Observations on the Developmental Cytology of the Fundic Region of the Rabbit's Stomach, with Particular Reference to the Peptic Cells

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With two plates (figs. 3 and 4)

SUMMARY

1. The first oxyntic cells, differentiating from a non-mucoid cell, appear on the 23rd day of the foetal life of the rabbit.
2. Bowie-positive granules appear in most epithelial cells during foetal life, reach a maximum on the 27th day, and then almost disappear before birth.
3. The first peptic cells containing Bowie-positive granules appear a few hours after birth. They increase after the end of the first week until the adult condition is reached.
4. During the first 4 weeks of postnatal life the pepsinogen granules contain a mucinogen component. This is lost between the fourth and sixth weeks. The loss starts in cells at the base of the glands and proceeds up the tubules towards the crypts.
5. Pepsinogen granules containing a mucinogen component are strongly eosinophil.
6. The first 'mature' peptic granules, that is ones that are Bowie-positive, PAS-negative and non-eosinophil, appear at the fourth week of postnatal life.
7. Mucous neck-cells (of Bensley) begin to appear at the end of the sixth week of postnatal life. Their development is being further investigated.

INTRODUCTION

WHEN, in 1932, Plenk wrote his authoritative work on the human stomach, there was no general agreement as to the origin of the principal cell-types in the gastric mucosa. Since that date several papers have appeared dealing with various aspects of the histogenesis of the mucosal cells, but the problem is no nearer being settled. In view of the confusion, the chief purpose of the present investigation has been to elucidate the origin of the main cell-types by using more specific stains and histochemical methods than have been used by earlier writers.

Concerning the embryology of the gastric glands, Kirk (1910), using Bensley's three-colour stain, neutral gentian, and Mayer's muchematein on sections of pig embryos, showed that the oxyntic cells appear at a very early stage (3 cm; birth being at 29 cm), and that they arise from an undifferentiated epithelium 'before any trace of mucus appears'. He states also that although they continue to arise from undifferentiated cells for some time they also 'almost immediately' reproduce themselves by mitotic division. He states that peptic cells develop at 20 cm; they also arise from non-mucous cells and that they show frequent mitoses in the foetus. He writes that he finds no genetic

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relation between oxyntic cells, and peptic or mucous cells. Lim (1922), who examined new-born and foetal cats, stillborn children, and one four-month human foetus, using Mallory's stain, gives the following results. The foetal cats show an epithelium 'entirely devoid of mucus', and at birth glands are present lined by oxyntic and mucoid cells. A week later the glands are larger, oxyntic cells more prominent, mucoid cells present in large numbers, and 'a few developing peptic(?) cells are visible'. These show no mucoid reaction. The human foetus shows mucoid cells and non-mucoid cells, and oxyntic cells are absent. At birth (i.e. the next stage he examines), peptic and oxyntic cells are fully developed. From these results he draws the following unjustifiable conclusion: 'It is quite clear that the gastric glands are in the first instance formed of non-mucoid cells. Later these cells become mucoid in character *throughout the whole stomach.*' The next type to differentiate is the oxyntic, and at a later stage still comes the peptic. Zimmerman (1925), using a $5\frac{1}{2}$-month human foetus and staining his sections with mucicarmine, could find only mucoid and oxyntic cells. As he states that oxyntic cells arise from an undifferentiated epithelium, one must suppose that the peptic cells develop out of the mucoid cell. Plenk (1931) says that peptic cells are present in the child born at full term, and that they definitely develop from an indifferent cell and not from a mucoid cell. Plenk (1932) in his review reaffirms this statement and says emphatically that he agrees with Kirk (1910) that both peptic and oxyntic cells arise from undifferentiated cells. He accepts the results of Lim (1922) quoted above, but does not agree with his conclusions. With regard to Zimmerman (1925) who found only oxyntic and mucous cells in one $5\frac{1}{2}$-month human foetus, Plenk appears not to accept the statement, for, as he says, he can himself see undifferentiated cells in both 5- and 7-month human foetuses.

