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The prenatal development of enterochromaffin cells in the human gastro-intestinal tract

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Following the first identification, almost a hundred years ago, of what are now generally known as the enterochromaffin or argentaffin cells of the gastro-intestinal tract, an extensive literature has accumulated regarding their morphology, distribution and nature. The relatively recent recognition of their association with 5-hydroxytryptamine has further stimulated interest in them. Studies on the development of these cells are, however, relatively few.

Enterochromaffin cells are considered to be of mesodermal origin by Kull (1925) and Dias Amado (1925), and of nervous origin by Danisch (1924) and Chung (1934), but the majority of workers hold that they differentiate *in situ* in the epithelium of the gastro-intestinal tract. The intra-uterine age at which these cells can first be identified in human embryos is stated to be 5–6 months by Kull (1925); 4–5 months by Parat (1924); 4 months by Masson (1928) and by Danisch (1924); and 12 weeks by Cordier (1926), Patzelt (1931), Clara (1934), Friedmann (1934) and Cole & McKalen (1962).

It is now accepted that there are two distinct types of silver-reducing cells in the epithelium of the gastro-intestinal tract—the true enterochromaffin or argentaffin cells, and the argyrophile or pre-enterochromaffin cells. The view that argyrophile cells represent a stage in the maturation of argentaffin cells receives strong support from the work of Monesi (1960), who finds that in chick embryos argyrophile cells appear distinctly earlier (14th day) than argentaffin cells (15½–16 days). However, Ghidini (1940) affirms that in chick embryos argyrophile and argentaffin cells appear simultaneously. In the proventriculus and gizzard of the chick Dawson & Moyer (1948) observe that argyrophile cells do not develop into argentaffin cells.

Clara (1934) states that at the time of their first appearance the granules of enterochromaffin cells already show the specific histochemical features (i.e. chromaffinity, argentaffinity and positive diazonium coupling reaction) which are now associated with the presence of 5-hydroxytryptamine. In calf embryos Faustini (1955) is able to detect the first traces of 5-hydroxytryptamine in extracts of intestinal tissues as soon as the first argentaffin cells can be identified.

MATERIAL AND METHODS

The material for this investigation consisted of a series of human embryos and foetuses at closely graded stages of development. Table 1 summarizes the C.R. length, fixatives used, parts sectioned and staining methods employed for each embryo or foetus.

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Argyrophile cells were demonstrated by the Bodian method. Several important considerations in the use of the Bodian method for this purpose are being reported separately (Singh, 1963*a*). For the demonstration of the argentaffin cells it was found that the Gomori–hexamine–silver method (used at 60° C.) gave a much more intense and specific impregnation than the Masson–Fontana or Masson–Hamperl methods, and was therefore used in preference to them. The staining time varied

Table 1. *Detailed data regarding embryos and foetuses used in the present investigation*

Code no.	C.R. length (mm.)	Fixation	Part sectioned	Staining methods
H 767	22	Alcohol–formol–acetic	Entire embryo	Bodian
H 950	23	Formalin	Entire embryo	Bodian, Gomori–hexamine
H 855	24	Carnoy	Entire embryo	Bodian
H 876	24	Bouin	Entire embryo	Bodian
H 795	28	Bouin	Entire embryo	Bodian
H 970	28	Formalin	Entire embryo	Bodian, Gomori–hexamine
H 983	28	Formalin	Entire embryo	Bodian
H 910	32·5	Bouin	Entire embryo	Bodian
H 694	35	Formalin	Entire embryo	Bodian
H 944	39	Formalin	Entire embryo	Bodian, Gomori–hexamine, Schmorl, diazonium
H 990	45	Formalin	Entire gut	Bodian, Gomori–hexamine, Schmorl, diazonium
H 679	46	Bodian	Entire embryo	Bodian
H 946	55	Formalin	Entire embryo	Bodian, Gomori–hexamine, Schmorl, diazonium
H 996	60	Formalin	Appendix, colon, rectum	Bodian, Gomori–hexamine
H 986	65	Dichromate–chromate–formol	Entire gut	Bodian, haematoxylin–eosin, acid fuchsin–thionin
H 828	75	Formalin	Entire gut	Bodian, Gomori–hexamine, Schmorl, diazonium
H 968	76	Formalin	Entire embryo	Bodian, Gomori–hexamine
H 993	80	Dichromate–chromate–formol	Entire gut	Bodian, haematoxylin–eosin, acid fuchsin–thionin
H 699	90	Bodian	Entire embryo	Bodian
H 935	96	Formalin	Entire gut	Bodian, Gomori–hexamine, Masson–Fontana, Schmorl, diazonium
H 812	97	Bouin	Entire gut	Bodian, Gomori–hexamine, Masson–Fontana, Schmorl, diazonium
H 744	100	Formalin	Entire embryo	Bodian
H 989	120	Formalin	Duodenum, appendix	Bodian, Gomori–hexamine, Schmorl, diazonium
H 818	140	Bouin	Entire gut	Bodian, Gomori–hexamine, Schmorl, diazonium
H 717	180	Bouin	Duodenum, appendix	Bodian, Gomori–hexamine, Schmorl, diazonium
H 839	220	Formalin	Entire gut	Bodian, Gomori–hexamine, Schmorl, diazonium

