The Oncological Characteristics of Colonic Polyps in Humans in View of Morphogenesis of Experimental Intestinal Tumors

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ABSTRACT

A comparative study of the morphology and morphogenesis of intestinal epithelial tumors induced by treatment with 1, 2-dimethylhydrazine in over 2,000 rats and 1,415 polypoid lesions in the human colon and rectum was conducted. The development of experimental cancer starts with the expansion of the proliferative zone in intestinal crypts. The first cancer lesion to occur is carcinoma *in situ* which develops in the superficial layers of flat mucosa. Further evolution of carcinoma *in situ* with invasion within the lamina propria of the mucosa leads to superficial cancer development. Invasive cancer develops, when neoplastic structures extend into the submucosal layer. Therefore, experimental intestinal adenocarcinoma appears *de novo*. Morphogenetic studies showed that the preinvasive stage of cancer may persist for a long time. In such cases, structural and cytologic signs of epithelial atypism and pleomorphism may be of vital importance for the detection of malignancy. Hence, when non-invasive polypoid lesions in humans are checked for malignancy, emphasis should be placed on the detection of the following morphologic manifestations of atypia: a considerable decrease or complete absence of goblet cells, epithelial pseudostratification or even a multilayer structure, location of mitoses in the superficial areas of tumors and an increasing proportion of abnormal mitoses, appearance of papillary and villous structures and changes in their configuration, bizarre outlines of tumor glandules, cellular and nuclear polymorphism, appearance of cribriform structures, numerous plasma cells and karyorrhexis-affected lymphocytes in tumor stroma, etc. Invasion was detected in the dissected intestinal segments in 70% of the cases in which the said changes were observed in biopsy. No morphologic signs of malignancy was detected in adenomatous polyps. On the other hand, such early stages of adenocarcinoma development as carcinoma *in situ* and superficial cancer at the back-

ground of intact flat mucosa were quite frequent. Moreover, sometimes, even very small (2–3 mm in dia.) exophytic neoplasms showed morphologic signs of malignancy, invasion included. All these findings suggest that polypoid cancers and glandular villous tumors are malignant *ab initio*. In the absence of invasion, they may be identified as carcinoma *in situ* or superficial cancer.

INTRODUCTION

An early detection of cancers of the rectum and large bowel by morphological means at a pre-invasive stage requires an adequate knowledge of the morphogenesis of these neoplasms. A study of tumor morphogenesis should be, in turn, based on the understanding of the biological characteristics of tissues and their morphogenetic potentialities. It is clear that an all-round study of these problems on human material is not feasible. Lockhart-Mummery and Dukes (1) have stressed that an investigation in tumors of the colon (as well as any other localizations — K. P. and O. Ch.) with clinical manifestations might yield scarce information on the process of their development. These authors also pointed to tremendous difficulties involved in a study of premalignant changes.

In this connection, experimental tumor models, which simulate human tumorigenesis adequately, may be of great help. The present paper is concerned with a comparative study of the morphology and morphogenesis of experimental intestinal tumors in rats and colonic and rectal neoplasms in man. It should be pointed out that such investigations were recommended by a recent Workshop on Colo-Rectal Cancer of the International Union Againsts Cancer (2).

Our study of human material was mostly concerned with polypoid lesions, the malignant potential of which is still being much discussed (3–9). Overt cancers, resulting from a far advanced progression, are generally easier to detect and, therefore, these lesions received less attention in our work.

Experimental intestinal tumors were induced in rats by the treatment with 1, 2-dimethylhydrazine. There is a consensus on the similarity of these tumors to those in humans with respect to such features as gross appearance and microscopic structure, extension, histochemical, electron microscopical and immunologic characteristics, clinical maniferstations, etc. (10–23).

MATERIALS AND METHODS

The morphogenesis of experimental intestinal tumors was studied in over 2,000 rats, which had been treated with 1, 2-dimethylhydrazine by different routes (intravenously, subcutaneously, intraperitoneally or *per os*), in

different doses (3, 7, 21, 42, and 200 mg per kg body weight) and at different intervals (daily, weekly, single administration) (13, 24). The material was examined microscopically at different intervals after carcinogen treatment; various methods of preparation staining were employed (hematoxylin and eosin, picrofuchsin by Van Gieson, Mayer's mucicarmine, alcian blue, methods of Hotchkiss, Foot, Gordon-Swift and Masson). In some cases, enzymohistochemical (14) and autoradiographic studies (13) were conducted.

One thousand four hundred and fifteen samples of polypoid lesions collected at the Laboratory of Pathomorphology of the Institute during 25 years (1950–1975) were used in the study of human colonic and rectal tumors. These specimens were obtained at the Institute's clinics by biopsy (1,119 cases) or by surgery (296 cases). In most cases, we studied histological preparations stained with hematoxylin and eosin. Sometimes, additional sections (often stepped ones) were made and stained with Mayer's mucicarmine, alcian blue and by the method of Hotchkiss.

Our diagnostic data were compared with those on record at the Laboratory of Pathomorphology by the "blind" method, i. e. the preparations from the collection had no accompanying documents and we examined them without knowing the final diagnosis of the Pathology Department.

Polypoid lesions of the colon were classified by the Pathomorphology staff into several groups (see Table 1). The so-called proliferating adenomatous and glandular-villous polyps revealed chiefly epithelial pseudostratification and a decreased number or even a complete absence of goblet cells as well as a frequent increase in mitoses. Since pure villous polyps are relatively rare, they were joined to an intermediate group and graded as Glandular-Villous Polyps. About half of the so-called malignant polyps showed a profound invasion of the underlying layers of the intestinal wall, the remainder revealed pronounced atypia and pleomorphism.

In addition, 100 invasive adenocarcinomas of the colon were examined to compare their structure and cytologic characteristics with those of the polypoid lesions under study. In order to establish the characteristics of intestinal epithelial proliferation, the dynamics of healing of experimental lesions of the rat's intestine (25) as well as preparations obtained from patients with chronic ulcerative colitis (16 cases) and chronic dysentery (31 cases) were studied.

RESULTS

Since the development of morphological changes involved in experimental tumorigenesis in the intestines was described in detail in our previous reports (12, 13), only a general outline of tumor morphogenesis is given below.

The zone of proliferation in intestinal crypts becomes extended at early stages of carcinogen treatment, as indicated by the patterns of mitoses and ^{3}H-thymidine-labelled epithelial cells in the superficial departments of the mucosa. Proliferating enterocytes are often observed even in the mouth of crypts. In our opinion, this occurs because transformed enterocytes do not differentiate and continue to proliferate during their passage along the crypt. Disturbances in the process of differentiation and proliferation seem to be caused by the mechanism by which DNA-synthesis by enterocytes does not cease as the latter reach a certain level of the crypt (26).