It is unfortunate that in the most recent paper that I have been able to find on the embryology of the gastric mucosa (Kammeraad, 1942), no positive statement is made as to the precursors of oxyntic and peptic cells. Using embryonic and new-born rats he says that the cells lining the pits and the surface epithelium stain with mucicarmine at birth, but he makes no comment on the cells lining the 'evaginations from the bottoms of the pits' (i.e. the primitive glands), except to state that they are present at this time. He states that oxyntic and peptic cells are both present (presumably in these glands) 24 h later. He writes that only a few zymogen granules are present in these early peptic cells and that these granules are not present in significant numbers until 15 days after birth.

Of the above writers one says that oxyntic cells develop from mucoid cells, whilst three say they arise from non-mucoid cells. Two say the peptic cells develop from mucous cells, and two state they arise from undifferentiated cells, and one writer produced no evidence to support his views (Lim, 1922).

The presence of hydrochloric acid and of rennin (Dudin, 1904) and of pepsin (Keene and Hewer, 1929) may be demonstrated in the fourth and fifth months in the stomach of the human foetus and 'consistently thereafter'. Werner (1948), studying staining reactions and peptic activity of extracts from the stomach walls, suggests that infants born prematurely may produce considerably less pepsin than those born at full term. Hammarsten (1874) found pepsin in the rabbit only after the end of the first week of postnatal life. Recently Hirschowitz (1957), quoting various writers, states that peptic activity is present in sheep and bovine embryos and in the rat at birth, and that it is not present until one to two weeks after birth in the dog, cat, pig, and rabbit.

Materials and Methods

The period of gestation in those rabbits used in the investigation, that came to term, was 30 days $\pm$ 12 h.

Twenty-six foetuses were used. Groups (of never less than 3) were examined at two-day intervals from the 19th to the 29th day (inclusive) of gestation. Thirty new-born rabbits were used. These were killed in groups of three at the end of 1 day, $3\frac{1}{2}$ days, and 1, 3, 4, $4\frac{1}{2}$, 5, $5\frac{1}{2}$, and 6 weeks after birth (six being killed at the latter date). The stomachs from four adult rabbits were also examined.

Histochemical and cytological techniques

Except with some of the foetuses, where the whole of the mucous membrane was examined, small pieces of the mucous membrane from the greater curvature of the stomach, directly opposite the entrance of the oesophagus, were pinned out on cork and subjected to the following procedures:

A. For aldehyde groupings: The periodic acid/Schiff test, (1) alone, (2) after incubation in 0·25% diastase, (3) after digestion with trypsin, (4) after digestion with pepsin, (5) after fat extraction with a boiling mixture of methanol and chloroform.

B. For glycogen: Bauer's test, (1) alone, (2) after incubation with diastase.

C. For pepsinogen granules: Bowie's method (1936), (1) alone, (2) after fat extraction as above.

D. For lipids: (1) Sudan black (for paraffin sections, Thomas, 1948), (*a*) alone, (*b*) after digestion with trypsin. (2) For phospholipids, a modification of Baker's acid haematein test for use with paraffin sections (Rennels, 1951, 1953).

E. By various routine methods and by Altmann's acid fuchsin, a method which demonstrates early oxyntic cells almost as distinctly as Sudan black.

F. By phase-contrast microscopy on formaldehyde-fixed frozen sections in media of various refractive indices from 1·33 to 1·656. This method was also repeated after 2 hours' digestion in 0·1% trypsin or pepsin.

Examination by the phase-contrast microscope and methods involving digestion with trypsin or pepsin were carried out only on the 27-day foetus. Methods involving fat extraction were applied only to the 27-day foetus and to the animals killed 3 weeks after birth; with these exceptions all the above techniques were used on all specimens.

Although Bowie's method (1936) referred to above stains nothing but pepsinogen granules in the adult gastric mucosa, it also stains the pancreatic zymogen granules, and therefore no histochemical specificity can be claimed for it.