considerably from tissue to tissue and frequent checks were necessary to prevent overstaining of the background. The Schmorl method and the diazonium coupling reaction (using the stable diazotate of 5-nitroanisidine in 0·1 M veronal acetate buffer at pH 9·2) were also used for studying the argentaffin cells. Although histochemically

not specific the Schmorl method, as applied to the gut, picked out the argentaffin cells with as much specificity as the silver methods; it had the advantage of being easily and rapidly performed and of giving a good contrast. The diazonium reaction, on the other hand, often gave a very pale staining and was unsuitable for quantitative estimations. In two foetuses argentaffin cells were demonstrated by fixation in a mixture containing 10 volumes of 5% potassium chromate, 2 volumes of formalin, and 7 volumes of distilled water. With counterstaining by haematoxylin and eosin, or by acid fuchsin and thionin, a good demonstration of these cells was obtained. Attempts to demonstrate the argentaffin cells by the chromaffin reaction in formalin-fixed material gave only a very poor staining or none at all.

For the purpose of quantitative comparisons of the density of the enterochromaffin cells at various stages of development the density was expressed as the number of enterochromaffin cells related to 1 mm.^{2} of basement membrane. This was calculated as follows. Sections of the region in question were projected on an Edinger apparatus at known magnification. The basement membrane lining the epithelium was drawn and its length measured with a map measurer. The number of cells in each section was counted at high magnification to avoid confusion with artefacts. The density of the cells (D) per mm.^{2} of basement membrane was then calculated by the formula $D = N/LT$, where N was the number of cells counted, L the true length of basement membrane in millimetres after correction for the magnification used in projection, and T the thickness of the sections concerned expressed in millimetres. To ensure accuracy a sufficient number of sections was drawn so as to include several hundred cells. Thus, at stages showing less cell density, more sections had to be drawn to achieve equivalent accuracy.

OBSERVATIONS

The stages of development at which argyrophile and argentaffin cells appear in various parts of the human gastro-intestinal tract are summarized in Table 2.

With regard to the C.R. lengths given in the second and third columns of the table the first figure represents the length of the oldest embryo studied in which the cells in question are not present and the second figure the youngest embryo in which they are observed.

From Table 2 it is clear that argyrophile and argentaffin cells do not appear simultaneously throughout the gastro-intestinal tract but follow a definite sequence. No argyrophile cells can be identified at the 24 mm. stage. At the 28 mm. stage argyrophile cells can be identified at the lower end of the oesophagus, the cardiac end of the stomach, the duodenum and the most proximal coils of the jejunum. In the duodenum and the jejunum they are most numerous at the duodeno-jejunal junction and sharply decrease in number when traced towards the pylorus or down the jejunum. By the 32·5 mm. stage argyrophile cells have appeared in the pyloric part of the stomach. At this stage they extend to the proximal half of the small intestine, and by the 35 mm. stage to the ileo-caecal junction. There is thus a definite cranio-caudal gradient in the differentiation of the argyrophile cells of the small gut. In the large intestine, however, argyrophile cells first appear in the rectum and can be identified in the colon and appendix appreciably later. In a

60 mm. foetus a very small number of argyrophile cells can be identified in the distal one-fourth of the colon. By the 65 mm. stage they can be identified throughout the colon and in the appendix, but are distinctly more numerous in the distal part of the colon, suggesting that a caudo-cranial gradient of differentiation probably exists.

