Neuromuscular structures specific to the submucosal border of the human colonic circular muscle layer

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The circular muscle layer of the human caecum and ascending colon is clearly subdivided into two portions: an outer one which includes the bulk of the circular muscle layer, and an inner one made up of only six to eight rows of cells. In the right transverse colon no demarcation can be observed, but a difference exists between the innermost and the outermost cells, since those of the two innermost rows possess some peculiarities with regard to the sarcoplasmic reticulum, glycogen particles, caveolae, and intercellular junctions. In the left part of the colon, the circular muscle layer is also divided into two portions. In fact, the innermost smooth muscle cells still possess peculiar morphologies, progressively increase in number, and become separate from each other making up a superficial muscle network. A fibrous lamella, along and inside which a ganglionated nerve plexus runs, is strictly apposed to the submucosal border of the circular muscle layer of the entire colonic length. A second nerve plexus runs between the two portions of the circular muscle layer. Both these plexuses are accompanied by interstitial cells of Cajal in the right colon only. The peculiar organization of the entire submucosal border of the human colonic circular muscle layer distinguishes it from other parts of the gut and probably represents a structural basis for control of human colonic motility. The presence of putative pacemaker cells (interstitial cells and peculiar smooth muscle cells) indicates that the inner border of human colonic circular muscle layer possesses pacemaking activities. Moreover, the interstitial cell – smooth muscle cell ratio differs depending on the colonic level; two main regions can be identified: the right and the left colon. Consequently, we might expect regional variation in pacemaking.

Key words: smooth muscle cells, interstitial cells of Cajal, human colon, ultrastructure.

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La couche musculaire circulaire du caecum et côlon ascendant de l'humain est à tous égards divisée en deux véritables couches: une externe qui constitue la plus grande partie de la couche même, et une seconde interne formée seulement par six à huit rangées de cellules musculaires lisses. Le côlon transverse droit ne présente pas cette particularité; tout de même les cellules des deux rangées plus internes se distinguent des autres par la richesse en granules de glycogène, caveolae, réticulum sarcoplasmique et contacts intercellulaires. Cellules pourvues de cettes mêmes charactéristiques se trouvent aussi du côté interne de la couche circulaire par toute la longeur du côlon gauche. Mais en plus cettes cellules sont progressivement séparées les unes des autres et des externes par des espaces remplis par tissu conjonctif. La couche circulaire du côlon gauche est en conséquant divisée en deux parties. Une lame fibreuse est étroitement accolée tout le long du côlon au-dessus de la couche circulaire du côté de la sous-muqueuse. Au-dessus et au-dedans de cette lame est relié un réseau nerveux dérivé du plexus de Meissner. Un second réseau nerveux, fin et à larges mailles, se trouve entre les deux couches circulaires. Des cellules interstitielles de Cajal ont été trouvées seulement au niveau du côlon droit, toujours étroitement liées à tous deux ces réseaux nerveux. Une organisation tout à fait particulière est donc présente chez l'humain tout le long de la couche circulaire, ce qui permet de distinguer le côlon d'autres niveaux du tube digestif et de laisser supposer qu'elle soit à la base d'une activité moteur typiquement colique. En particulier, la présence de présumables cellules pacemakers indique que la couche circulaire du coté de la sous-muqueuse de l'humain puisse manifester des propriétés pacemaking. Le rapport entre cellules interstitielles et cellules musculaires, tout de même, varie selon les différentes régions coliques. Pour cela on peut dévisager au-dedans du côlon humain deux régions coliques principales: le côlon droit et le côlon gauche et, en conséquence des variations entre le pacemaking selon les régions semblent présumables.

Mots clés : cellules musculaires lisses, cellules interstitielles de Cajal, côlon de l'homme, ultrastructure.

Introduction

The motor activities of the colon are different from those of ier parts of the gut. Quite recently, studies have been per-rmed to identify slow wave origin and the modality of propa-tion inside the colonic muscle wall. In cat, pig, and dog, two gions seem to be involved: the submucosal border of the cir-ar muscle layer and the area between the circular and longi-dinal muscle layers (Caprilli and Onori 1972; Huizinga et al. 83; Durdle et al. 1983; Smith et al. 1987*a*, 1987*b*; Huizinga and Chow 1988). To date there has been very little morphological evidence to support these physiological data. Most evidence consists of electron microscopic investigation which attempts to identify the structures responsible for these colonic motor activities at the submucosal border of the circular muscle layer. Indeed, in most mammals studied, this area presents peculiarly organized neuromuscular structures that are specific to this gut level. Thus, it is reasonable to assume that these structures may account for specific colonic motile activities.

Some laboratory mammals, such as the rat, the mouse, or the dog, possess a crowded and strictly apposed nerve network on the innermost portion of the circular muscle layer; particu-

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larly numerous interstitial cells of Cajal (ICC) are located in the meshes of this network (Stach 1972; Faussone-Pellegrini 1983, 1985; Christensen et al. 1987; Berezin et al. 1988). In addition, in the mouse (Faussone-Pellegrini 1985), the innermost portion of the circular muscle layer is subdivided into two distinct portions, i.e., an inner and an outer one.

To date, the submucosal border of the circular muscle layer of the entire human colon has not been fully studied. The only data available are for the descending colon (Faussone-Pellegrini and Cortesini 1984), where a complex organization has also been observed. In fact, at this level, in the human as in the mouse, two clearly distinct portions of the circular muscle layer were found. However, contrary to those of the mouse, in the human the smooth muscle cells of the inner portion are rich in glycogen particles, caveolae, sarcoplasmic reticulum, and intercellular junctions. A fibrous lamella borders the submucosal surface of this muscle network and, as in other mammals, a nerve plexus runs along and inside it. However, this nerve plexus is missing in the ICC in humans.

In short, even if the organization of this colonic area is different for each animal species studied, the morphological data show the presence of a population of putative pacemaker cells in all of them, i.e., peculiar smooth muscle cells and (or) ICC, as well as a rich network of nerve endings. These data are, therefore, in favour of the presence of structures responsible for pacemaking. This interpretation certainly applies to the dog. In this animal species, in fact, the morphological data (Berezin et al. 1988) have been confirmed by the physiological evidence (Durdle et al. 1983; Smith et al. 1987*a*; Sanders et al. 1989; Barajas-Lopez et al. 1989). Furthermore, it has been found that the spontaneous electrical activities are controlled in this animal species by the nerve endings of the inhibitory neurons located in the submucosus plexus (Sanders and Smith 1986; Smith et al. 1989) and are generated by the ICC (Barajas-Lopez et al. 1989; Langton et al. 1989).

The manifestation of a myogenic control system has also been recorded in the circular muscle of human colon (Couturier et al. 1969), but the exact location of the pacemaker area has not yet been demonstrated. It is generally assumed that every colonic level has its own motor activities. In fact, the frequency of the electric signal of the myogenic control system is lower in ascending colon than in descending colon (Sarna et al. 1980). Dapoigny et al. (1988) found after a meal a relative hypomotility of the right colon compared with that of the left colon, and Gill et al. (1986) found a maximum spontaneous active stress of the right colon at greater degrees of stretch than in the left colon. Conversely, the morphological data from the studies performed on humans, contrary to those of the dog, are not yet sufficient to identify with certainty the structures responsible for the control of the colonic activity and to describe the structural variations with regions. In fact, putative pacemaker structures have been found both in the myenteric area and in the submucosal border of the circular muscle layer, but the myenteric ones have an identical cell composition at all colonic levels and the study of the submucosal border of the circular muscle layer is limited to th descending colon (Faussone-Pellegrini and Cortesini 1984).

