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CLINICAL AND ENDOSCOPIC ASSESSMENT OF THE OCCURRENCE AND DEVELOPMENT OF EPITHELIAL NEOPLASMS OF THE COLON

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Abstract

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РФ

МОСКОВСКИЙ НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ
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На правах рукописи

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КЛИНИКО-ЭНДОСКОПИЧЕСКАЯ ОЦЕНКА ВОЗНИКНОВЕНИЯ И РАЗВИТИЯ ЭПИТЕЛИАЛЬНЫХ НОВООБРАЗОВАНИЙ ТОЛСТОЙ КИШКИ

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Автореферат
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The dissertation was performed at the Research Institute of Proctology of the M3 of the Russian Federation.

Scientific consultant - Doctor of Medical Sciences, Professor **G.I. Vorobyov**.

Official opponents:

Doctor of Medical Sciences, Professor **D. V. Komov**,
Doctor of Medical Sciences, Professor **G. A. Frank**,
Doctor of Medical Sciences, Professor **A. A. Ovchinnikov**

The leading institution is the Research Institute of Emergency Medicine. N.V. Sklifosovsky.

The defense will take place on December __, 1992 at 2 p.m. at a meeting of a specialized council (D-084. 17. 01) at the Moscow Scientific Research Oncological Institute. P. A. Herzen at the address: 125284, Moscow, 2nd Botkinsky passage, house 3.

The dissertation can be found in the library of the institute.

The abstract was sent to ___ _____ 1992.

Scientific Secretary of Specialized
Council, MD,
Professor **I. A. Maksimov**

GENERAL DESCRIPTION OF WORK

Relevance of the problem. Despite the implementation of programs for mass examinations and prevention of colon cancer in most industrialized countries, so far there has been no significant decrease in the frequency of this disease. Statistical data, on the contrary, indicate that the upward trend in the incidence and mortality rates of patients with colon cancer continues (E.S. Simkina, 1979; V.D. Fedorov, 1984; D.G. Zaridze et al., 1988; R.G. Ziegler et. al., 1986). In this regard, there is reason to believe that the risk groups identified within these programs do not fully correspond to the structure of the incidence of colon cancer due to the lack of sufficiently accurate information about the peculiarities of the occurrence and development of epithelial tumors.

Modern ideas about the occurrence and development of tumors of the mucous membrane of the colon are based on generally accepted concepts of carcinogenesis. In support of the most popular of them, numerous arguments are made about the multifactorial relationships between the growth of adenomatous polyps and the development of colon cancer (V.L. Rivkin et al., 1969; V.S. Morson, 1962, 1968, 1978; R. Hermanek et al., 1978 et al.). The rate of development of epithelial tumors, according to this concept, seems to be quite low, and the minimum period for malignancy of polyps is about 5 years (T. Muto et. a1., l975; B.C. Morson, 1978; P. Deyhle, 1980). As well as an alternative point of view about the more frequent development of cancer against the background of an unchanged mucous membrane (J.S. Spratt, L.V. Ackerman, 1958; K.M. Pozharsky, 1978, etc.), both of these concepts are based mainly on the results of morphological studies of surgical drugs and experimental data and are significantly less confirmed by clinical or endoscopic observations.

At the same time, according to the literature, there are significant contradictions between theoretical data and accumulated clinical observations about the features of the occurrence and growth rates of benign epithelial tumors and cancer. So, in most patients, colon cancer is detected in clinical stages III-IV (A.M. Ganichkin, 1970; V.D. Fedorov et al., 1978, etc.), and the number of patients with so-called "early cancer" does not exceed 3-8%, including the detection of malignant polyps. There are also no sufficiently reliably proven observations in the literature of the stage of transition of glandular polyps to cancer, although theoretically and experimentally this variant of cancer development is justified and is unlikely to be questioned. Hardly convincing is the opinion of many authors about the long-term (up to 10 years) asymptomatic or low-symptomatic course of colon cancer, which, from their point of view, is one of the main reasons for its late diagnosis. These data are also based predominantly on indirect evidence. In addition, recently, as research has deepened, a large number of contradictory data have appeared about the features of tumor growth, which are becoming increasingly difficult to explain from the standpoint of concepts formulated in past years.

Given the above, we conducted our own clinical and endoscopic observations of patients with colon tumors, observing the necessary deontological rules.

The purpose of the study: to study the features of the appearance and development of epithelial neoplasms of the colon.

The main objectives of the study:

1. To analyze the results of clinical and endoscopic follow-up of all groups of patients with colon epithelial tumors:

a) for patients with small glandular polyps who have not undergone endoscopic removal;
b) in patients after endoscopic removal of polyps;
c) in patients undergoing clinically radical cancer surgery.