Table 2. *Times of appearance of argyrophile and argentaffin cells in various parts of the gastro-intestinal tract*

Region	C.R. length (mm.)	
	Argyrophile cells	Argentaffin cells
Stomach—cardiac end	24—28	39—45
Stomach—pyloric end	28—32·5	39—45
Duodenum	24—28	28—39
Proximal jejunum	24—28	28—39
Distal jejunum	28—32·5	39—45
Terminal ileum	32·5—35	45—55
Appendix	60—65	60—65*
Colon	60—65	60—65*
Rectum	39—45	45—55

* See explanation in text.

A distinct time-lag exists between the appearance of argyrophile cells and of argentaffin cells in a particular region. Such a delay in the appearance of argentaffin cells in the colon and appendix is not obvious in Table 2. However, the youngest foetus in which argyrophile and argentaffin cells can be seen throughout the colon and appendix (65 mm. C.R.) shows that, while argyrophile cells are easily found, argentaffin cells can be identified only on careful and prolonged searching, indicating that they are just beginning to appear. Thus in this region the argyrophile cells evidently appear earlier than the argentaffin cells. The most striking delay in the appearance and multiplication of argentaffin cells is seen in the stomach. Although argyrophile cells can be identified here at the 28 mm. stage no argentaffin cells can be seen till the 45 mm. stage. Unlike other regions of the gut the increase in the number of argentaffin cells is very slow and in foetuses 55 and 75 mm. long they are difficult to identify. They are easily spotted at the 97 mm. and subsequent stages.

At the 39 mm. stage argentaffin cells can be clearly demonstrated (in the duodenum) only by the Gomori–hexamine–silver method. These cells also give a very weak Schmorl reaction, but a positive diazonium coupling reaction cannot be obtained. By the 55 mm. stage, however, silver-reducing, Schmorl and diazonium positive cells can be seen in the duodenum, the whole of the jejunum and ileum, and in the rectum.

Careful examination of a large number of embryos shows conclusively that enterochromaffin cells differentiate *in situ* in the epithelium of the gut. No enterochromaffin cells can be seen in any other part of the gut wall at any stage of development. Cells that apparently seem to be situated in the submucosa invariably turn out to belong to tangentially cut intestinal glands. The stages in the histogenesis of the cells are basically similar in all parts of the gut; the same stages can be observed during the differentiation of both the argyrophile and the argentaffin cells.

The earliest stages of the differentiation of the argyrophile cells are well seen in the stomach of a 28 mm. embryo. At this stage the epithelium is a simple lining without folding. Between the basement membrane and the level of the nuclei of the epithelial cells there is a wide zone of clear cytoplasm. The earliest differentiating argyrophile cells can be seen in this clear zone. As a similar clear zone is not present in the small intestine, differentiating argyrophile cells are less obvious. The differentiation of the enterochromaffin cells can be divided into the following stages:

Stage 1

Scattered here and there in the clear zone referred to above, some nuclei (indicated by arrow in Pl. 1, fig. 1) that are more oval and less elongated than those of other epithelial cells, and situated at a lower level, can be identified. No argyrophile granules are present in relation to these nuclei, but the fact that they belong to cells that are destined to become argyrophile is obvious from the subsequent stages.

Stage 2

Some nuclei occupying the same position as those described in stage 1 show a few argyrophile granules which are applied to the surface of the nucleus (Pl. 1, fig. 7). This stage is difficult to identify in sections stained by the Bodian method but older embryos stained by the Gomori–hexamine–silver method show numerous cells at this stage; identification is facilitated as black argentaffin granules can be easily recognized against the brown colour of the nuclear material.

Stage 3

Argyrophile granules gradually accumulate in relation to the nuclei in question (Pl. 1, figs. 2–6, 8–10). At the 28 mm. stage only a few infranuclear granules can be seen. They stain less intensely and are less clear-cut than at later stages of development. Careful focusing usually reveals a very small number of granules just above the nucleus also.