It should be mentioned that it is in the superficial department of the crypt, outside the normal zone of proliferation (where transformed enterocytes continue to divide) that carcinomas *in situ* develop at later stages (Fig. 1 a). Carcinomas *in situ* are confined to the crypt; they may be of triangular or elongated oval shape, and are lined with pseudostratified basophilic epithelium with enlarged and frequently hyperchromatic nuclei. They reveal numerous mitoses (abnormal ones included), and most enterocytes appeared to be labelled in the experiments involving the treatment of animals with ^{3}H-thymidine one hour before their sacrifice. Carcinomas *in situ* arose in the microscopically-unaltered mucosa; special studies showed no hyperplastic changes to precede tumor formation. Once the tumor locus extends beyond the crypt limits, i. e. as the lamina propria of the mucosa is invaded, superficial cancer begins to develop (Fig. 2 a). Changes in tumor glandule configuration and their budding were assumed by us to indicate such initial invasion. It should be mentioned that superficial carcinomas often revealed papillary and villous structures. Numerous wandering connective-tissue cells are observed around the loci of carcinoma *in situ* and, particularly, in superficial cancer. As superficial cancer grows, the surrounding and underlying mucosa becomes hypertrophic and, therefore, this cancer is generally located in the superficial layers of dome-like eminences.

Superficial cancers continue to grow and, finally, extend through the entire thickness of the mucosa. Invasive adenocarcinomas develop as tumor structures extend through t. muscularis mucosae. The tumors which sat on the crests of mucosal folds were, as a rule, exophytic, while those, which arose in the inter-fold spaces, were mostly endophytic and had a wide zone of invasion.

Histochemical (14), biochemical (27) studies and electron microscopy (15) showed that some characteristics, typical of induced adenocarcinomas, are initially observed in carcinomas *in situ* and, subsequently, they do not undergo any changes. The available evidence demonstrates that carcinoma *in situ* is virtually a cancer rather than a pre-cancer, as it is believed by some

authors (28). Hence, experimental intestinal cancer develops *de novo*; at any rate, it is not preceded by the formation of adenomatous polyps and hyperplasia of the mucosa. Application of different dosage and intervals of exposure to carcinogens has an effect on the localization, extent and time of formation of tumor but does not influence their morphogenesis.

It is, probably, the most significant practical conclusion of the present morphogenetic study that adenocarcinomas are seldom characterized by pronounced pleomorphism. This peculiarity is a source of frequent difficulties involved in the assessment of such lesions when invasion is not apparent. It is not surprising, therefore, that in many experimental reports overt non-invasive adenocarcinomas are often regarded as adenomatous polyps (29–35). It is certain that only an adequate understanding of all successive changes leading to invasive cancer formation may provide a means for detection of the disease as early as at the preinvasive stage.

Our attention was focused on the following manifestations of structural and cytological atypia in the study of polypoid lesions in human intestines. The most frequent one is the decline in the secretory activity of the intestinal epithelium. As a result, the number of goblet cells decreases or they disappear completely. Some authors maintain that such changes manifest the dedifferentiation and dysplasia of the intestinal epithelium (36–38).

The pseudostratification of the epithelium is another equally frequent abnormal feature. Kozuka (39) made an attempt to work out a quantitative gradation of epithelial pseudostratification in the mucosal polyps of the large intestine and established five grades of the degree of this phenomenon. In our study, we considered only Grades IV and V (according to Kozuka), i. e. when nuclei were scattered throughtout the greater part of the height of the epithelium, since we thought that less pronounced changes are manifestations of some functional conditions of the epithelium rather than tumor lesions. It seems still more likely because, according to Kozuka, the initial grades of epithelial pseudostratification are generally observed in juvenile and hyperplastic polyps which are not usually referred to as tumors, and are considered as having no relation to carcinogenesis whatsoever.

Certain investigators (36, 40, 41) believe the pseudostratification of the epithelium to be a result of its enhanced proliferation. Other authors (42–44) detail a separate group of proliferating polyps predominantly on the basis of this characteristic. However, application of modern special techniques (mitotic index and labelled nuclei index determinations) has not so far succeeded in showing that pseudostratification is due to an enhanced epithelial proliferation only and is not actually a kind of tumor atypia. It is not likely that the single-layer enterodermal epithelium may normally develop pseudo-

stratified structures. To test this hypothesis, we conducted a study on intestinal lesions which undeniably involve proliferation (experimental post-injury cell regeneration (25); chronic ulcerative colitis and chronic dysentery) and failed to detect in them anything similar to epithelial pseudostratification observed in tumors.

In some neoplasms, the layers of epithelial cells are so distinct that the top layers are not connected to the basal membrane. In such cases, it is even possible to say that the epithelium has a multi-layer structure. Pseudostratification and multi-layer structure generally occur in conjunction with other manifestations of epithelial atypia, such as loss of polarity, basophilia of cytoplasm, nuclear hyperchromatosis, enlarged nuclei, increased number of nucleoli, etc. Moreover, the outlines of tumor glandules usually show all kinds of variation. These glandules often have a back-to-back appearance, with very little intervening stroma.

The above features of atypia are particularly frequent and pronounced in tumors with papillary and villous structures. There is convincing evidence that intestinal neoplasms with villous structures are characterized by an increased malignant potential (40, 45, 46). Another atypical structure is the change in the outlines of villi which form flask-like extensions where secondary glandules develop.

We consider the location of mitoses on tumor surface a significant feature of epithelial atypia. Our experimental findings (see above) and the data of other authors (26, 47) show it to be a manifestation of disturbed differentiation of enterocytes. Andreassen (40) observed the shift of mitoses toward the gut lumen in all villous adenomas and most glandular-villous tumors; such a shift is much less pronounced in adenomatous polyps. Lane *et al.* (48) reported the arrangement of mitoses and Deschner and Lipkin (49) — that for ^{3}H-thymidine-labelled cells on the surface of adenomatous polyps. However, we are inclined to think that their illustrations show non-invasive malignant tumors rather than adenomatous polyps. Our experience shows that superficial mitoses occur in tumors with distinct atypia only, particularly, when villi are observed (Fig. 3). Mitoses often occur even in areas where cells are shed. Among mitoses, there may be abnormal ones. A special study of mitotic conditions in colonic neoplasms (43) revealed that the number of abnormal mitoses in the so-called proliferating villous polyps with grand atypia is four times that in normal mucosa. There are generally few mitoses in adenomatous polyps and all of them are located in the deeper layers of a neoplasm.