2. Study the features of the occurrence and development of colon adenomas.
3. Study the features of the occurrence of cancer tumors of the colon.
4. Develop methods of lifetime chromocolone- and colonomicroscopy, as well as criteria for evaluating the results of using these studies when using devices with different magnifications.
5. To develop microendoscopic semiotics of changes in the epithelial surface of malignant tumors, benign adenomas, and mucosal microformations.
6. To evaluate the structural features of the macroscopically unchanged colonic mucosa in patients with various tumors and in the control group.
7. To study the results of long-term follow-up of patients operated on for cancer after endoscopic polypectomy and in the control group after their colonomicroscopy; to compare the pattern of baseline changes detected by colonomicroscopy with subsequently detected tumors in this segment of the colon.

Scientific novelty:

- It has been established that the growth of adenomatous polyps of the colon is most often uneven.
- It has been shown that the appearance of new epithelial tumors in the colon is the predominant form of their growth in frequency compared to an increase in the size of previously detected polyps or their recurrence.
- The impossibility of preventing the development of cancer by periodically removing all polyps in a significant part of patients has been established.
- Three main types of cellular architectonics of the colon epithelium have been identified, as a result of which the mucous membrane is more often mosaic.

- Various morphological types of epithelial formations of the colon: adenomas, hyperplastic polyps and cancer are located on the types of epithelial surface characteristic of them.
- For the first time, diffuse hyperplasia of the mucous membrane of the colon was described, its endoscopic, microendoscopic semiotics and prevalence in the colon were studied; morphological identification of hyperplasia of this type was carried out.
- Data have been obtained that showed that there is reason to consider diffuse hyperplasia of the mucous membrane of the colon as one of the factors that can affect the possibility of developing colon cancer.
- The appearance of cancerous tumors in the colon (excluding recurrent adenomas) is preceded by moderate diffuse hyperplasia without focal changes; a few months before the detection of cancer in individual observations, the appearance of small adenomas with moderate epithelial dysplasia was noted, which suggested the complicity of these structures in the development of cancer.
- Data have been obtained on the possibility of developing a method that allows more accurate prediction of the likelihood of developing a river of the colon by assessing changes in the surface epithelium.
- The expediency of studying the morphogenesis of colon cancer based on the study of the pathology of intercellular interactions is shown.
- Current secondary prevention programs for colon cancer do not appear to be able to significantly reduce the incidence of colon cancer and therefore need to be improved.

Practical significance of the work:

- The feasibility of endoscopic removal of polyps from the colon was confirmed.

- Observation of patients with small polyps (up to 0.5 cm), provided that there is no anamnestic data on previous polypectomies, cancer treatment, as well as widespread diffuse mucosal hyperplasia in the colon, should, as a rule, be carried out at intervals of 2-3 years and even less often if the growth of polyps is not noted.
- The activation of the growth of polyps during the observation of patients may indicate an increased likelihood of developing colon cancer, and therefore observation during such periods should be carried out more often - 1 once every 6 months.
- Remove small adenomas (0.3-0.5 cm) located within diffusely hyperplastic areas of the epithelial surface, regardless of the severity of dysplastic changes in them. To a greater extent, this applies to patients observed after removal of large polyps, polyps with severe epithelial dysplasia and operated on for cancer.
- Patients, especially of young age, in the presence of widespread diffuse hyperplasia, need periodic monitoring 1 once every 3-4 years, even in the absence of adenomas in the colon.
- The time intervals between patient observations after endoscopic polypectomy should be differentiated depending on the number of removed polyps, their growth rate, the severity of epithelial dysplasia in them, as well as the severity and prevalence of diffuse mucosal hyperplasia; it is necessary to take into account the age and well-being of patients.
- The appearance of symptoms characteristic of colon cancer most often corresponds to the III clinical stage of the disease; this stage of the process, apparently, there is no sufficient reason to consider the result of a long development of the disease due to the fact that colon cancer often develops rapidly within a few months.

- Patients at any age, operated on for colon cancer, need more careful monitoring, the frequency of which should depend on their well-being.

Putting results into practice:

Theoretical provisions and practical recommendations are set out in 20 publications, included in the educational process at the Department of Proctology for cadets of Central Order of Lenin Institute of Advanced Medical Training of the Ministry of Health of the Russian Federation. Based on the results of the studies, training cycles are conducted with doctors of diagnostic centers, city and district hospitals studying endoscopy at workplaces at the Research Institute of Proctology of the M3 of the Russian Federation. The dissertation materials were used to train specialists at republican seminars on proctology and endoscopy in Moscow (I988-I99I), field seminars in Kazan (1987), Samara (1990), Tula (1987), Nizhny Novgorod (1986).