Stage 4

With further increase in the number of the specific granules they form a dense mass which fills the infranuclear part of the cell (Pl. 1, fig. 11). The cells assume various forms presumably depending upon pressure of neighbouring cells. In the intestine the infranuclear granules assume a more or less columnar or triangular form; the columnar form is most obvious in the rectum. A significant number of supranuclear granules is only rarely seen, but a thin layer of supranuclear granules extending to the lumen is sometimes observed, especially in the appendix (Pl. 1, fig. 12). In the stomach, the clear zone of cytoplasm already referred to is no longer obvious by the 55 mm. stage and the nuclei are difficult to distinguish from those of other epithelial cells. The granules become progressively more and more compressed against the basement membrane so that by the 90 mm. stage the cells have the typical adult morphology of a thin layer of argyrophile granules with the related nuclei difficult to identify (Pl. 1, fig. 14).

Stage 5

This stage is seen only in the appendix. In the 140 mm. and subsequent stages the appendix shows several cells in which the granules, along with the overlying nucleus, have moved towards the lumen so that the nuclei of these cells now occupy a position nearer the lumen than those of other cells of the epithelium (Pl. 1, fig. 13). Some of these cells also show supranuclear granules abutting against the lumen. This stage is, however, transitory and no similar cells are observed in adult appendices.

The results of the estimation of the density of the distribution of argyrophile and of argentaffin cells in the duodenum and appendix at various stages of development are given in Table 3.

Table 3. *Density of argyrophile and argentaffin cells in the duodenum and appendix at various stages of development*

C.R. length (mm.)	Number of cells covering one square millimeter of basement membrane			
	Duodenum		Appendix	
	Argyrophile	Argentaffin	Argyrophile	Argentaffin
24	0	0	0	0
28	44	0	0	0
39	290	29	0	0
55	377	244	0	0
75	965	475	612	69
97	1230	538	2251	1088
120	1250	610	3100	2874
140	1352	815	2060	1760
180	928	400	1750	1540
220	546	93	1426	1200
Adult	—	—	190	178

This table shows that following the appearance of argyrophile and of argentaffin cells their numbers relative to the total area of basement membrane increase rapidly. This increase in density is more rapid and dramatic in the appendix, so that in spite of the considerably later onset of differentiation of the cells a peak density is attained at about the 120 mm. stage, whereas in the duodenum the cells reach their maximum density at the 140 mm. stage. The maximum density of cells in the duodenum is only about half that attained in the appendix. Thereafter there is an equally spectacular fall in density of the distribution of the cells but at the 220 mm. stage it is still considerably greater than in the adult.

DISCUSSION

The majority of investigators who have studied the development of the enterochromaffin cells agree that they differentiate *in situ* in the epithelium. This is postulated mainly because there is no evidence of migration of these cells into the epithelium from an outside source. The early stages in the differentiation of the enterochromaffin cells in human embryos observed in the present investigation

further confirm this view. Indirect evidence of the endodermal origin of the cells is provided by the fact that they may be found in metastases from epithelial growths of the intestine (Friedmann, 1934); and by the fact that islets of ectopic intestinal mucosa in the stomach show large numbers of enterochromaffin cells with morphology typical of these cells in the intestine (Singh, 1963*b*).

Danisch's (1924) claim that the enterochromaffin cells develop from embryonic sympathetic elements is based on the observation that in the first half of the fourth month of intra-uterine life argyrophile cells can be observed in relation to the differentiating fibres of Meissner's plexus and in the second half of this month they can be seen in the epithelium of the gut. This argument is without foundation in view of the fact that argyrophile and argentaffin cells can be identified in the epithelium of the gut much earlier than the fourth month of foetal life.

Masson's (1914) view that the enterochromaffin cell is formed by oblique or transverse division of an epithelial cell in such a manner that the basal daughter cell becomes enterochromaffin and the overlying daughter cell an ordinary epithelial cell is obviously based on the assumption that the enterochromaffin cell always remains buried in ordinary epithelial cells and never reaches the luminal surface. As cell boundaries in the epithelium of the gastro-intestinal tract are usually indistinct with methods used for the demonstration of enterochromaffin cells, the extent of the cells has obviously been equated with the extent of their granules. The present study suggests that as a rule the enterochromaffin cells, like other cells of the intestinal epithelium, reach the lumen but this is generally not apparent as the supranuclear part of the cells is usually agranular. This is shown first by the fact that a thin row of granules can often be identified extending to the lumen, and secondly by the very striking shifting of the granules and of the nucleus towards the lumen in the appendix of older foetuses. This movement of the nucleus is apparently due to the accumulation of granules below the nucleus; this is possible only if the cell in the first place extends to the lumen. A corresponding position holds in immature enterochromaffin cells of the stomach, but as they reach maturity they are excluded from the luminal surface.