Results

The adult fundic mucosa

The surface epithelium of the stomach dips down into crypts (fig. 1). The gastric tubes are arranged perpendicularly to the surface of the mucosa and penetrate its whole thickness. They are simple branched tubules which open either singly or in groups of two or three, through a constriction into the bottom of the crypts. The blind ends are slightly thickened and coiled, and sometimes divide into two or more branches. In textbooks the tubules are frequently described in three sections. These are the neck, the body, and the base (fig. 1), which almost reaches the muscularis mucosae.

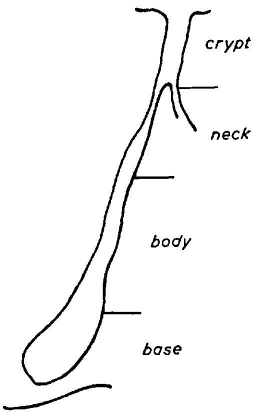

FIG. 1. A diagram of a gastric gland from the stomach lumen (above), down to the base near the muscularis mucosae.

The surface epithelium. This is a simple columnar epithelium. It is very regular and contains no goblet cells such as were described in the pig by Kirk. The cells on the surface of the stomach are frequently somewhat taller than those in the bottom of the crypts. The nucleus is ovoid and placed towards the basement membrane. Numerous granules, giving a PAS-positive reaction, fill the supranuclear part of the cells. In many cases in cells further down the crypts the granules are more nearly confined to the luminal region of the cytoplasm at the free border of the cells, but in other cases there is no difference between surface and crypt epithelial cells. There is no Bowie-positive material in any of these cells.

The oxyntic cells. These cells are easily recognizable, even in unstained sections, by their large size and their spherical or triangular shape. They have a readily visible cell border and possess an ovoid, centrally placed nucleus. They have a granular cytoplasm and intracellular canals are occasionally visible even when special techniques are not employed. Oxyntic cells are plentiful in the bodies and bases of the glands, but are more numerous in the neck region. I have seen them in the crypts and between cells on the surface epithelium, but in the adult this is a rare curiosity.

The peptic cells. With Bowie's method these are at once recognizable by the deep blue colouring of the pepsinogen granules that they contain. The cells occupy the bodies and the bases of the glands, becoming more numerous as they approach the base.

The mucous neck-cells (of Bensley). These cells very rarely lie adjacent to another but are placed between the oxyntic cells in the neck region of the glands, and frequently extend down as far as the uppermost peptic cells. I have never seen them in the bodies or bases of the glands in the rabbit. Except where two lie next to each other, when they are roughly cuboidal in shape, they are the most irregularly shaped cells in the mucosa. This is probably due to their being slotted between adjacent oxyntic cells. Although their shape is irregular, it is certain that part of the cells touches the basement membrane (as does part of the oxyntic cells). They have flattened nuclei occupying the bases of the cells, and their cytoplasm is filled with numerous fine PAS-positive granules.

The fundic mucosa in the foetus

The 19-day foetus (3 specimens). A tall columnar epithelium lines the fundic area of the stomach. The surface undulates slightly, and here and there forms pit-like evaginations towards the underlying mesenchyme. None of the adult cell-types already mentioned can be seen. There is no PAS-positive material present. (This is in contrast to the large amount already present in the form of granules and ring-like structures in the cells of the pyloric region.)

The 21-day foetus (3 specimens). More pits are present in the mucosa, although there is, as yet, no sign of tubules. The PAS test shows a few granules and rings in the supranuclear region of a few cells. A few primitive blood-cells colour with Bowie's method, otherwise the method is negative.

The 23- and 25-day foetuses (8 specimens). PAS-positive material in the form of granules and sometimes rings is present in the supranuclear region of many cells, both surface cells and those lining the pits. Bowie's method shows a thin line of granules close to the free border of the cells, in similar situations.

Occasional oxyntic cells are seen in some of the embryos, usually situated at the bottom of the pits, but never situated near cells containing PAS-positive material. So far as the above results are concerned, it is impossible to distinguish between the 23rd and 25th day.

The 27-day foetus (6 specimens). More pits are present in the epithelium than at earlier stages. Very occasionally a constriction appears in a pit towards its base, the lumen being narrower below this point. This is probably the first sign of the future crypts and tubules of the adult.