When these atypical features are marked, neoplasms often reveal gland budding and cribriform structures which are pathognomonic for cancer,

Table 1. *Comparison of Diagnostic Data of Department of*

Diagnosis of Department of Pathology	Number of cases	Diagnosis after: Adenomatous polyp	Juvenile polyp	Hyperplastic polyp
Adenomatous polyp	511	206	95	15
Proliferating adenomatous polyp	462	52	6	2
Glandular-villous polyp	42	6	2	
Proliferating glandular-villous polyp	132	5		1
Proliferating adenomatous or glandular-villous polyps, malignancy suspected	68			
Malignant adenomatous or glandular-villous polyps	200		1	
Total	1415	269	104	18

according to Ekelund and Lindström (37).

Epithelial atypism usually occurs in conjunction with changes in tumor stroma which appear as clusters of plasma cells and lymphocytes. The latter seem to penetrate into the basal layers of the epithelium and probably disintegrate there, because fragments of nuclei are often to be seen there. This, however, does not involve the necrosis of epithelial cells and, therefore, nuclear detritus does seem to be caused by the karyorrhexis of lymphocytes. It may be supposed that these changes are a morphologic manifestation of some immunologic reactions to epithelial atypia development.

Pathologists often resort to the diagnostic criteria of gastrointestinal cancer suggested by Swinton and Warren (50). They believe that, at least, two of the following three manifestations are sufficient for the diagnosis of cancer: (1) anaplasia, (2) architectural irregularities and (3) invasion. It is evident that the above-described atypical features of the epithelium correspond to the first two manifestations.

In view of the said criteria, we have classified the polypoid lesions under study into several groups (Table 1). The morphology of such lesions as juvenile and hyperplastic polyps as well as inflammatory pseudopolyps has been studied sufficiently (51) and does not require further elucidation. We referred glandualar lesions, which extended into the gut lumen and did not differ much from the glands of normal colonic mucosa, to as adenomatous polyps (adenomas). Superficial layers of these benign tumors alone revealed some-times a decreased secretion of mucus and moderate epithelial basophylia. Most of the adenomatous polyps had a distinct connective-tissue pedicle.

Pathology and Results of Morphologic Re-Assessment

re-assessment						
Ca *in situ* and superficial cancer	Exophytic adenocarcinoma	Malignant glandular villous tumor	Other lesions (carcinoids, ontogenetical defects, etc.)	Inflammatory pseudopolyps	Hypertrophic fold of mucosa	Diagnosis uncertain
76	10	52	4	11	29	13
115	43	213		2		29
2		28				4
5	3	107		1		10
9	8	51				
7	25	161	2			4
214	89	612	6	14	29	60

We failed to detect any changes in the adenomatous polyps that could be identified as malignancies.

Carcinomas *in situ* and superficial cancers usually sat on the hypertrophic folds or dome-like swellings of the mucosa, and the greater the loci of superficial cancer, the more marked the hyperplasia of the underlying mucosa was. Carcinomas *in situ* were located within the boundaries of one or several crypts (they were literally "in place"), while superficial cancers spread beyond these limits, invaded the lamina propria of the mucosa and extended over relatively larger areas. Mostly carcinomas *in situ* revealed a markedly reduced secretion of mucus, no goblet cells, pseudostratification of the epithelium with loss of polarity, cytoplasmic basophilia and hyperchromatic nuclei with an increased number of nucleoli and mitoses in superficial layers of tumors (Fig. 1 b). Superficial cancers may have similar features, though they may be characterized by a greater pleomorphism (Fig. 2 b).

We referred round-shaped pedunculated polypoid tumors with structural and cytologic characteristics of malignancy to as exophytic adenocarcinomas (Fig. 4). All of them appeared to consist of homogeneous tumor tissue. There was only one tumor with a stalk which showed intermittent features of an overt adenocarcinoma and adenomatous polyp. Yet, this lesion was not identified by us as a malignant adenomatous polyp. Such tumors will be further considered in the Discussion.

Neoplasms with marked villous features were identified as glandular-villous tumors. Since typical villous tumors are very rare, they were not classified as a separate group. A highly pronounced structural and cytologic

atypia was particularly frequent in glandular-villous tumors. Morphologic changes were minor in 19 glandular-villous tumors only and this suggested that those tumors were not malignant. However we found tumor invasion into the submucosal and muscular layers in the three surgical preparations of those neoplasms. Hence, invasion cannot be ruled out on the basis of biopsy even though glandular-villous tumors may be quite morphologically — benign in appearance (Fig. 5). It should be pointed out that even the smallest glandular-villous tumors examined by us (2–3 mm in dia.) had anaplastic features and some of them showed invasion (Fig. 6). One of the peculiarities of these neoplasms is that they transform into mucinous carcinoma in the deeper layers. Therefore, we identified all tumors of this type as malignancies. We did not regard the loci of marked polymorphism as signs of malignancy in some neoplasms with distinct atypia but considered them to be a result of the further progression of the tumor, because the anaplastic background itself conformed to the criteria of malignancy.

Apart from the said glandular-villous tumors, we observed their modifications which consisted of light goblet-cell epithelium. Although such tumors are benign in appearance, they may invade the pedicle of the neoplasm (Fig. 7). A thorough examination may reveal anaplastic areas in them. According to Starr (52), a significant production of mucus in polypoid lesions should arouse relevant suspicion, since an elevated pressure may promote invasion development.

Sometimes, diagnosis could not be made due to the irregular orientation of the tissue specimen or artificial changes which took place during biopsy.

As it is evident from Table 1, our assessment of the morphologic material yielded a much greater number of tumors with malignant features, and a considerable proportion of much early forms as carcinoma *in situ* and superficial cancer fell into that category.

Out of 514 cases*) in which our retrospective examination of the biopsy material led to a diagnosis of malignant glandular-villous tumor or exophytic adenocarcinoma, 183 patients had been operated on radically. The invasion of the submucosal and still deeper layers of the intestinal wall had been found in 126 patients (69%). Those lesions were mostly glandular-villous neoplasms. Such a high rate of detection of invasive lesions shows that the structural and cytological criteria of malignancy used in our study are reliable.

*) This figure does not include 186 cases in which the primary diagnosis of malignant adenomatous or glandular-villous polyps was established by the Department of Pathology.

DISCUSSION

The experimental study of the morphogenesis of intestial cancer shows it to develop *de novo*. Disturbances in the proliferation and differentiation of enterocytes accompanied by local disorders in the steady state of intestinal epithelium lead to the formation of carcinoma *in situ*. The latter process culminates in invasive cancer development. The formation of carcinoma *in situ* is not preceded by the hyperplasia of the mucosa. Hyperplasia takes places and progresses as the locus of cancer grows in size.