Using argyrophile methods enterochromaffin cells can be recognized in human embryos very much earlier than has hitherto been reported. By the use of the Gomori–hexamine–silver method true argentaffin cells can also be observed at stages much earlier than those reported by previous workers. Cole & McKalen (1962) also use this method, but their entire material consists of only two embryos. The only previous investigation that involves any significant number of human embryos is that of Patzelt (1931). He relies on the chromaffin reaction obtained by fixation in Orth's fluid for identification of these cells. He can identify argentaffin cells only at about the 60 mm. C.R. stage, for while his method displays mature argentaffin cells it is unsatisfactory for cells containing very few granules. Failure of previous workers to identify argentaffin cells in younger embryos is possibly also due to the fact that these cells do not assume their typical adult morphology, with a dense mass of infranuclear granules, till about the 55 mm. stage. Parat's (1924) hypothesis correlating the time of appearance of the enterochromaffin cells with the onset of pancreatic secretion has already been shown to be unfounded by Cordier (1926) and in view of the findings of the present investigation is even more untenable.

The cranio-caudal gradient in the differentiation of both argyrophile and argentaffin cells in the small intestine is a finding of interest. Parat's (1924) observation that at the time of their first appearance these cells are mainly located in the duodenum and jejunum fits in with this finding. Preliminary observations on human foetuses and adults suggest that this cranio-caudal gradient of differentiation is reflected in the subsequent density of distribution of enterochromaffin cells. Schofield (1953) also observes that in man and in guinea-pig argentaffin cells are most numerous in the duodenum and become progressively less frequent towards the ileum. A similar gradient in differentiation and subsequent concentration of enterochromaffin cells is observed by Monesi (1960) in the chick. In the rat similar observations are made on the differentiation of these cells by Sharples (1945), and on their distribution in adult animals by Münch (1939). This shows that a cranio-caudal gradient in differentiation and distribution of enterochromaffin cells of the small intestine of man is part of a well-established pattern which would appear to bear a significant relationship to whatever role enterochromaffin cells play in the physiology of the intestine.

My findings suggest that in the large gut a gradient exists in the differentiation of enterochromaffin cells in a direction opposite to that in the small gut. Preliminary observations on human foetuses and adults show that a similar gradient is possibly present in the density of distribution of the cells. Tehver's (1930) observation that in cattle the number of enterochromaffin cells increases in the terminal part of the large intestine, and Faustini's (1955) finding that in the colon of the adult bull, calf, sheep, pig, adult horse and foal the maximum concentration of 5-hydroxytryptamine is to be found in its distal part, support this conclusion.

An interesting, and possibly important, finding is that in all regions of the gut Bodian positive argyrophile cells can be recognized distinctly earlier than true argentaffin cells. This is consistent with the view that argyrophile cells are precursors of argentaffin cells and agrees with the findings of Monesi (1960) in the chick. That argyrophile cells never develop into argentaffin ones in certain situations indicates that argyrophile cells may also have an independent significance of their own.

Most workers who have studied the development of the enterochromaffin cells ignore quantitative considerations. Monesi (1960) uses the average number of cells seen in one high-power field as an indication of density. This is reasonable where the amount of tissue seen in different fields is more or less uniform. This is hardly true of tissues at different stages of development, and even less so when different regions are being compared. A method is, therefore, called for that is not affected by magnification used, by the amount of epithelium present at a given stage of development in a given section, or by differences produced by variations in complexity of folding of the mucosa. The obvious solution is to express the number of cells in terms of a given amount of epithelium. As the area of the basement membrane is directly proportional to the extent of the epithelium, the density of the cells is expressed as the number of cells related to one square millimetre of basement membrane. The use of the basement membrane as a measuring unit also eliminates error due to varying thickness of the epithelial lining, as all enterochromaffin cells lie in direct relation to this membrane.

The manner in which enterochromaffin cells increase in numbers (Table 3) is in agreement with that found by Monesi (1960) in the chick duodenum. The behaviour of the cells in the human appendix and duodenum is basically similar and it is likely that this pattern is representative of what is happening throughout the gastro-intestinal tract.