Oxyntic cells are much more numerous, two or three sometimes lying alongside each other. They are somewhat more frequent at the bases of the pits than they are along their sides.

All the cells of the epithelium, other than oxyntic cells, contain granules which are PAS-positive (figs. 2, A; 3, A). These granules are more abundant in the cells lining the stomach lumen than they are in the cells lining the pits. They are present in large quantities at the free borders of the cells. An area clear of granules is left immediately above the nucleus. Other granules, less numerous, occupy a position alongside the nucleus. It is doubtful if any PAS-positive material occurs below the nucleus. Where it seems to do so it appears to be in an underlying cell or in a cell cut obliquely. After digestion with trypsin or pepsin and after fat extraction, both supra- and paranuclear groups of granules are still PAS-positive.

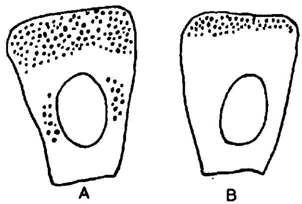

FIG. 2. A diagram of two epithelial cells.
A, PAS. B, Bowie's method.

All cells, except oxyntic cells, after Bowie's method contain some bright blue granules (figs. 2, B; 3, B). As with the PAS technique, the granules are more numerous in the cells lining the stomach lumen than in those lining the pits. The granules again occupy a supranuclear position at the free borders of the cells, being less numerous than the corresponding PAS-positive granules. No blue granules, however, are ever seen in a paranuclear position (compare figs. 2, A, B), either before or after fat extraction.

A few supranuclear and many paranuclear sudanophil granules are present in the cells that have just been described. The granules are spherical except alongside the nucleus, where many appear elongated.

Both the supranuclear and paranuclear granules (described as PAS-positive) can be seen by phase-contrast microscopy. There is no difference in clarity between the two groups of granules, both being clearest in a medium of refractive index 1·43. In media with refractive indices above 1·481 none can be seen. Both groups are also visible after digestion with trypsin and pepsin and after fat extraction.

The 29-day foetus (6 specimens). PAS-positive granules are visible in all cells, except the oxyntic, as at the 27-day stage, but most of the cells show an increase in quantity in the supranuclear position. In many cells at the base of the tubules the PAS-positive material appears foamy, a condition seen only in the adult in the mucous neck-cells after formaldehyde fixation.

Bowie-positive granules are far less numerous than in the 27-day embryo, the great majority of the cells showing none at all. Here and there, a group of a few cells either on the stomach lumen or deep in the pits and tubules show some in a supranuclear position. Some of these cells show only a single line of granules at their free borders.