The belief that experimental epithelial adenocarcinomas develop *de novo* is supported by Schauer *et al.* (53), Schauer and Kunze (54), Ward (55) and Maskens (56). Spjut and Spratt (57), Spjut (31) described carcinogenesis unrelated to adenomatous polyps which, according to their opinion, do not become malignant.

Our experimental findings suggest that adenomatous polyps do not play any important role in the genesis of colo-rectal cancer in humans and actually constitute a sort of concomitant pathology. Such a hypothesis seemed still more convincing since the possibility that these benign tumors may become malignant is held in doubt by many investigators (3-7, 36, 58-62). Our investigation failed to detect any morphologic signs of adenomatous polyp malignancy, too. However, we observed frequent carcinomas *in situ* and superficial cancers in almost intact mucosa, and attributed their formation against the background of slight mucosal hyperplasia to the secondary changes in the mucosa in response to malignant growth. This concept is corroborated, first of all, by experimental results showing that hyperplasia may occur only after the formation of carcinomas *in situ* and it increases as superficial cancer grows. It is further supported by the available correlation between the size of superficial cancer and the degree of mucosal hyperplasia in humans. Moreover, it is significant that even the smallest neoplasms (2-3 mm in dia.) revealed signs of malignancy, invasion included. All these facts suggest that adenocarcinomas of the large bowel in man develop *de novo*, too. This applies especially to endophytic carcinomas. Theoretically speaking, of course, it may be supposed that separate adenomatous polyps may become malignant, but this possibility does not affect the genesis of intestinal cancers materially. This is supported by the experience of American oncologists who attached great importance to the early detection and removal of colonic polyps during 20 or 30 years. Yet, these precautions failed to reduce the morbidity and death rates for the cancer of this localization (4, 5).

Those authors who think that cancer develops from adenomatous polyps

maintain that early morphologic changes, such as carcinoma *in situ*, are very seldom observed in intact mucosa (9, 63). Our experience refutes this point of view. Moreover, it should be remembered that histologic examinations usually involve the use of gross lesions. There is every reason to believe that a purposeful search for early forms of colon cancer will detect them much more frequently (64). At any rate, the experience of gastric pathology shows that adenocarcinomas limited by the boundaries of the mucosa are not so rare (65).

The development of colonic and rectal cancers from adenomatous polyps in man is generally proved on the basis of indirect evidence and according to the principle *post hoc, ergo propter hoc*. When an attempt to visualize their morphogenesis is made, the main attention is focused on concomitant morphologic changes. Such an approach may lead to the development of unjustifiably complicated and artificial schemes (66). We are not in a position to evaluate the vast and controversial literature on the malignant potential of adenomatous polyps here for lack of space (for reviews see 63, 67, 68). Below, only the arguments the validity of which can be tested by experimental morphogenetic studies will be considered. It is generally believed that the remnants of adenomatous polyp observed in the exophytic malignant tumor constitute the most convincing direct proof of cancer development from polyps. However, our experimental findings show that these arguments are open to question, because the growth of a polypoid cancer involves normal mucosa into the tumor, similarly as the formation of the polyp pedicle involves the submucosa, t. muscularis mucosae and even muscular coat (Fig. 8). We also observed that the lower the rate of malignant tumor growth, the more frequent the structures of normal mucosa are. Tumors with such structural features were often observed in our experiments, following one administration of carcinogen or small single doses, when tumor induction period lasted 1/3～2/3 of the life-span of the animal. Therefore, we think that this phenomenon may also take place during the development of intestinal polypoid cancers, which are often characterized by slow growth (69). Hence, the detection of structures, similar to those in adenomatous polyp tissues, in exophytic malignant tumors cannot be used as a criterion of the development of the latter from the former. One such case was recorded in our study (Fig. 8 b) (see Results).

Similarly interesting data which also question the role of adenomatous polyps in carcinogenesis may be provided by comparative pathology. For instance, the rates of incidence of adenomatous polyps are very high in pigs —13.8% (up to 40% in certain breeds) of animals suffer from these lesions (70). It is noteworthy that not only their histologic structures are

identical to those in man but their frequency increases with age, too. At the same time, no malignant adenomatous polyps have been detected in pigs. On the other hand, sheeps are known to have intestinal cancer in some geographical areas (71, 72). But the disease development has no connection with polyps whatsoever, since the latter do not occur in sheep.

It should be mentioned here that there is a hypothesis that gastric polyps in man do not become malignant (73), while polypoid malignant tumors are early-onset cancers which develop as a result of the atypical proliferation of the epithelium of gland necks rather than from polyps (74).

Unlike the controversial conceptions on the malignant potential of adenomatous polyps, there is almost a unanimous consensus that villous tumors are a precancer. The frequency of malignancies among them varies from 40 (8) to 70 (45) or even 90% (75). They tend to recur and to replace the surrounding mucosa (76–79). Furthermore, 30–60% of such neoplasms reveal invasion (76, 80) whereas metastases into the lymph nodes may be detected in one-third of cases (81). It seems unlikely that human pathology can cite another similarly convincing example of such an inevitable process of benign tumors turning malignant. In this respect, villous tumors stand strangely aloof.

Our study of experimental intestinal tumors often revealed villous structures in superficial cancers. Typical villous and glandular-villous neoplasms were invariably invasive. It was precisely such human tumors, however small, that had anaplastic and, sometimes, invasive features which give a similar characterization to glandular-villous tumors with a relatively insignificant atypia. It should be mentioned that a morphologic examination of the villous polyps of the stomach, colon and rectum cannot guarantee that they are not malignant (82–84), and distant metastases are sometimes found after the removal of tumors previously identified as bengin (85). Some authors stress the essential differences between the villous tumors and adenomatous polyps of the colon, both with respect to their pathohistologic features and clinical course of development (40, 59, 80, 86). Villous neoplasms were shown ultramicroscopically to be very similar to highly-differentiated adenocarcinomas, while adenomatous polyps do not differ from normal mucosa (41, 87, 88). Villous tumors share more common enzymatic characteristics with adenocarcinomas than with adenomatous polyps (89).

Literature data and our experimental results show that villous and glandular-villous tumors are malignant *ab initio* (Fig. 9). It is not surprising, therefore, that their radical removal should be recommended (40, 83), despite the benign appearance of bioptic preparations. They may be regarded as carcinoma *in situ* or superficial cancer, when there is no invasion through t.

muscularis mucosae. Therefore, our data support the concept that the nature of tumor (benign or malignant) is predetermined at the time of its formation (36, 60, 90).