SUMMARY

1. The development of the enterochromaffin cells of the human gastro-intestinal tract is studied in a closely graded series of embryos and foetuses.

2. Enterochromaffin cells differentiate *in situ* in the epithelium and do not migrate into the epithelium from either the submucosa or the nerve plexuses.

3. Bodian positive argyrophile cells are first seen in the epithelium of the cardiac end of the stomach, the duodenum, and the proximal part of the jejunum at the 28 mm. C.R. stage; at the pyloric end of the stomach and the distal part of the jejunum at the 32·5 mm. stage; in the terminal ileum at the 35 mm. stage; in the rectum at the 39 mm. stage; and in the colon and appendix at the 65 mm. stage.

4. True enterochromaffin cells are first seen in the duodenum and proximal part of the jejunum in a 39 mm. embryo; in the stomach, distal part of the jejunum and rectum in a 45 mm. embryo; in the terminal ileum in a 55 mm. foetus and in the colon and appendix in a 65 mm. foetus.

5. There is a distinct interval between the appearance of Bodian positive argyrophile cells and that of true enterochromaffin cells in all parts of the gastro-intestinal tract, suggesting that the argyrophile cells are pre-enterochromaffin.

6. There is a cranio-caudal gradient in the differentiation and subsequent distribution of the enterochromaffin cells of the small gut, and a caudo-cranial gradient of differentiation and concentration in the large intestine.

7. Following their first appearance the density of the enterochromaffin cells in the epithelium rapidly increases to a peak level at about the 120–140 mm. stage and thereafter decreases.

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REFERENCES

CHUNG, I. (1934). Beiträge zur Kenntnis der Entwicklung der gelben Zellen im Darm. *J. Chosen Med. Ass.*, **24**, 52. In Japanese. German summary, p. 52.

CLARA, M. (1926). Beiträge zur Kenntnis des Vogeldarmes. III Teil. Die basalgekörnten Zellen im Darmepithel. *Z. mikr. anat. Forsch.* **6**, 28–54.

CLARA, M. (1934). Über die Entwicklung der basalgekörnten Zellen beim Menschen. *Z. ges. Anat.* 1. *Z. Anat. EntwGesch.* **103**, 131–139.

COLE, J. W. & MCKALEN, A. (1962). Argentaffin cells in the intestinal epithelium of human embryos. *Nature, Lond.*, **193**, 198.

CORDIER, R. (1926). Recherches morphologiques et experimentales sur la cellule chromo-argentaffine de l'épithélium des vertébrés. *Arch. Biol. Paris*, **36**, 427–463.

DANISCH, F. (1924). Zur Histogenese der sogenannten Appendix karzinoide. *Beitr. path. anat.* **72**, 687–709.

DAWSON, A. B. & MOYER, S. L. (1948). Histogenesis of the argentophile cells of the proventriculus and gizzard of the chicken. *Anat. Rec.* **100**, 493–515.

DIAS AMADO, L. (1925). Sur l'existence des cellules argentaffines dans le tissu conjonctif des villosités intestinales. *C.R. Soc. Biol., Paris*, **93**, 1548–1549.

FAUSTINI, R. (1955). The enteric distribution of 5-hydroxytryptamine (enteramine, serotonin) in some large domestic mammals and the appearance of 5-hydroxytryptamine and the enterochromaffin cell system in the embryonic calf. *Amer. J. vet. Res.* **16**, 397–400.

FRIEDMAN, I. (1934). Ein Beitrag zur Kenntnis den basalgekörnten, gelben Zellen des Darmtraktes beim Menschen. *Z. mikr.-anat. Forsch.* **36**, 99–136.

GHIDINI, G. M. (1940). Ricerche embriologiche e sperimentali sulle cellule enterocromaffini nel pollo. *Anat. Anz.* **89**, 197–204.

KULL, H. (1925). Die chromaffinen Zellen des Verdauungstraktus. *Z. mikr.-anat. Forsch.* **12**, 163–200.

MASSON, P. (1914). Le glande endocrine de l'intestin chez l'homme. *C.R. Acad. Sci., Paris*, **158**, 59–61.

MASSON, P. (1928). Carcinoids (argentaffin cell tumours) and nerve hyperplasia of the appendicular mucosa. *Amer. J. Path.* **4**, 181–212.

MONESI, V. (1960). The appearance of enterochromaffin cells in the intestine of the chick embryo. *Acta Anat.* **41**, 97–114.