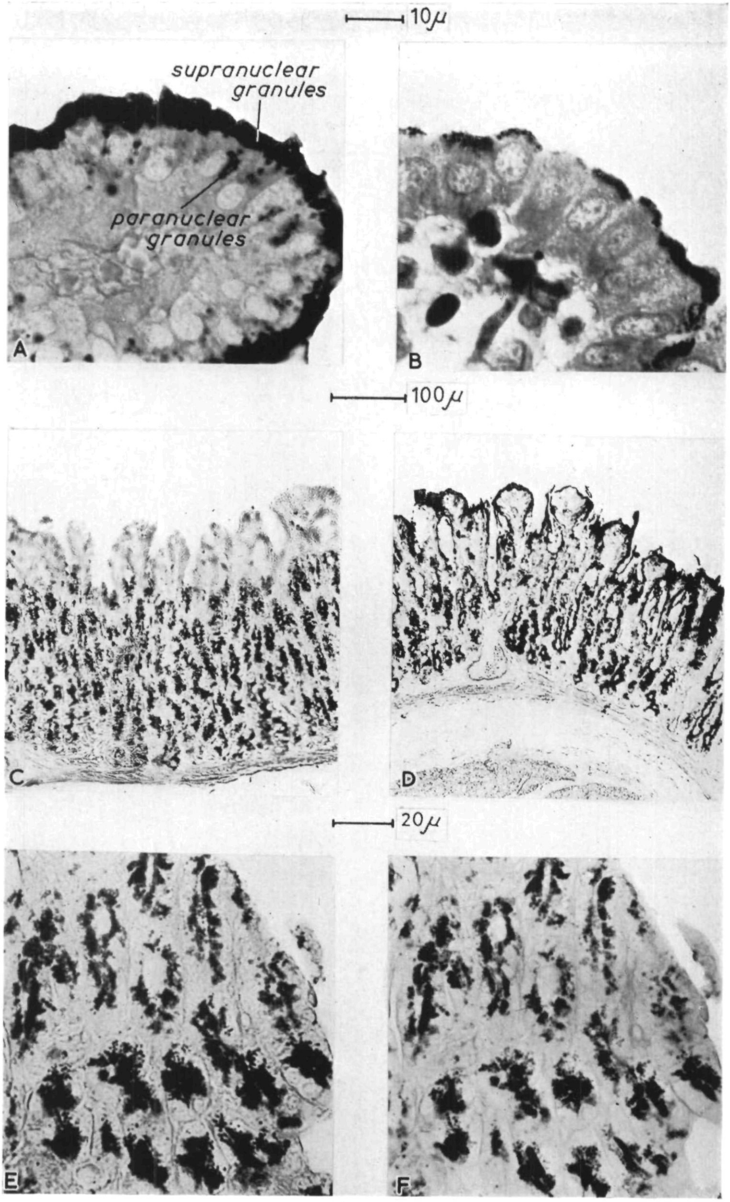

FIG. 3

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The fundic mucosa in the new-born rabbit

One day old (3 animals). All the cells except the oxyntic show much PAS-positive material in the form of granules and ring-like structures. In addition to the supranuclear and paranuclear groups that were present as in the embryo, some granules and many rings are situated in the basal part of the cells below the nucleus. The rings are frequently quite large, presenting a similar picture in this respect to the cells in the pyloric glands in the 19-day foetus.

None of the cells along the stomach lumen or in the upper third of the pits show any granules that colour with Bowie's method. But, in the lower two-thirds of some of the pits and tubules, and especially in the basal portions, some cells contain greyish-blue granules after Bowie's method. These cells are not numerous but occur here and there in all sections from all animals. Cells that contain these blue granules can also be shown to contain PAS-positive granules.

Three-and-a-half and seven days old (6 animals). There are more oxyntic cells than previously and an occasional intracellular canal can be seen in some of them. The oxyntic cells are as numerous along the bodies of the tubules as at their bases. Only one was seen on the surface of the stomach.

PAS-positive granules are seen in all cells except oxyntic.

The Bowie method shows greyish-blue granules in a few cells. Again these cells are situated in the deeper half of the tubules and are few in number, it being doubtful if there are many more present than in the 1-day-old rabbits. Not only do these cells contain Bowie-positive granules and PAS-positive granules, but it can be shown to be the same granules that colour with both techniques. This fact was established by colouring with Bowie's method, choosing cells, decolorizing, and examining them again after they had been subjected to the PAS technique.

Three weeks old (3 animals). Many more oxyntic cells are present. Bowie's method (fig. 3, C) shows many cells containing greyish-blue granules. These cells are in many sections mainly in the bases and bodies of the tubules, but other sections show them frequently extending into the neck of the tubules (fig. 3, C), right up to the base of the crypt.

The PAS technique (fig. 3, D) shows positive granules in probably all cells

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FIG. 3 (plate). A, 27-day foetus. PAS. Shows supranuclear and paranuclear groups of granules.

B, same as A. Bowie's stain. Shows supranuclear granules. (Note that immature red blood-cells also colour.)

C, 3-weeks-old animal. Bowie's stain. Shows granules in peptic cells lining the gastric tubules from the bases of the glands up to the crypts.

D, 3-weeks-old animal. PAS. The granules in the peptic cells, the surface epithelium, and the epithelium of the crypts are coloured.

E, 3-weeks-old animal. Bowie's stain. For comparison with F.