The idea that villous polyps are benign tumors persists, in our opinion, because most pathologists still rely on such criteria of cancer as highly-pronounced atypism and pleomorphism, and some add invasion as an indispensable criterion (8, 81). However, it should be remembered at the same time that the malignant nature of a neoplasm does not necessarily involve considerable morphologic alterations (37, 40, 63, 77). Furthermore, the nature of cytologic atypia in polypoid lesions and its further evolution are not always clear and much is anticipated from experimental cancer research (91). Indeed, it was morphologic studies of experimental tumors in animals that revealed the first atypical changes to be malignant, followed by their inevitable transformation into invasive cancer. These findings stimulate further interest in cytologic disturbances in the case of human malignant tumors. Such an approach suggests that more emphasis should be laid on the early detection of cancer at its preinvasive stage rather than the so-called precancerous changes. This looks particularly promising at present in view of the development of the methods of endoscopic examination of patients with diseases of the large bowel. Application of these principles in the research in cancer of other localizations (stomach, cervix uteri, etc) has given beneficial results in the treatment of cancer patients.

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Legends to Figures

Fig. 1. Carcinomas *in situ* in superificial areas of flat mucosa of the intestine. a) Rat. Descending colon. Weekly treatment with DMH (21 mg/kg). Experiment duration—66 days. H&E. × 200; b) Female, 56 years. Rectum. H&E. × 80; c) Detail of preparation in Fig. 1 b. × 200.

Fig. 2. Superficial cancers of the intestine against the background of slight hyperplasia of mucosa. a) Rat. Descending colon. Weekly treatment with DMH (21 mg/kg). Experiment duration—90 days. Van Gieson. × 80. b) Male, 63 years. H&E. × 80.

Fig. 3. Arrangement of proliferating epithelial cells on crests of villi in malignant glandular-villous tumors. a) Rat. Transverse colon. Single administration of DMH 200 mg/kg). Experiment duration—460 days. Numerous labelled cells one hour after injection of ^{3}H-thymidine. Autoradiograph. H&E. × 800. b) Male, 45 years. Rectum. Mitosis (shown by arrow) on crest of villus in area of extrusion. H&E. × 1130.

Fig. 4. Exophytic adenocarcinomas. a) Rat. Descending colon. Weekly treatment with DMH (21 mg/kg). Experiment duration—132 days. Van Gieson. × 32. b) Male, 64 years. Sigmoid colon. H&E. × 18. c) Detail of preparation in Fig. 4 b. Back-to-back appearance and loss of the stroma between glands; branching of glandular lumens; pluristratification of the epithelial glandular lining.

Fig. 5. Villous tumors with marked invasion and without pronounced signs of atypism and pleomorphism. a) Rat. Ascending colon. Weekly treatment with DMH (21 mg/kg). Experiment duration—166 days. H&E. × 50. b) Male, 59 years. Rectum. H&E. × 32.

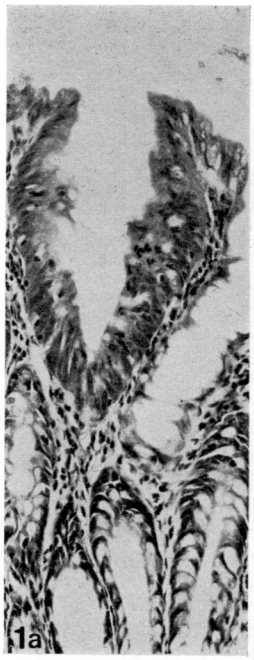
Fig. 6. Invasive glandular-villous tumors. a) Rat. Ascending colon. Weekly treatment with DMH (21 mg/kg). Experiment duration—177 days. Van Gieson. × 25. b) Female, 31 years. Rectum. Tumor measuring 3×2 mm. Mayer's mucicarmine. × 28.

Fig. 7. Malignant glandular-villous tumors. a) Rat. Rectum. Weekly treatment with DMH (21 mg/kg). Experiment duration—152 days. Van Gieson. × 116. b) Female, 52 years. Rectum. Tumor measuring 5×4 mm, formed mostly by goblet-cell epithelium, almost unaltered in appearaence. Profound invasion is quite apparent. H&E. × 15.

Fig. 8. Exophytic polypoid adenocarcinomas. Inserts carry diagrams of tumors. a) Rat. Descending colon. Single treatment with DMH (200 mg/kg). Experiment duration—562 days. Tumor involves all intestinal layers. H&E. × 10. b) Male, 67 years. Rectum. H&E. × 17.

Symbols: parallel lines —intestinal mucosa; thick squared hatching— adenocarcinoma; thick square-and-dot hatching —invasion into tumor stroma; thin rhomb-like hatching— the so-called adenomatous tissue; distinct curve- and branched lines —muscular coat of the intestine; dots— lymphoid follicle.