MÜNCH, H. (1939). Über Menge und Verteilung der basalgekörnten Zellen im Darm der weissen Ratte. *Z. mikr.-anat. Forsch.* **45**, 244–254.

PARAT, M. (1924). Contribution à l'histophysiologie des organes digestifs de l'embryon. L'apparition correlative de la cellule de Kultschitzky et de la sécrétine chez l'embryon. *C.R. Soc. Biol., Paris*, **90**, 1023–1024.

PATZELT, V. (1931). Die feinere Ausbildung des menschlichen Darmes von der 5. Woche bis zur Geburt. *Z. mikr.-anat. Forch.* **27**, 269–518.

SCHOFIELD, G. (1953). The argentaffin and mucous cells of the human intestine. *Acta Anat.* **18**, 256–272.

SHARPLES, W. (1945). The histogenesis of the argentaffin cells in the stomach and duodenum of the rat. *Anat. Rec.* **91**, 107–117.

SINGH, I. (1963*a*). The staining of enterochromaffin cells by the Bodian silver impregnation method. *Acta Anat.* (in the Press).

SINGH, I. (1963*b*). A note on enterochromaffin cells in islets of ectopic intestinal mucosa in the human stomach. *J. Anat. Soc. India* (in the Press).

TEHVER, J. (1930). Über die enterochromaffinen Zellen der Haussäugetiere. *Z. mikr.-anat. Forsch.* **21**, 462–496.

EXPLANATION OF PLATE

Fig. 1. Photomicrograph of a section through the stomach of a 28 mm. C.R. length human embryo. An oval nucleus (indicated by arrow) is seen lying in the clear zone below the level of the other nuclei of the epithelium. Bodian, × 1460.

Fig. 2. Photomicrograph of a section through the stomach of a 28 mm. C.R. length human embryo. A nucleus (arrow) similar in position to that in fig. 1 is seen with just a few argyrophile granules related to it. Bodian, × 1460.

Fig. 3. Photomicrograph of a section through the stomach of a 28 mm. C.R. length human embryo showing an argyrophile cell with a number of granules related to it. Bodian, × 2058.

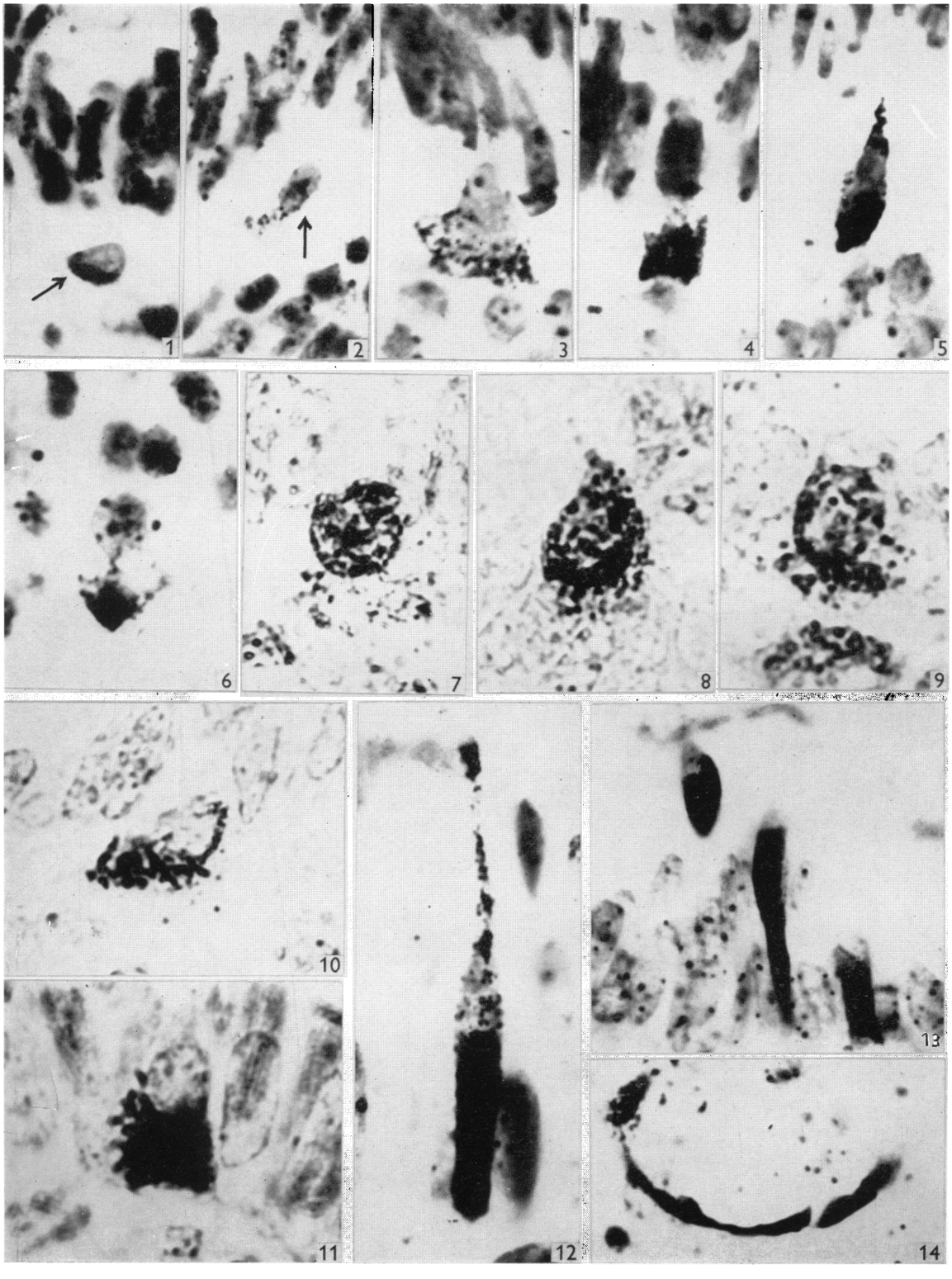
Fig. 4. Photomicrograph of a section through the stomach of a 28 mm. C.R. length human embryo showing an argyrophile cell with a compact mass of infranuclear granules. Bodian, × 2058.