Consequently, the aim of this work is to verify whether i humans the submucosal border of the circular muscle layer ha peculiar structures at all colonic levels and to ascertai whether or not the structures observed are identical to thos previously described for the descending colon. This stud gives evidence of a morphological substratum accounting fo the typical colonic motility and the functional difference between right and left regions[2].

Materials and methods

Fragments including both muscle layers (circular and taenia) ar fragments of the intertaenial regions of caecum, ascending colo right and left transverse colon and descending colon were studie The specimens were obtained from 12 patients (aged between 48 ar 62 years, mean age 53.5 years) undergoing surgery for cancer. Th segments of excised colon had a normal appearance and were take far from the carcinomatous areas (5 cm or more away from the si of cancer) and were histologically free of tumor and inflammatio The patients had not taken any drugs affecting colon motility.

Immediately after surgery, specimens about 1–2 cm long ar 0.5 cm large and macroscopically unaffected by disease were clampe at both their extremities to avoid spiralling of the circular musc layer and shortening of the longitudinal muscle layer. At this poin the two clamped extremities were tied with cat-gut thread. Then thes specimens were immersed in a solution of 2% cacodylate-buffere glutaraldehyde pH 7.4 contained in a custom-made polystyrene bo At the same time of fixative immersion they were also gently stretche and anchored at both ends by means of a cut-gut thread to the opposi walls of this box. These segments were prefixed in this solution ar kept in this controlled distension for between 6 and 24 h accordin to the size and thickness of the muscle wall. Then both the extremiti and the cut surface of each specimen were resected and the muco was removed by sharp dissection. A thin layer of submucosa remaine attached to these segments. The remnant segments of these specime were then cut into smaller and thinner strips of about 1 mm thickne and 2 mm length and rinsed in a buffered solution of saccharos They were postfixed with 1% phosphate-buffered OsO_4 pH 7.4 dehydrated with acetone, and embedded in Epon using flat moulds obtain transverse or longitudinal sections.

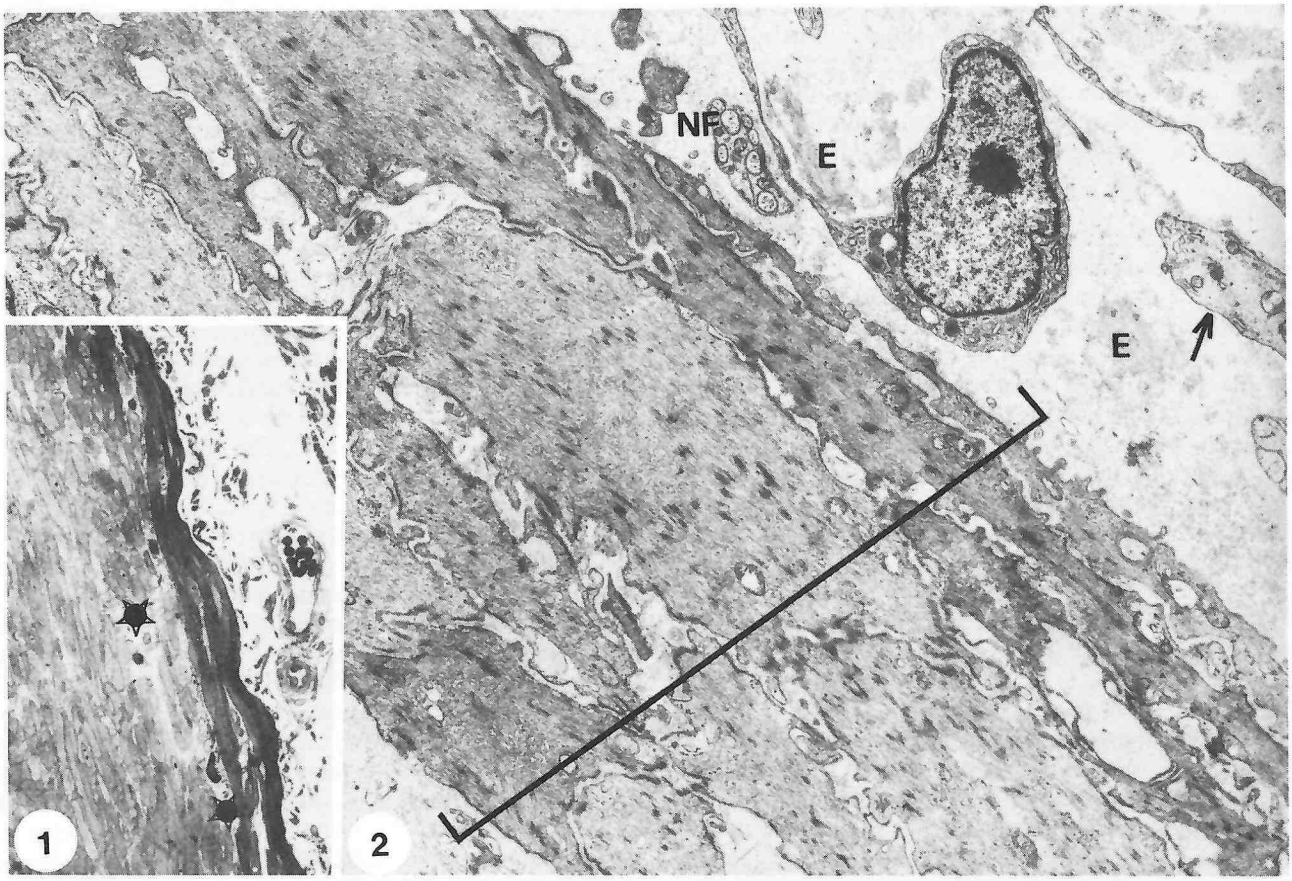
The semithin sections were stained with a solution of toluidine blu and photographed under the light microscope. All areas showing disarray of the muscle layers and unsuitable distension of the smooth muscle cells were excluded from both light and electro microscope examination. The ultrathin sections, obtained with Porter-Blum MT1 ultramicrotome using a sapphire knife, we stained with an alcoholic solution of uranyl acetate followed by solution of either concentrated bismuth subnitrate or lead citrate (heavily stain glycogen particles). These sections were examined und Siemens Elmiskop IA and 102 electron microscopes.

Results

Light and electron microscope examination revealed th existence of peculiar structures at the level of the submucos

[2]Preliminary data were presented at the 43th Congress of th Italian Society of Anatomy, Messina, 1988.