Fig. 9. Initial stages of malignant glandular-villous tumor development a) Rat. Weekly treatment with DMH (21 mg/kg). Experiment duration—127 days. Though tumor is extremely small, there is invasion (arrow). H&E. × 200. b) Male, 67 years. Rectum. Though tumor is extremely small, its atypia is apparent. H&E. × 70.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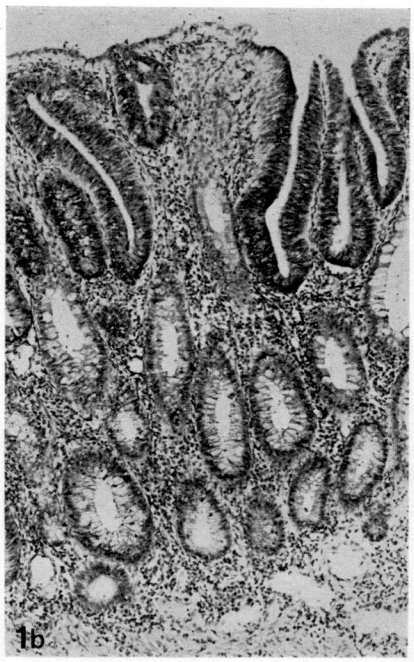
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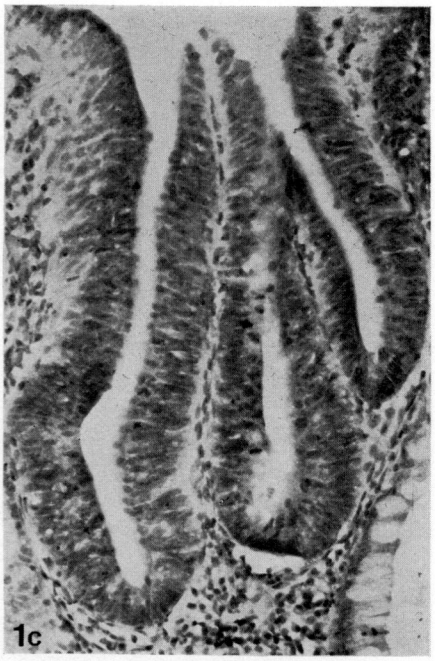
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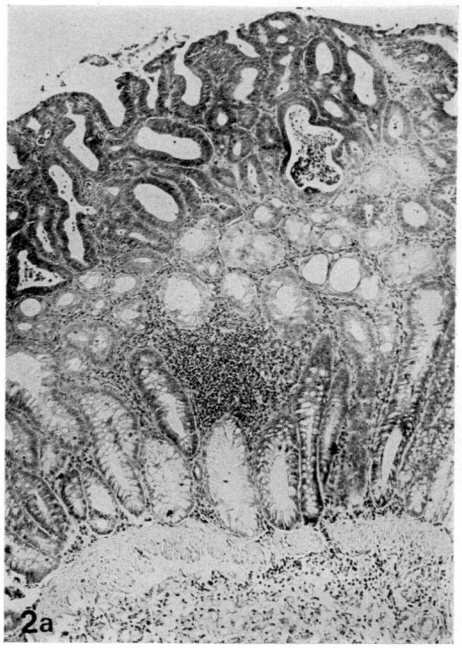
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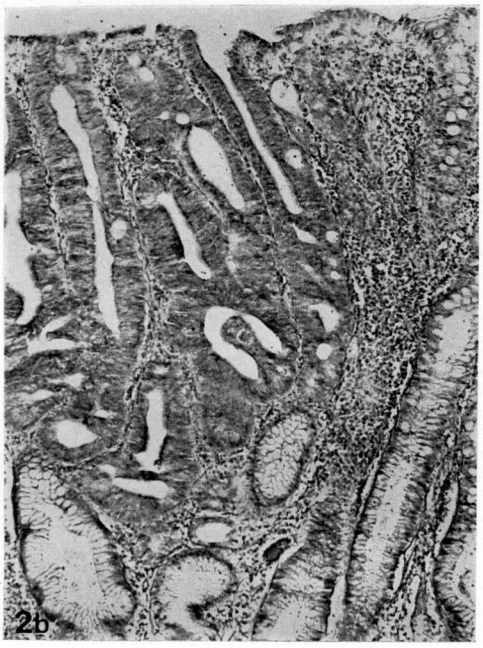
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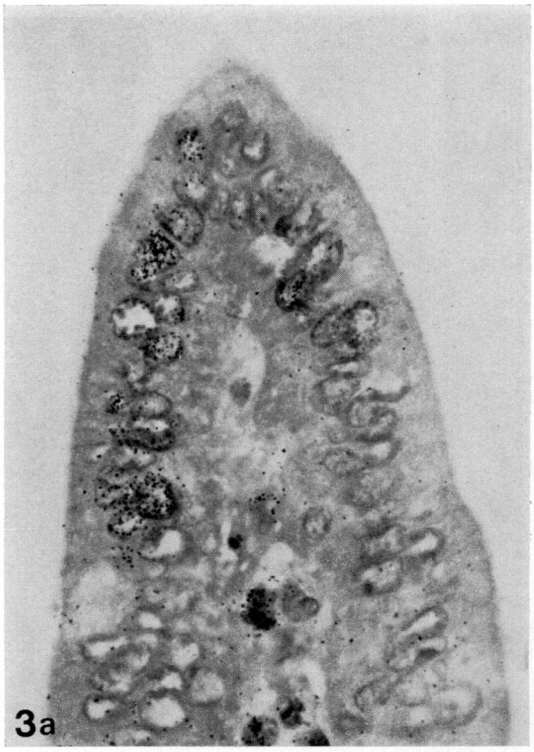
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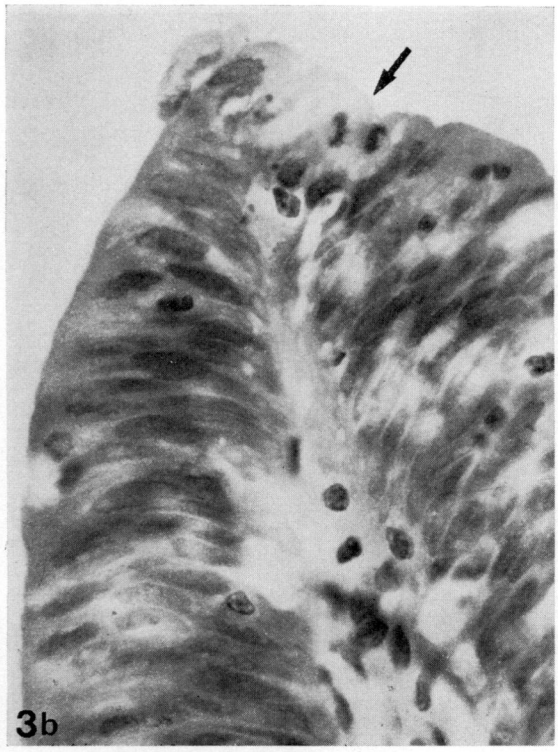
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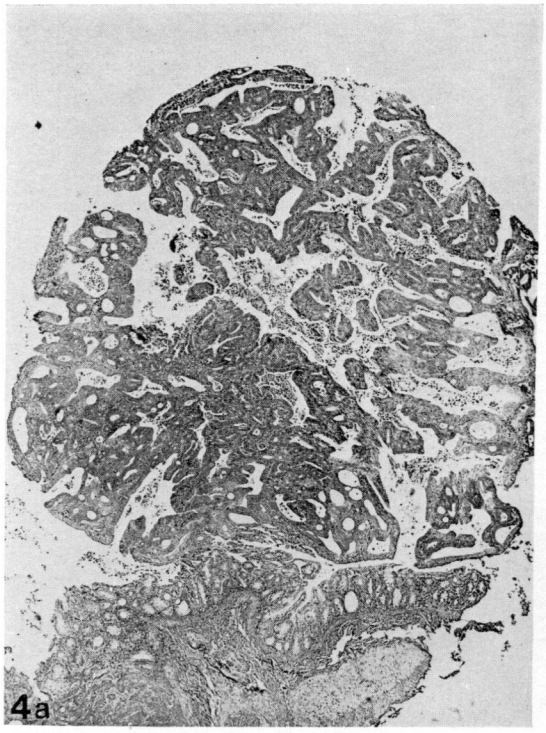