F, 3-weeks-old animal. PAS. This is the *same* section as E, with Bowie stain removed by alcohol before the PAS method was applied. The photomicrograph shows that the granules that colour with Bowie's method are the same as those colouring after PAS.

of the mucous membrane, except the oxyntic cells. Again the granules that colour blue by Bowie's method are PAS-positive (figs. 3, E, F). Further, it was observed that these same granules are very strongly eosinophil. They are not sudanophil, nor do they show the presence of phospholipid.

These granules do not colour by Bauer's method and they remain PAS-positive both after incubation in diastase and after immersion in boiling methanol and chloroform.

Four weeks old (3 animals). Apart from a marked increase in the number of cells present in the 4-weeks-old animals, similar results are obtained, except that there are small groups of cells in the basal regions of adjacent tubules that contain no PAS-positive material (fig. 4, A, arrow). Some of these are oxyntic cells, and the rest can easily be shown to contain Bowie-positive granules. This is the first appearance of a cell which contains Bowie-positive granules that are not at the same time PAS-positive. Further, the granules which are PAS-positive are a greyish blue after Bowie's method, whereas those which are PAS-negative are a bright blue after Bowie's method. Moreover, the former granules which are both PAS-positive and Bowie-positive, colour intensely with eosin, whereas the latter granules which are PAS-negative but Bowie-positive are not eosinophil.

From 4½ to 5½ weeks old (9 animals). The groups of PAS-negative cells in the basal region described above become progressively larger and more frequent until in some of the 5½-weeks-old animals there are almost no PAS-positive granules in the lower one-half to two-thirds of the tubules (fig. 4, B). At this stage the granules which remain PAS-positive in the upper half or one-third of the tubules colour a greyish blue with Bowie's method, whereas granules in peptic cells in the lower one-half to two-thirds of the tubule colour a bright blue after this method.

There is some variation in the nine animals described, but generally speaking an animal in one *age group* shows similar results to one of equal *size* and *weight* in another age group. Also, in some individual sections where peptic granules are PAS-negative in the lower half of the tubules, here and there in small groups there are tubules whose 'peptic' cells from crypt to base show PAS-positive granules.

Six weeks old (6 animals). The cell-types and their distribution are almost

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FIG. 4 (plate). A, 4-weeks-old animal. PAS. Shows many PAS-positive peptic granules in cells lining the tubules, and an area (arrow) in the base where there are no PAS-positive granules. This area, however, was filled with Bowie-positive granules (see text).

B, 5½-weeks-old animal. PAS. Shows that at this stage (compare A) the mucinogen component of the peptic granule (PAS-positive) is lost in many cells in the lower half of the gastric glands.

C, an animal from the 6-weeks-old group. PAS. Shows that the vast majority of cells containing PAS-positive granules are now in the surface epithelium, in the epithelium of the crypts, and in a layer of cells in the neck region.

D, the same animal as C. Bowie's stain. Shows not only that Bowie-positive granules are present in peptic cells along the whole length of the tubules, but also that the cells that are PAS-positive in the neck region of C contain Bowie-positive granules as well.

