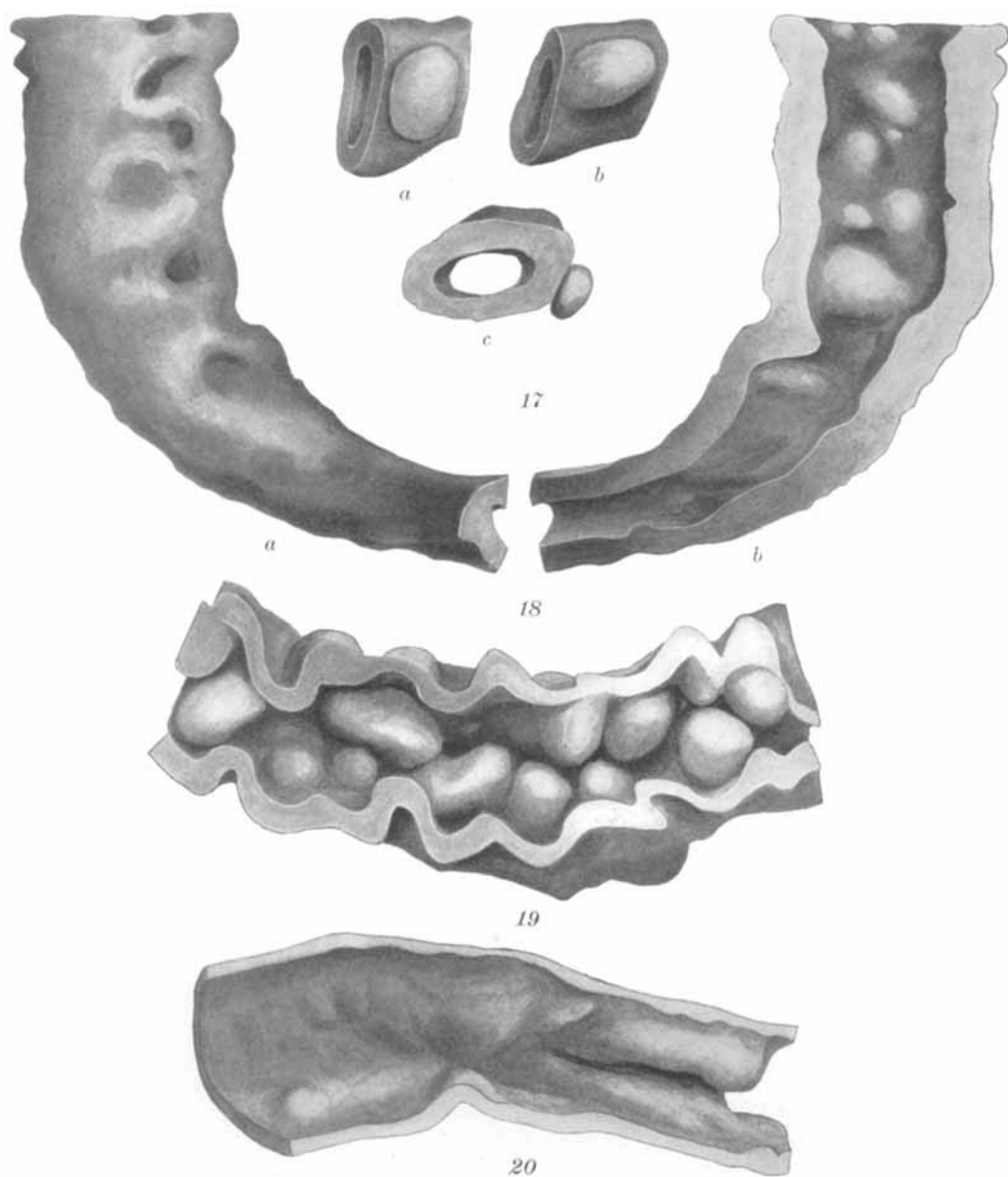


PLATE VI

EXPLANATION OF FIGURES

21. Wax reconstruction of epithelium of small intestine (mid-region). Human embryo of 55 mm., embryo 249. Viewed from interior. $\times 89$.

22. Same, viewed from exterior. $\times 89$.

23. Wax reconstruction of small intestine (mid-region). Human embryo of 134 mm., embryo 30. Showing villi, intestinal glands, and persistent intestinal pocket. $\times 89$.

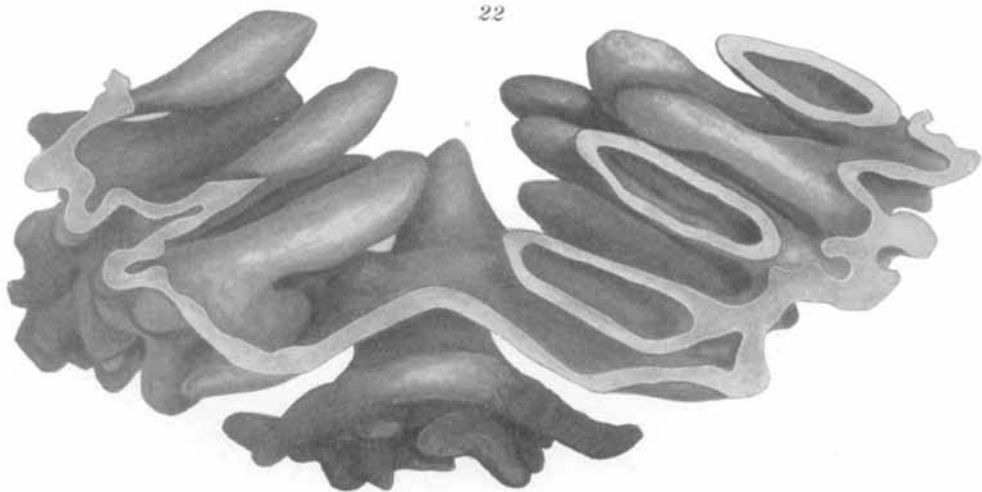
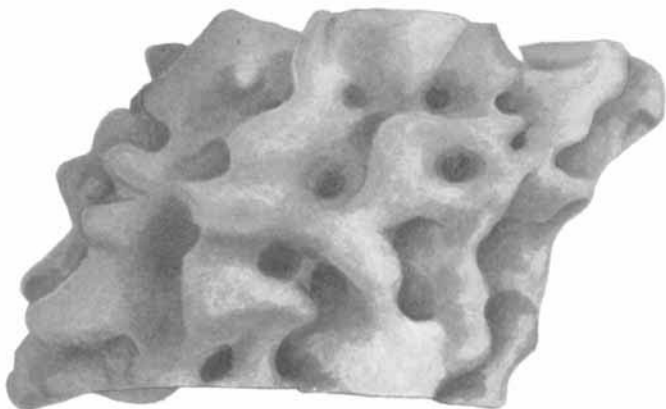


PLATE VII

EXPLANATION OF FIGURES

24. Wax reconstruction of epithelium of duodenum (upper third). Human embryo of 240 mm., embryo 186. Showing villi, intestinal and duodenal glands. $\times 178$.