FIGS. 1–3. Caecum and ascending colon. Inner portion of the circular muscle layer. FIG. 1. The smooth muscle cells of the inner portio appear deeply stained in semithin sections and are clearly separated (asterisks) from those of the bulk of the circular muscle layer. Toluidi blue. ×200. FIG. 2. At the border between the tela submucosa and the inner portion of the circular muscle layer (bracket), a nerve fiber (N and an interstitial cell of Cajal (arrow). E, elastic fibers. ×6250. FIG. 3. Nerve plexus (N) running between the two portions of the circul muscle layer and its relative ICC (*a*) ×10 000. (*b*) Semithin section. Toluidine blue. ×800. (*c*) Detail of the contact areas between ICC (arro and between them and smooth muscle cells (double arrows) ×15 000.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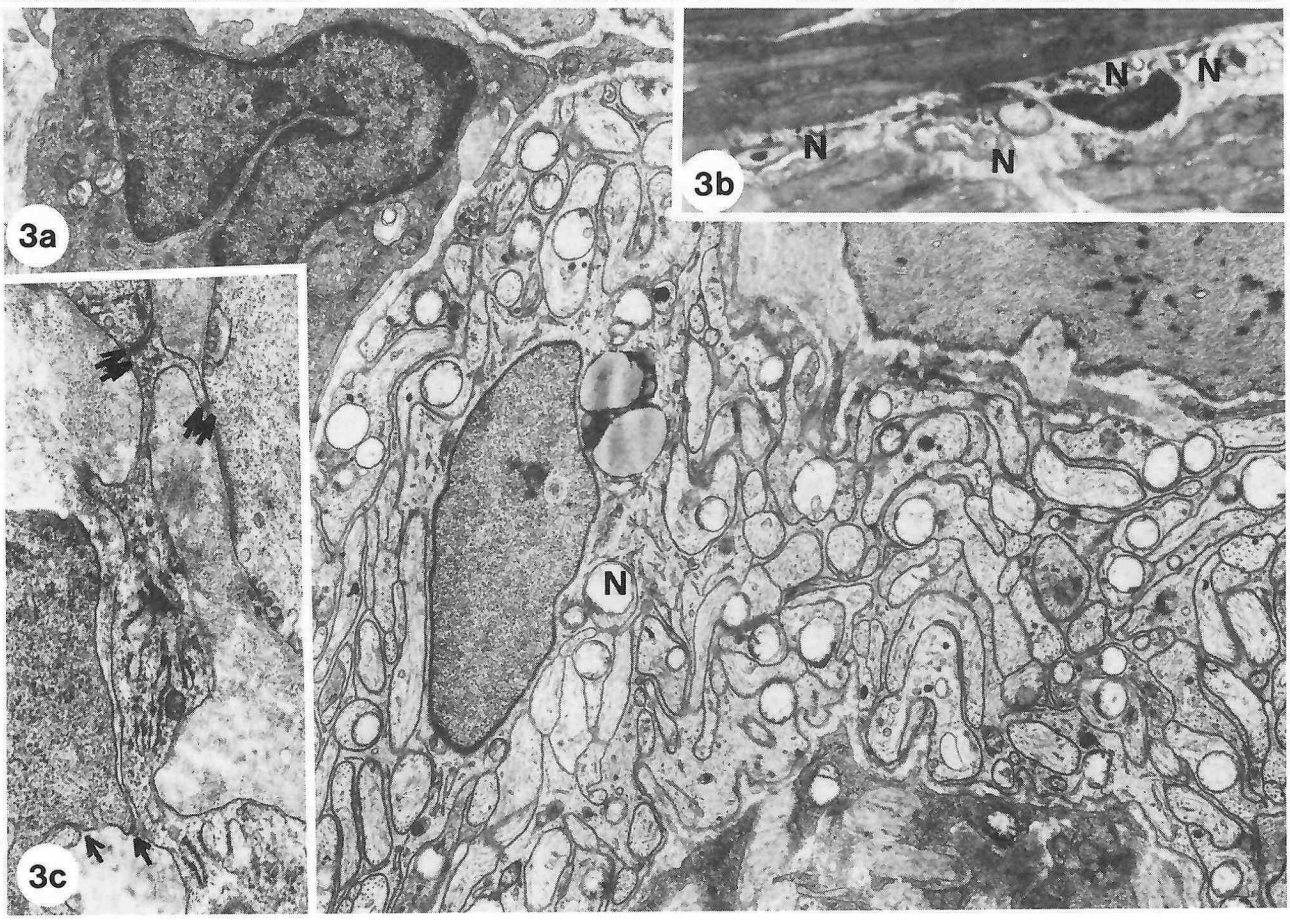
N
N
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3a
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3c

border of the circular muscle layer. These structures were found along the entire length and circumference of the colon (both taeniated and intertaeniated regions). They differed from each other according to the region examined. However, to facilitate the description we made a distinction between these two regions, i.e., the right and the left colon.

Right colon

The right colon includes the caecum, the ascending colon, and the right transverse colon.

At the level of the more proximal region of the right colon, i.e., the caecum and the ascending colon, the structural organization was very similar to that of the inner circular muscle layer of the human small intestine (Faussone-Pellegrini and Cortesini 1983). In fact, the smooth muscle cells of the six to eight innermost rows appear more deeply stained in the semithin sections than the others (Figs. 1 and 3*b*). As evident in the electron micrograph, some of them have an electron dense cytoplasm (Fig. 2). Wide areas occupied by connective tissue are present between them and the bulk of the circular muscle layer (Figs. 1 and 3*b*). Large nerve fibres rich in nerve endings (Figs. 3*a* and 3*b*) run throughout these connective spaces. Thus, two circular muscular regions can be identified, i.e., an inner and an outer muscle layer. Rarely are cells similar to those that characterize the human ICC (i.e., rich in smooth endoplasmic reticulum, filament bundles, and caveolae) and that contact both smooth muscle cells and nerve endings observed near the nerve endings located between these two layers (Fig. 3*a*). The gap at the ICC − smooth muscle cell contact area is 20−30 nm, devoid of basal lamina. Exceptionally small gap junctions between ICC and between them and smooth muscle cells (Fig. 3*c*) can be found.

As shown under the light microscope, on the contrary, the right transverse colon (Fig. 4) does not show two distinct regions inside the circular muscle layer. All smooth muscle cells are, in fact, closely apposed, and only here and there are some of the innermost ones deeply stained. With the electron microscope, however, we can clearly distinguish between two smooth muscle cell types since those of the two innermost rows have a peculiar morphology that differs from both that of the outermost cells and that of the inner smooth muscle cells of the circular muscle layer of the more proximal colon. In fact, the sarcoplasmic reticulum cisternae always appear extremely long, wide, and ramified . Those aligned along the plasma membrane facing the tela submucosa are even longer, wider, and more ramified (Fig. 5). Clusters of sarcoplasmic reticulum cisternae are also frequently found near the nucleus (Fig. 6*a*). Caveolae are usually scattered everywhere, but preferably they form extremely long rows along the plasma membrane facing the tela submucosa (Fig. 5) as well as along the contact areas between adjacent smooth muscle cells (Fig. 6*b*). Moreover, these contact areas are often very wide, reaching 5 or more μm in length, and caveolae open onto the opposite plasma membranes (Fig. 6*b*). Large nerve bundles accompanied by ICC run between the bulk of the circular muscle layer and these two innermost rows of circular smooth muscle cells (Figs. 7*a*, 7*b*). As in ascending colon, few small gap junctions between ICC and between them and smooth muscle cells can be observed.

Other structural peculiarities were found along the entire right colon. Glycogen particles forming large clusters are present in all the innermost smooth muscle cells (Figs. 8*a* and 8*b*). Branchings of the submucosus plexus form a nerve network (Figs. 9 and 10) with large meshes, along the submucosal border of the circular muscle layer. Small neurons and branchings of this nerve network penetrate (Figs. 2, 10, and 11) connective lamella (Fig. 9) rich in elastic fibres (Fig. 2) which borders the submucosal surface of the circular muscle layer. These nerve fibres are occasionally accompanied single (Figs. 2 and 11) or grouped (Fig. 13) ICC. These IC may lie, at a minimum gap of 20−30 nm devoid of basal lamina, close to both the nerve endings and the innermost smooth muscle cells (Fig. 12).

Left colon

The left colon includes the left transverse colon and the descending colon as far as the sigmoid colon.