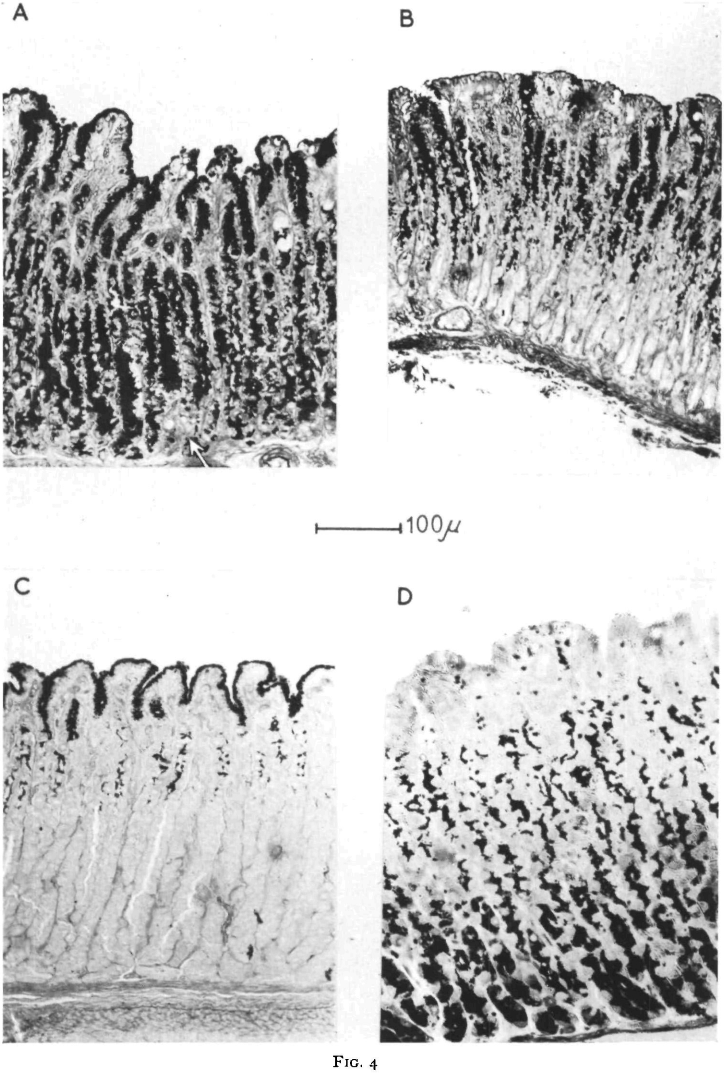

FIG. 4

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similar to the adult's, though the mucosa is only one-third of its full depth. In four animals, Bowie-positive granules are found in cells higher in the neck (fig. 4, D) than in the adult and these granules are PAS-positive (fig. 4, C) and strongly eosinophil. Typical mucous neck-cells are still few in number in all specimens.

DISCUSSION

In discussing the origin and development of cell-types in the gastric mucosa it appears that some authors have adopted the presumption that a cell arises from the same type of cell during embryonic development as during normal replacement or regeneration in the adult. For example, Hirschowitz (1957), under the heading of 'embryology', states that peptic cells arise from mucous neck-cells, and quotes Plenk (1932) as an authority. Plenk (1932, p. 143) certainly wrote that in the fully adult stomach the replacement of peptic cells must occur through the differentiation of mucous neck-cells, and one must assume that this is the basis for Hirschowitz's statement. Plenk also wrote, however (ibid., p. 101), that peptic cells develop in the embryo from an undifferentiated non-mucoid cell, reaffirming his own investigations of 1931 and those of Kirk (1910). It appears therefore that this presumption is not necessarily true, and it becomes essential to study the development in the embryo itself without preconceived ideas derived from regenerative phenomena in the adult.

In the foetal stages in the rabbit the results show that the oxyntic cells develop from undifferentiated non-mucoid cells about the 23rd day. This finding agrees with the observations of Kirk (1910) and of Plenk (1932), but is not in agreement with the statements of Lim (1922).

At the 27th day there are PAS-positive granules in all cells except the oxyntic. These are usually arranged in two groups, supranuclear and paranuclear. Sudanophil material is conspicuous in the paranuclear group, where it appears to be applied around some of the granules. Since all the PAS-positive granules are still positive after incubation in diastase and after chloroform extraction, when the sudanophil material is absent, they are presumably a mucinogen and neither glycogen nor glycolipid. Phase-contrast microscopy shows no difference between the groups of granules, nor can any difference be demonstrated by peptic or tryptic digestion. They do not digest, but this may be due to the special method of fixation and prolonged postchroming.

Bowie-positive granules appear in cells at the 23rd day; they increase to their maximum per cell at the 27th day, and then decrease rapidly and are much less numerous in the last days of foetal life, when many sections show none at all in the whole length of the epithelium. They always occupy a supranuclear position, and even at the 27th-day stage there are never as many per cell as there are PAS-positive granules. Phase-microscopy of PAS-sections does not reveal any granules in a supranuclear position other than PAS-positive ones; therefore it is almost certain that the Bowie-positive granules are in fact PAS-positive.