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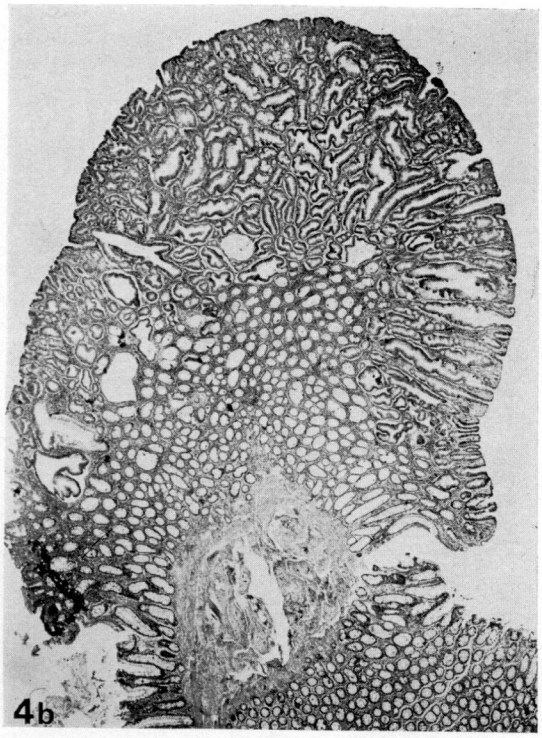

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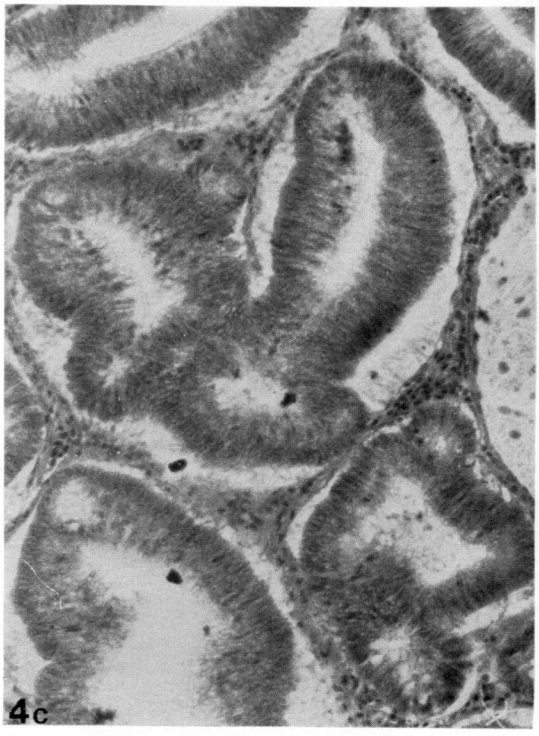