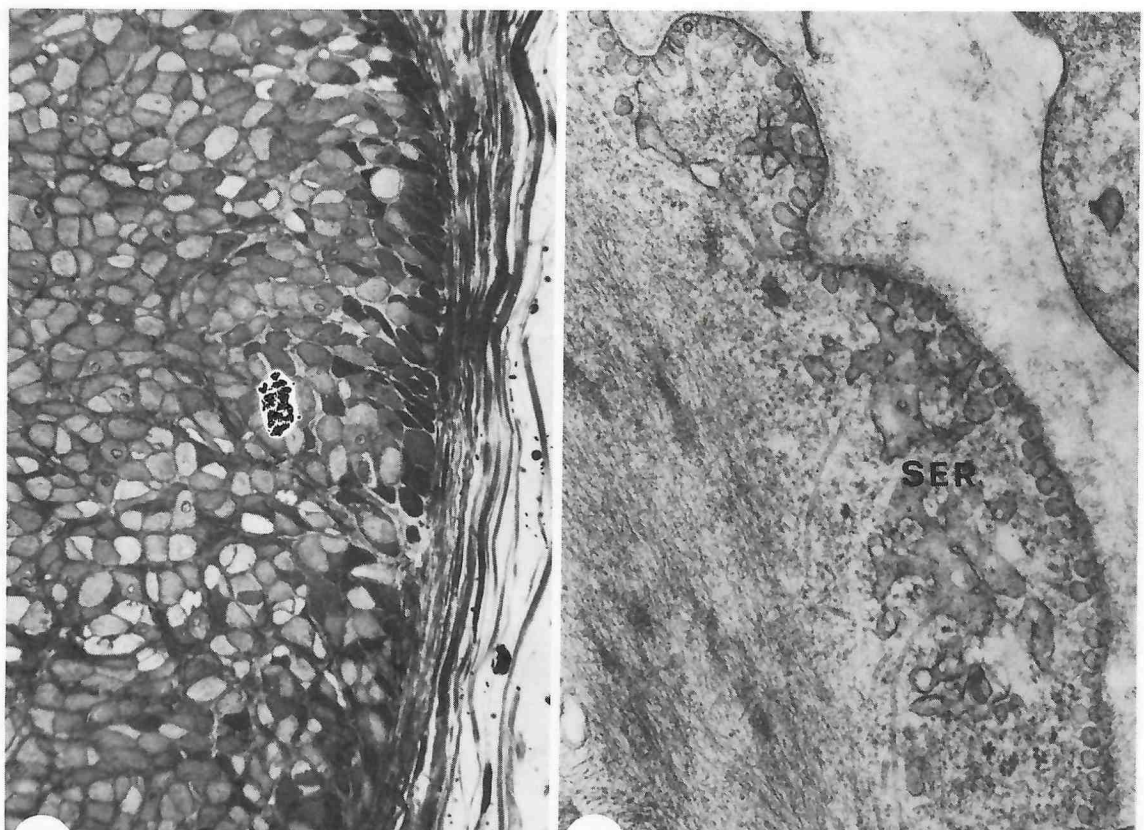
The morphology of the entire left colon is basically identical to that previously described for the descending colon (Faussone-Pellegrini and Cortesini 1984). The changes from the organization typical of the right colon to that characteristic of the left colon gradually occur all along the transverse colon in all the cases examined. In fact, moving from right to left, even if the beginning and (or) ending of the typical appearance of one another colon shows individual variations, it is possible to see the innermost smooth muscle cells separate from each other and also separate themselves from those of the bulk of the circular muscle layer (Figs. 14 and 15). In this way, they form a muscle network with large meshes (Fig. 17) apposed to the bulk of the circular muscle layer. As we proceed distally, the muscle network, i.e., the inner circular muscle layer of the left colon, thickens even more owing to a gradual increase in the row number (from 2−3 up to 8−10). The cytology of the inner smooth muscle cells (Fig. 16) is, however, absolutely identical to that of those located innermost in the right transverse colon (Figs. 5 and 6).

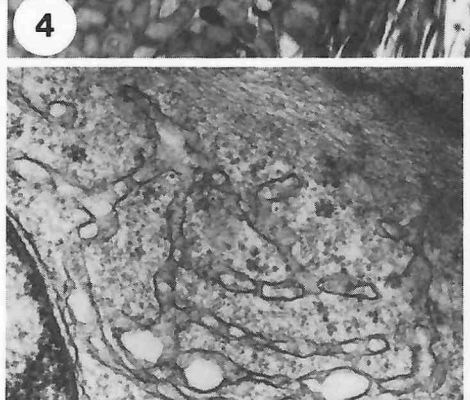
Just as in the right colon, a ganglionated nerve plexus with large meshes is present along (Fig. 18*b*) and inside (Fig. 18) the fibrous lamella that borders the inner surface of the circular muscle layer, and several nerve fibers run between the inner and the outer portions of the circular muscle layer (Fig. 18*c*). In the left as opposed to the right colon, neither of these plexuses is ever accompanied by ICC.

Discussion

Peculiar neuromuscular structures have been observed along the submucosal border of the circular muscle layer of the entire human colon (from the caecum as far as the sigmoid colon). These structures, which must play some specific role in colonic motility, are characteristic of this level and are not found in any other region of the gut. This study also reveals that these structures differ according to the colonic level. So it must be assumed that their role is region-specific.

To sum up, our data allowed us to identify two portions (an inner and an outer one) in the circular muscle layer of the entire human colon, as previously stated for the descending colon (Faussone-Pellegrini and Cortesini 1984). The smooth muscle cells of these portions differ in their organization and cytology. But in examining the entire colon we found that the cytological features and the number of smooth muscle cell rows in the inner portion differ in the distal (transverse and descending) and proximal (caecum and ascending) colon. Furthermore the present data reveal that in humans two nerve networks are present, both running along the entire colonic length. One of these corresponds to the outermost portion of the submucosus plexus, and runs along and inside a fibrous lamella which borders the submucosal surface of the colonic circular muscle layer. The second nerve network runs between the outer and





FIGS. 4–6. Right transverse colon. Inner portion of the circular muscle layer. FIG. 4. No subdivision of the circular muscle layer is evide only here and there some of the inner smooth muscle cells are deeply stained. Semithin section. Toluidine blue. ×600. FIGS. 5 and 6. Cytolo al peculiarities of the innermost smooth muscle cells as revealed by electron microscope. FIG. 5. Long rows of caveolae and wide cister of the sarcoplasmic reticulum (SER) are distributed along the submucosal surface of the innermost smooth muscle cells ×37 500. FIG. 6. Numerous interconnected cisternae of the sarcoplasmic reticulum are located near the nucleus ×37 500. (*b*) Wide, branching cisternae of sarcoplasmic reticulum and long rows of caveolae are distributed along the cell periphery and the contact areas between adjacent smooth mus cells. Note at the level of contact areas, the caveolae opening onto the plasma membranes of the two opposite smooth muscle cells ×25 0