In view of what has just been said, the question arises whether the Bowie-positive granules are in fact pepsinogen, and if a temporary stage of peptic activity occurs during foetal life which later diminishes, or disappears, to reappear in postnatal life. Unfortunately this question cannot be answered at the present moment, for two reasons. In the first place, no evidence has been provided to indicate that pepsin is present in the stomach of the rabbit before the end of the first week of postnatal life. But at the same time it must be borne in mind that various writers in the past have given widely differing dates for the onset of peptic activity in other mammals (Keene and Hewer, 1929). In the second place, as already indicated, it cannot be asserted that Bowie's method is specific for pepsinogen. Further, it is not even possible to say if the future peptic cells develop from the cells that contain Bowie-positive granules in the foetus, since in any case just before birth the majority of the undifferentiated epithelial cells show no Bowie-positive granules. It might, however, be relevant to mention at this point that the foetal Bowie-positive granules are PAS-positive also, as are in fact the peptic granules in the first few weeks of postnatal life. This might be considered as circumstantial evidence in support of the notion that the Bowie-positive cells of the foetus are indeed a special sort of peptic cell.

At birth, routine staining methods demonstrate a few cells in the bases of the tubules which all previous writers have called peptic cells. I shall continue to call them peptic cells, for they are present when pepsin can be found in the stomach, but, as they also contain PAS-positive granules, it must be borne in mind that some, if not all, may prove to be 'stem cells', that is to say cells from which not only adult peptic cells but other cells may develop.

From birth to the fourth week no granules can be seen in any of the peptic cells other than PAS-positive ones (and these are also Bowie-positive—see below). Between the fourth and sixth weeks the granules lose their PAS-positive reaction. This loss commences in cells at the base of the tubule, and proceeds upwards towards the lumen until approximately the end of the 6th week, when the adult condition is reached; there is then no PAS-positive material in the peptic cells. Although, unfortunately, exact physiological data are lacking, this loss of the mucinogen component of the peptic granules does not occur at the end of the first or second week, when it is said that peptic activity can first be detected in the rabbit (Hirschowitz, 1957). It is of interest to note that the animals used were weaned during this period of 4 to 6 weeks after birth.

The number of peptic cells present at birth and containing Bowie-positive granules remains approximately constant up to the end of the first week and then steadily increases until the adult condition is reached. The peptic granules, which are PAS-positive, colour a greyish blue after Bowie's method, whereas those that have lost their mucinogen component colour a bright blue.

The results establish without doubt that the peptic cells, in the rabbit, not only differentiate from cells containing mucinogen (as was in my opinion demonstrated by Zimmerman, 1925) but retain a mucinogen component for several weeks. This does not agree with Kirk's statement that the peptic cells arise directly from primitive embryonic cells and not from mucous cells. This discrepancy between Kirk's observations and those reported here may have been due to the fixative he used, a mixture of mercuric chloride and potassium dichromate in alcohol for only 2 h, or perhaps there is a species difference, for he used pig embryos. Again Plenk, writing of human embryos, states that the peptic cell definitely develops from an indifferent cell and not from a mucoid one. This I imagine was due to the paucity of methods available, for I have noticed in a 3-weeks-old child that peptic cells contain Bowie-positive granules which can easily be shown to be PAS-positive also, and further, in a 5-months-old Rhesus monkey foetus numerous Bowie-positive granules are present in the peptic cells and these are PAS-positive also. It may be of interest to note here that in some species I have examined, for example, cat, dog, and fennec fox (*Fennecus zerda*), the adult peptic cells contain a few PAS-positive granules, whilst in adult guinea pigs it would appear that most if not all the pepsinogen granules are both PAS- and Bowie-positive.

Fergusson (1928) continuing the work of Griffini and Vassale (1888), Cade (1901), Harvey (1907), and Malesani (1909) found that both peptic and oxyntic cells can arise from mucoid cells. However, neither Fergusson nor any of these investigators was studying the development of the foetus: all were investigating the repair of traumatic injuries to the adult mucous membrane. Although it seems there is no difference between normal development and regeneration following trauma in regard to peptic cells, this is not true of oxyntic cells.

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