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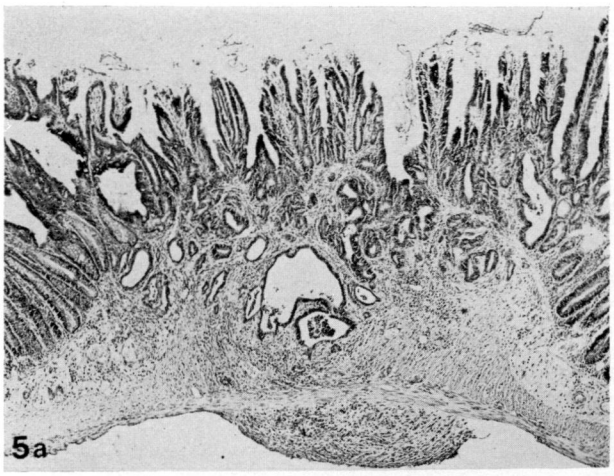
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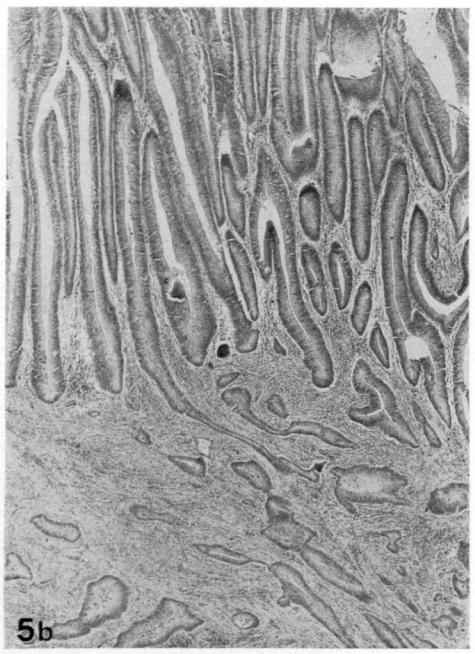
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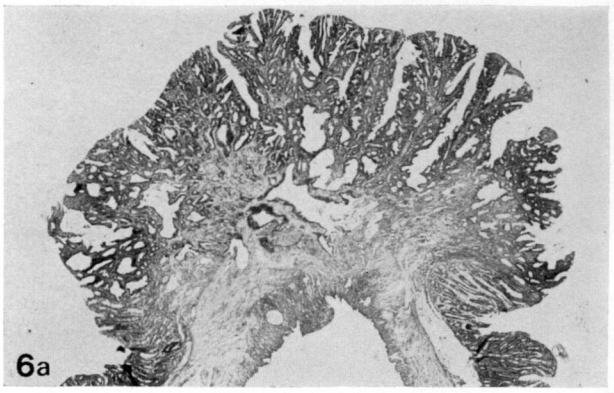
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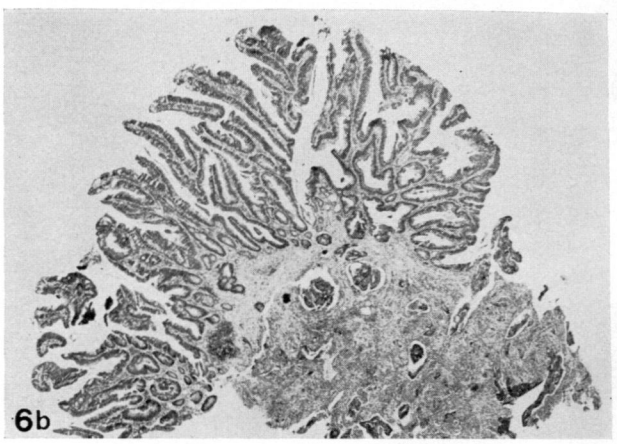
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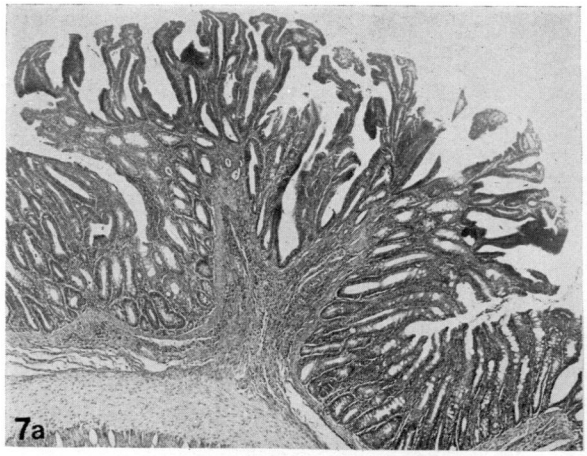
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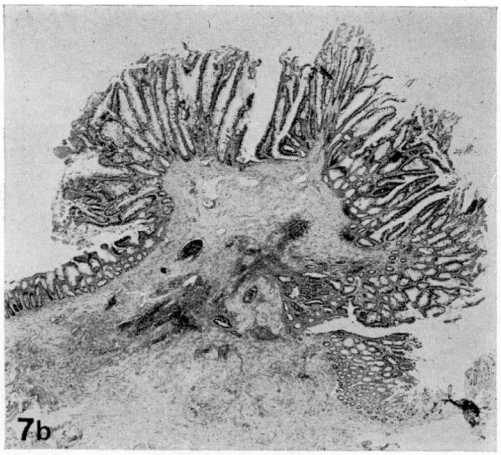
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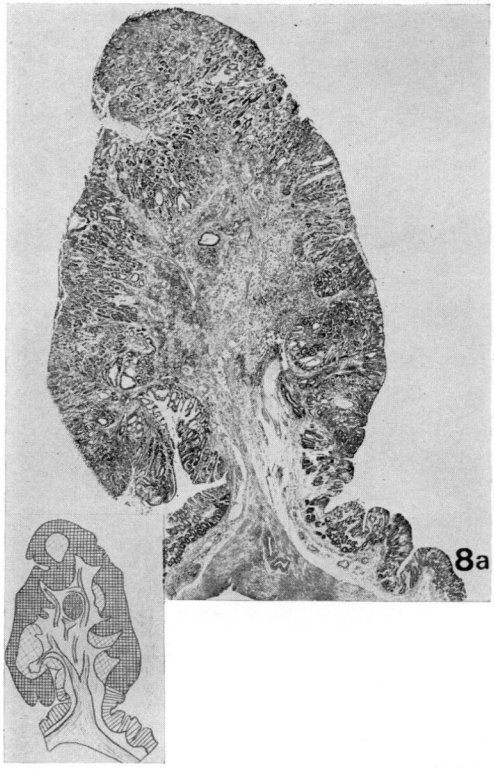
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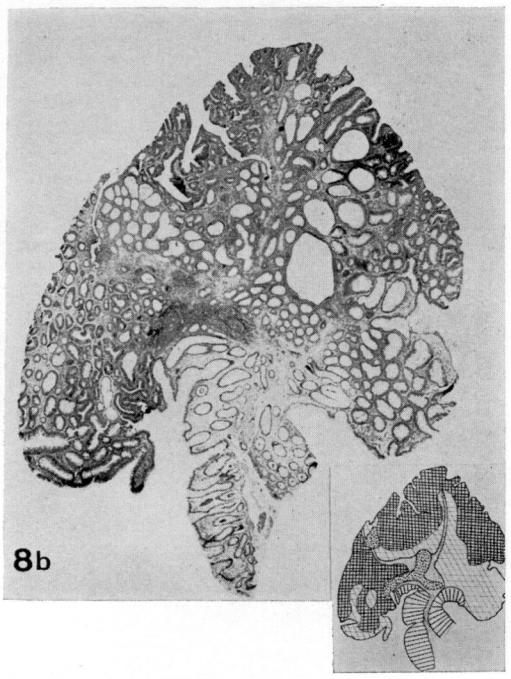
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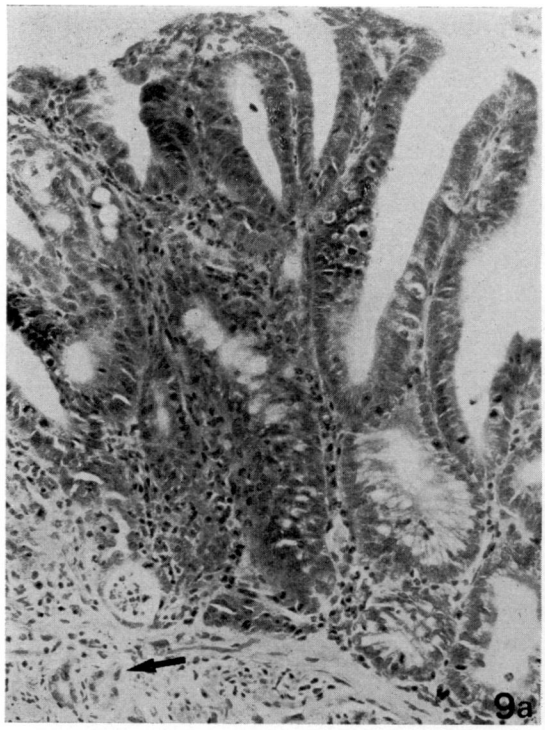
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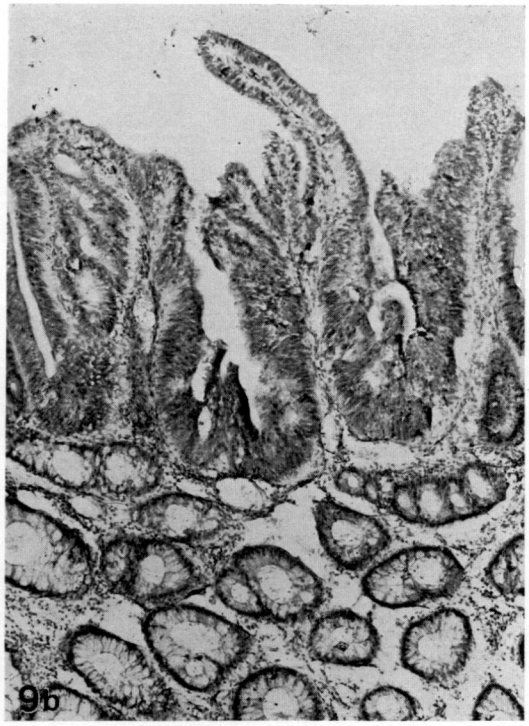
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