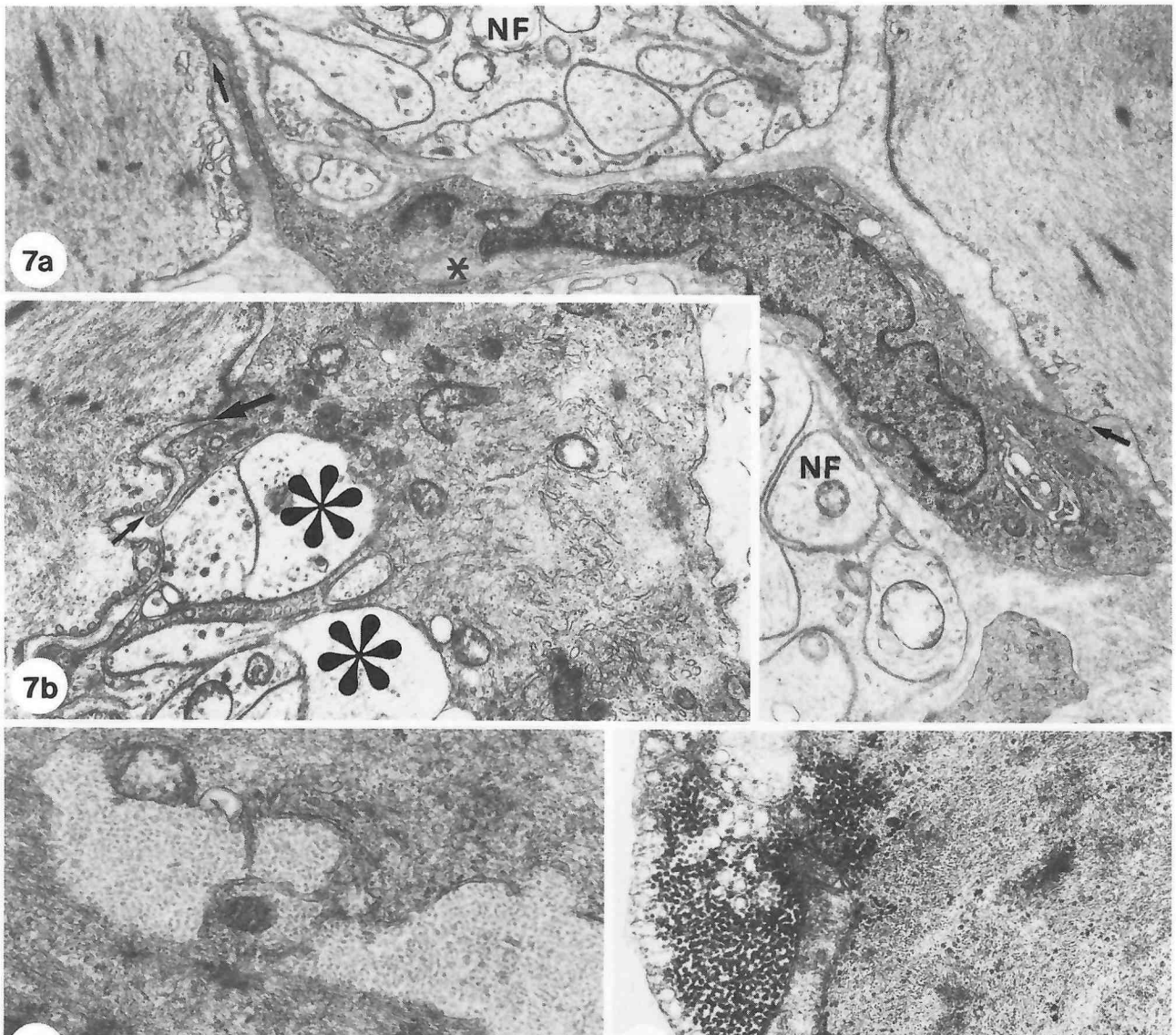
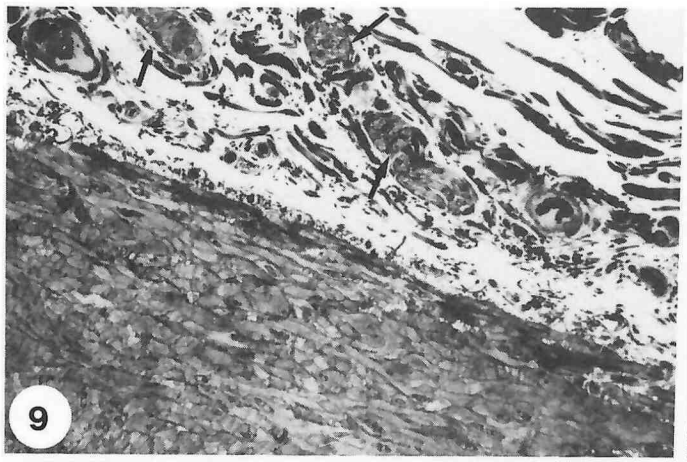


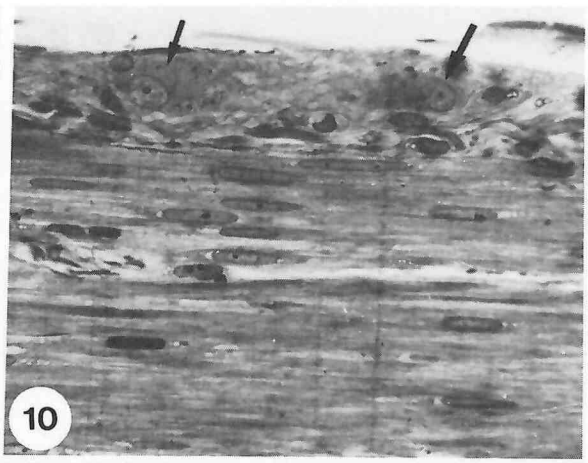
FIG. 7. Right transverse colon. (*a*) An ICC intercalated between two nerve bundles (NF) and bridging two smooth muscle cells (arrow ×13 000. (*b*) Detail of the cytoplasm of an ICC and of its relationships with nerve endings (large asterisks) and smooth muscle cells (arrow ×9000. FIG. 8. Right colon from caecum as far as the right transverse colon. Clusters of glycogen particles. (*a*) Uranyl acetate and bism subnitrate, ×25 000. (*b*) Uranyl acetate and lead citrate, ×37 500.

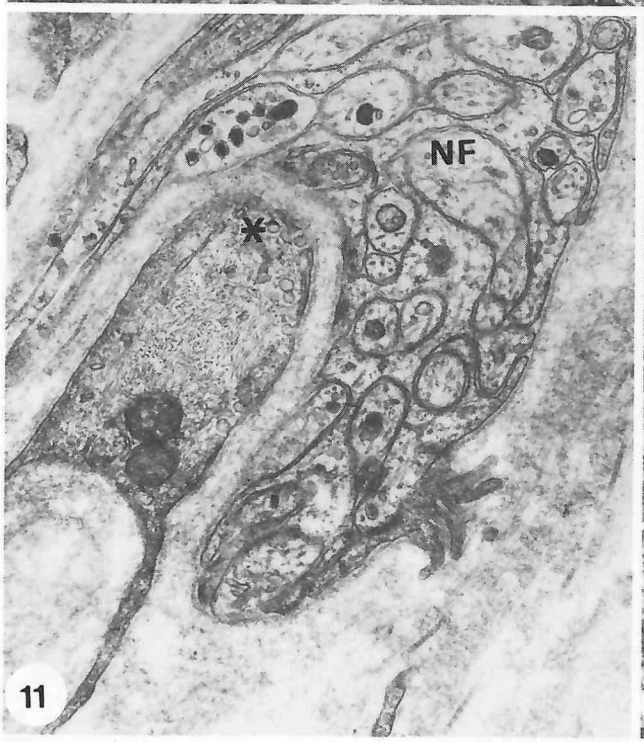
inner subdivisions of the circular muscle layer. Moreover, only in the right colon do some ICC accompany these plexuses.