Fig. 5. Photomicrograph of a section through the stomach of a 28 mm. C.R. length human embryo showing an argyrophile cell with infranuclear and supranuclear granules. Bodian, × 2058.

Fig. 6. Photomicrograph of a section through the duodenum of a 28 mm. C.R. length human embryo showing an argyrophile cell with a dense mass of infranuclear granules. Bodian, × 2058.

Fig. 7. Photomicrograph of a section through the duodenum of a 39 mm. C.R. length human embryo showing a differentiating argentaffin cell having a rounded nucleus with intensely staining argentaffin granules applied to its surface. Other nuclei of the epithelium are virtually unstained. Gomori–hexamine–silver, × 2058.

Fig. 8. Photomicrograph of a section through the duodenum of a 39 mm. C.R. length human embryo showing a differentiating argentaffin cell at a more advanced stage than that in fig. 7. The unusual relation of the granules to the nucleus is due to obliquity of the section.



INDERBIR SINGH

(*Facing p.* 386)

Fig. 9. Photomicrograph of a section through the duodenum of a 39 mm. C.R. length human embryo showing a differentiating argentaffin cell with a small aggregation of granules below the nucleus. Gomori–hexamine–silver, × 2058.

Fig. 10. Photomicrograph of a section through the appendix of a 97 mm. C.R. length human foetus showing an argentaffin cell possessing abundant infranuclear granules which, however, do not form a compact mass. Gomori–hexamine–silver, × 2058.

Fig. 11. Photomicrograph of a section through the appendix of a 97 mm. C.R. length human foetus showing a typical mature argentaffin cell. Gomori–hexamine–silver, × 2058.

Fig. 12. Photomicrograph of a section through the appendix of a 220 mm. C.R. length human foetus showing an argyrophile cell with a dense mass of infranuclear granules and a thin layer of supranuclear granules extending up to the lumen. Bodian, × 1692.

Fig. 13. Photomicrograph of a section through the appendix of a 220 mm. C.R. length human foetus showing three argyrophile cells with nuclei situated at varying levels, illustrating the shifting of the nucleus and underlying granules towards the lumen. Bodian, × 1200.

Fig. 14. Photomicrograph of a section through the stomach of a 97 mm. C.R. length human foetus showing characteristically flattened, mature, argyrophile cells. Bodian, × 1460.