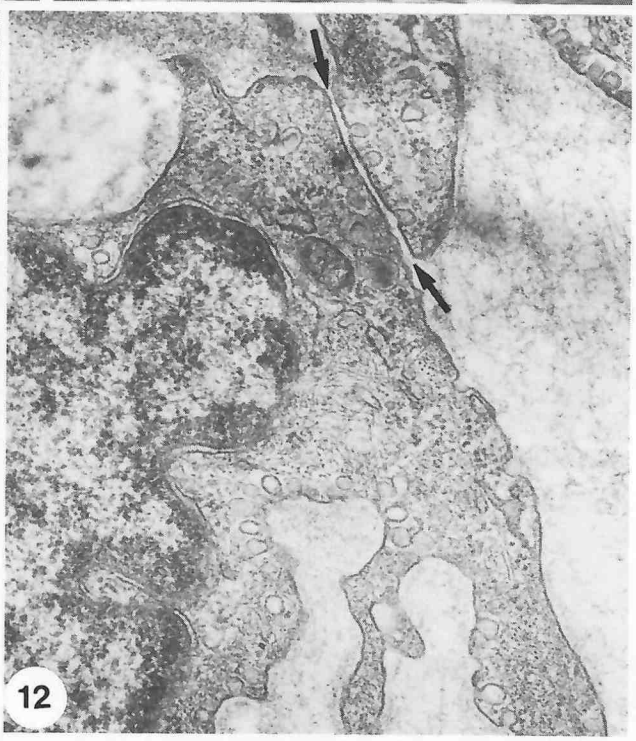
When we consider the specific organization of both these muscular and nerve structures in each colonic level, we can conclude that the organization of the left transverse colon is identical to that of the descending colon, but it is very different from that found in both the caecum and ascending colon. The organization of both the latter regions, moreover, shares noticeable similarities with that of the human small intestine (Faussone-Pellegrini and Cortesini 1983), whereas the right transverse colon has an organization partially similar to that of the right colon and partially similar to that of the left colon. From the above, consequently, we can identify two main colonic regions: a right (proximal) region, which is similar to the small intestine, and a left (distal) region of a purely "colonic" type.

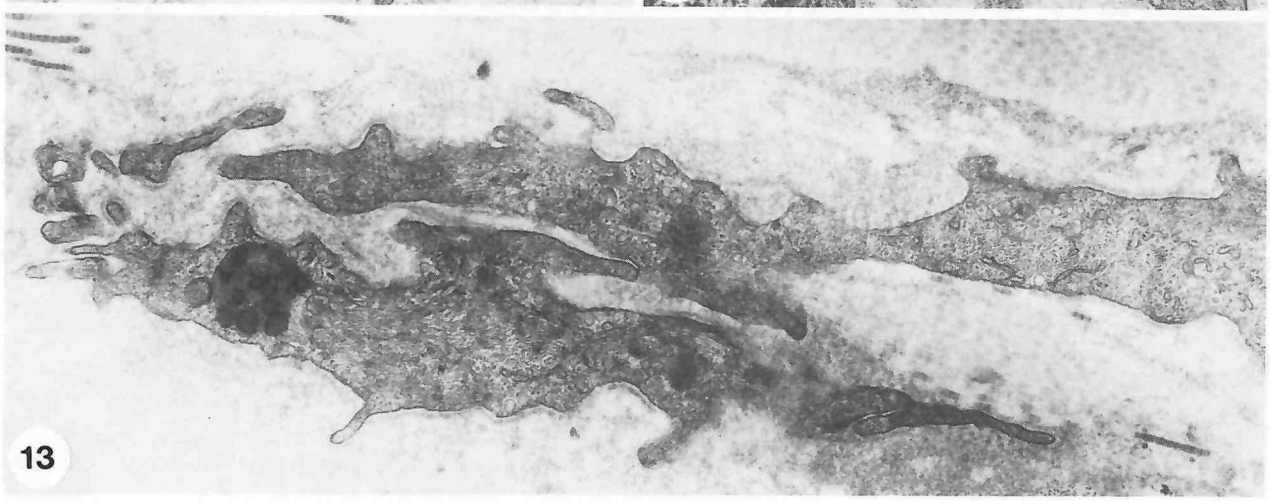
Data we obtained also showed that the peculiar organizat of the submucosal border of the colonic circular muscle la is completely different from that of other animal species. example, only humans share a "special" morphology of innermost circular smooth muscle cells. Moreover, in huma in addition to the ganglionated nerve plexus running, as other mammals (Stach 1972; Faussone-Pellegrini 1983, 19 Christensen et al. 1987; Berezin et al. 1988), all along the s mucosal border of the circular muscle layer, there exists a r nerve network between the two circular muscle layers. Furth more, while in other mammals ICC are frequent through the entire colon, in humans they only occur in the right co and are uncommon. Furthermore, gap junctions between I and between them and smooth muscle cells are infrequent, are not apparent between the smooth muscle cells of both cular muscle layers.



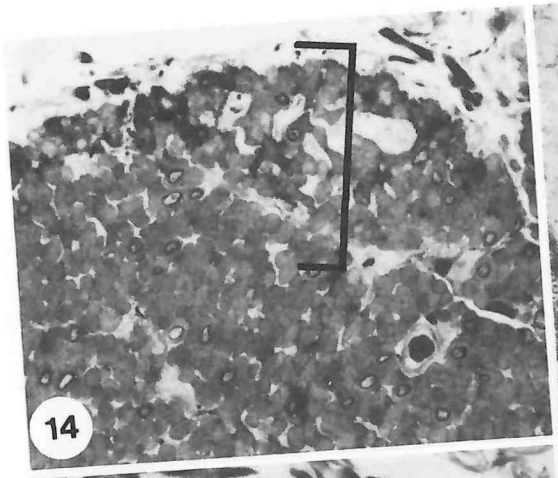








FIGS. 9–13. Ascending (FIG. 9) and right transverse (FIG. 10) colon. Nerve plexus, comprehensive of both nerve fibers and neurons (arrow running near (FIG. 9) and inside (FIG. 10) the fibrous lamella bordering the submucosal border of the circular muscle layer. Semithin sectio Toluidine blue. FIG. 9, ×200. FIG. 10, ×600. FIGS. 11–13. Right colon, from caecum as far as the transverse colon. FIG. 11. A single IC (asterisk) located inside the fibrous lamella and accompanying the nerve fibers (NF) of the plexus shown in FIGS. 9–10, ×25 000. FIG. A single ICC contacting, with a gap of 20 nm, one of the innermost smooth muscle cells (arrows), ×37 500. FIG. 13. A group of ICC, ×25 0



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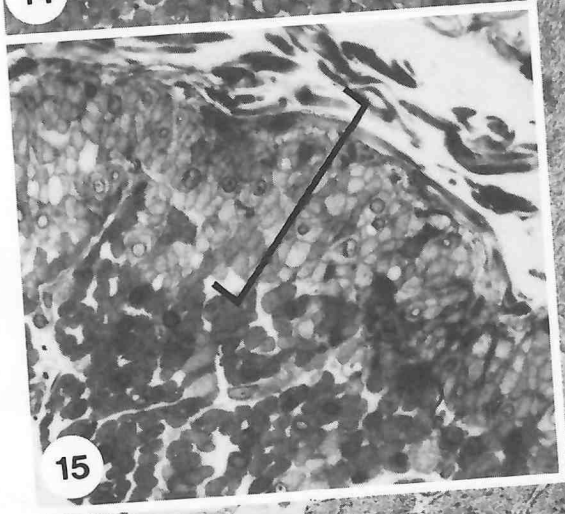

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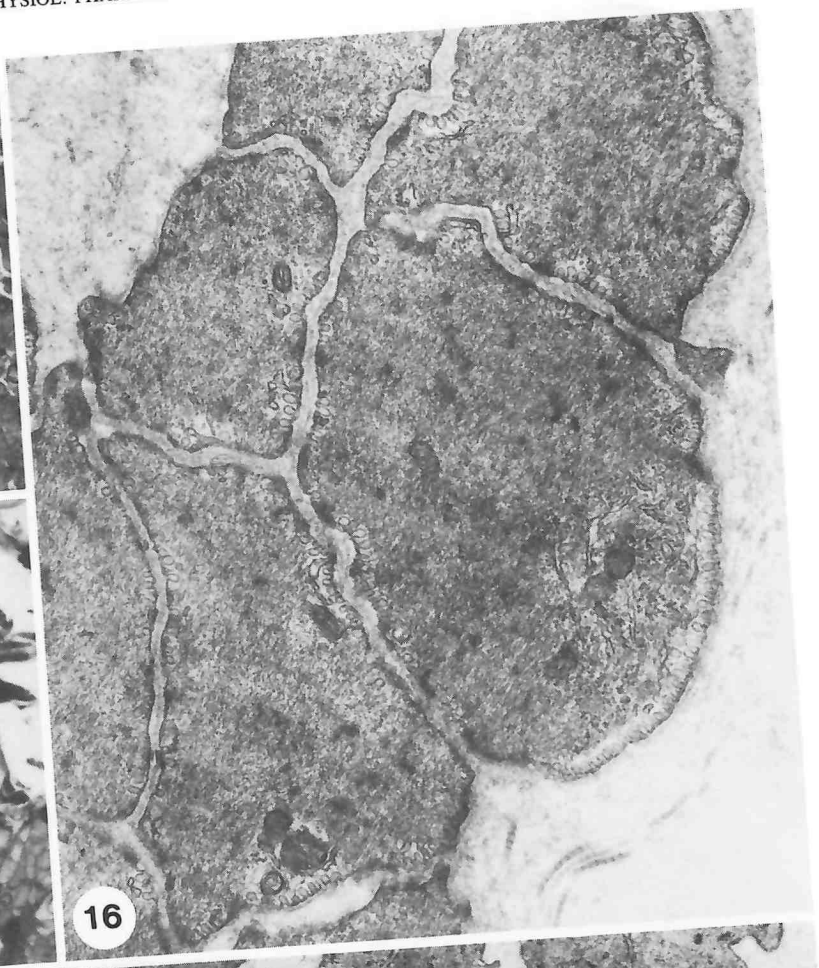

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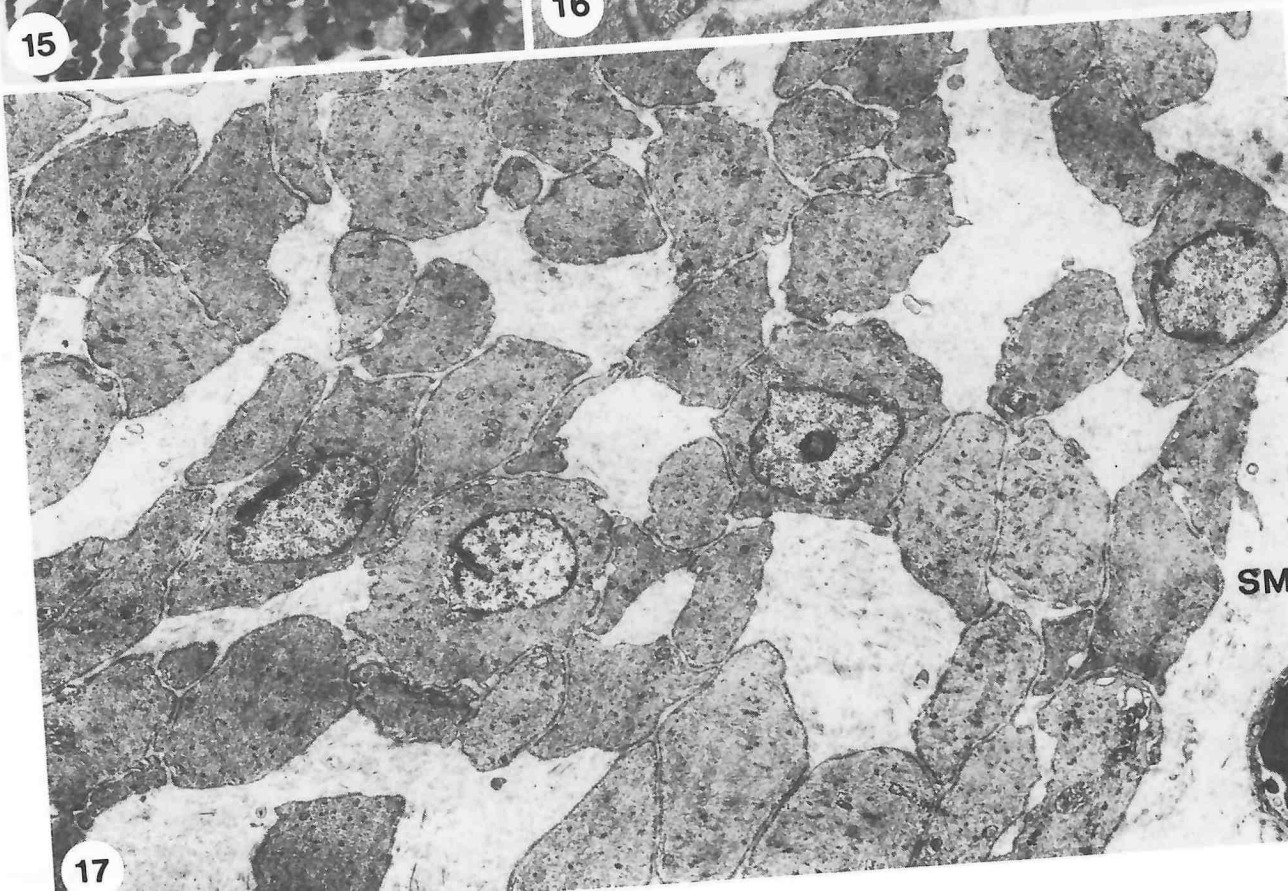

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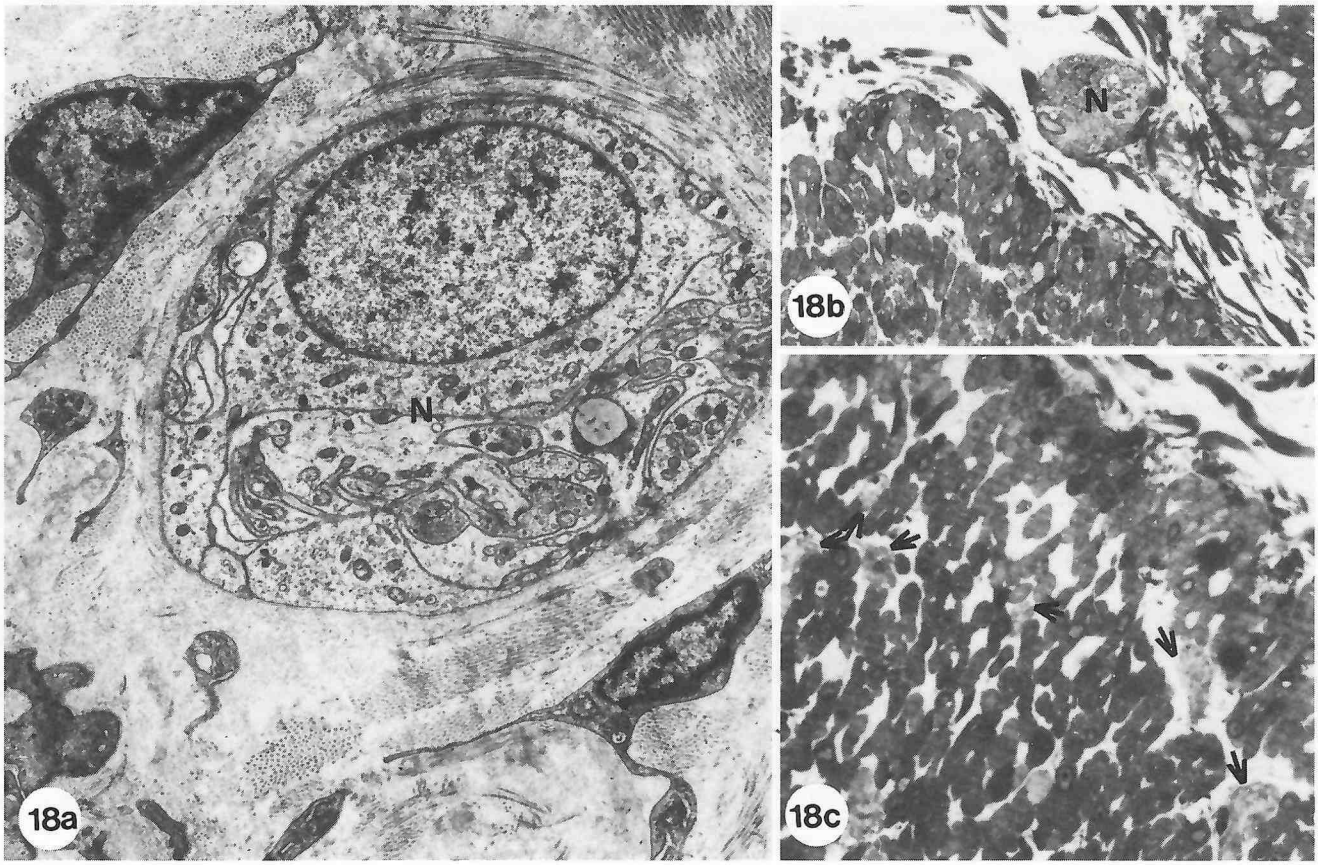

FIG. 18. Left colon nerve plexuses. (*a* and *b*) Nerve bundles and a ganglion (N) on the submucosal surface of the circular muscle layer. (*a*) ×20 000. (*b*) Semithin section. Toluidine blue. ×600. (*c*) Nerve bundles (arrows) running between the two subdivisions of the circular muscle layer. Semithin section. Toluidine blue. ×600.

The functional importance of the complex organization of the inner border of the circular muscle layer needs to be elucidated. In some laboratory mammals, as cat, pig, and dog, this border possesses spontaneous electrical activities (Caprilli and Onori 1972; Huizinga et al. 1983; Durdle et al. 1983; Du et al. 1987; Smith et al. 1987*a*; Du and Conklin 1989; Barajas-Lopez et al. 1989), indicating the existence at this level of a population of pacemaker cells. In the dog ICC have been found at this level (Berezin et al. 1988) and recordings of their spontaneous electrical activities were obtained (Barajas-Lopez et al. 1989; Langton et al. 1989).

Couturier et al. (1969) recorded slow waves from human circular muscle, but they were unable to demonstrate their possible site of origin. From the present study we can recognize in humans two putative pacemaker cell types at the level of the inner circular muscle layer, i.e., ICC and smooth muscle cells. Moreover, the latter share a "special morphology" (i.e., they are rich in sarcoplasmic reticulum, glycogen particles, caveolae, and wide cell-to-cell junctions). However, at variance with the dog, we must also note in humans the paucity of ICC. Therefore if the submucosal border of the colonic human circular muscle layer is a pacemaker region, then perhaps the pacemaker role is played by the "special" smooth muscle cells, as previously suggested (Faussone-Pellegrini and Cortesini 1984) for the descending colon. This hypothesis is mainly based on the fact that these cells are present over a wide colonic area and their morphology is identical to that of the pacemaker cells in the human renal pelvis (Rizzo et al. 1981). On the other hand, the possibility that a pacemaking tissue might be located within the bulk of the circular muscle seems to be excluded since neither ICC nor "special" smooth muscle cells were detected there. However, it must be remembered that in the human, at variance with other mammals, a putative pacemaker tissue has been described at the myenteric plexus level (Faussone-Pellegrini et al. 1990). This report is in agreement with Huizinga et al. (1985) and Huizinga and Chow (1988) physiological data, but does not exclude the possibility of a second pacemaker tissue located at the submucosal

FIGS. 14–17. Left colon (left transverse colon as far as the sigmoid colon). Inner portion of the circular muscle layer. FIGS. 14 and 15. The innermost smooth muscle cells, as we proceed distally, are even more separated from each other and from the outer circular muscle layer, forming a muscle network (bracket) of increasing thickness apposed to it. Semithin sections. Toluidine blue. FIG. 14. Left transverse colon ×600. FIG. 15. Descending colon ×600. FIG. 16. Long rows of caveolae and wide cisternae of the sarcoplasmic reticulum characterize the innermost smooth muscle cells ×25 000. FIG. 17. Muscle network or inner portion of the circular muscle layer. The meshes of this muscle network are occupied by connective tissue completely devoid of nerves and other cell types. SM, tela submucosa ×4400.

border of the circular muscle layer, as in the dog.

Then, two neuromuscular structures distinguish the human colon from the other parts of the gut which presumably represent the morphological substratum of the motility of the "colonic" type. In addition, the regional structural differences, which characterize exclusively the submucosal border of the circular muscle layer should represent the substratum of the specific motility for each colonic region. In our opinion, these structural differences and, in particular, the differences in the presence and distribution of both ICC and smooth muscle cells with a "special" morphology, are the most intriguing results we obtained in humans in regard to the functional implications for regional variation in pacemaking. In fact, the hypothesis that the "special" smooth muscle cells are the colonic pacemaker cells may be difficult to sustain for the entire colon, and therefore, we should consider that the pacemaker role is played by the "special" smooth muscle cells from the transverse colon as far as the sigmoid regions, where they constitute the prominent cell type, and by ICC in the other regions (in the caecum and ascending colon). Nevertheless, the attribution of this role to two different cell types depending on their location in one or other regions might be too simple and remains to be confirmed for each colonic level. In the human right transverse colon, for example, ICC and "special" smooth muscle cells are simultaneously present, and in the proximal colon, even if only ICC are present, we must bear in mind that the innermost portion of the circular muscle layer has a similar organization to that of the small intestine (Faussone-Pellegrini and Cortesini 1983). This assumption, however, might agree with the functional data (Sarna et al. 1980; Gill et al. 1986; Dapoigny et al. 1988), indicating the existence of two "types" of human colon, i.e., the right and left colon. Moreover, with these data we can consider the transverse colon, which is similar to both the distal and proximal regions, as a transitional region.

The main question arises as to whether or not ICC and "special" smooth muscle cells play the same role or possess identical electrical properties. For example, the presence of one or another cell types might explain the differences in frequency of the electric signals recorded in the various colonic regions of humans (Sarna et al. 1980). Future recordings from every cell type (ICC and smooth muscle cells) and characteristic of every gut region would enable us to clarify the roles they play.

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