The results of the work are recommended to be implemented in the practice of diagnostic centers, endoscopic, surgical, gastroenterological and proctological departments of regional, city and district hospitals.

Provisions put forward for protection:

1. Periodic removal of all polyps from the colon does not prevent the possibility of developing cancer in it.

2. Three main types of cell architectonics of the superficial epithelium of the colon were identified, differing in the location and nature of the intravital color of colonocytes, as a result of which the mucous membrane is more often mosaic.

3. Different morphological types of epithelial formations: tubular adenomas, hyperplastic polyps and cancerous tumors are located on the types of epithelial surface characteristic of them.

4. Diffuse hyperplasia of the mucous membrane of the colon is described, its endoscopic, microendoscopic semiotics and

prevalence in the colon are studied; morphological and identification of hyperplasia of this type was carried out.

5. Data have been obtained on the existence of two types of colon cancer, differing in the rate of development. Less often, there was a slow development of cancer from recurrent adenomas, more often - the rapid development of cancer tumors against the background of diffuse epithelial hyperplasia. Sometimes, immediately before the appearance of cancerous tumors in the area of their location, small adenomas with moderate epithelial dysplasia were found, which suggested the complicity of these structures in the development of the most dynamically developing cancerous tumors.

Thesis scope and structure. The dissertation is presented on 325 pages of typewritten text, contains 3 diagrams, 27 color and black-and-white illustrations and 78 tables. The work consists of an introduction and 7 chapters: a literature review and 6 chapters of own research, conclusion, conclusions, practical recommendations and an index of literature, including 333 domestic and foreign sources.

THESIS CONTENT

Material and research methods. To achieve the goal and solve the set tasks, the results of clinical and endoscopic observations of 4134 patients with colon tumors (excluding patients with colon adenomatosis) aged 16 to 86 years were analyzed (see Table No. I). Three groups of patients with various anatomical and morphological types of colon tumors were monitored: with failed polyps, the size of which did not exceed 0.5 cm - 239 people, after endoscopic removal of polyps larger than 0.5 cm - 2079 people, after clinical-radical operations for colon cancer - 1816 people. The main condition for observing the applied method was the mandatory removal of all identified adenomas, the dimensions of which exceeded 0.5 cm.

The studies were carried out using clinical and endoscopic observations carried out according to the scheme developed at the

institute and necessarily included methods of digital examination of the rectum, sigmoidoscopy, sigmoidoscopy and colonoscopy with examination of all parts of the colon.

Table 1

Groups of long-term ballroom
at the Research Institute of Proctology of the M3 of the Russian Federation

Gender of patients Groups of observed patients	Men		Women		Total quantity patients	
	abs.	%	abs.	%	abs.	%
Patients with small colon polyps	107	2,6	132	3,2	239	5,8
Patients with endoscopic polypectomy	1091	26,4	988	23,9	2079	50,3
Sufferers who underwent radical surgery for colon cancer	1005	24,3	811	19,6	1816	43,9
TOTAL:	2203	53,3	1931	46,7	4134	100,0

The methodological basis of this study was the analysis of data contained in outpatient charts and medical histories of patients observed and treated at the Research Institute of Proctology. The fate of patients who ceased to be observed at the institute was clarified by sending questionnaires, calling patients for a second examination.

The causes of death were established on the basis of requests from registry offices at the place of residence of patients or autopsy protocols.

Studies of microscopic changes in the colon epithelium were carried out using specially developed methods of chromocolonoscopy, colonomicroscopy with 30-fold magnification

and contact colonomicroscopy with 170-fold magnification, which included a set of additional techniques and devices. The study of the results obtained was carried out solely on the basis of photo documentation, and a morphometric approach was used to objectify them.

In total, about 28,000 colonofibroscopies and endoscopic interventions, 270 chromo- and colonomicroscopies were performed in the observed patients, morphometric analysis of about 4,000 endomicroslaids was performed. The obtained data were verified by the results of morphological studies of drugs, biopsies of the colon mucosa, autopsy data. More than 400 special morphological studies were also carried out, including stereomicroscopy of drugs, special methods for coloring drugs, as well as scanning electron microscopy.

Results obtained and their discussion.

1. Nature of baseline changes in the colon during the follow-up period and quantitative characteristics of its results:

a) Follow-up results of patients with small failed polyps.

Long-term follow-up of 239 patients with failed solitary and multiple small polyps in the colon made it possible to establish that most of them - 185 (77.4%) did not have significant changes; 54 patients (22.6%) had various changes, expressed mainly in the appearance of new polyps, less often in an increase in the size of previously diagnosed adenomas. The development of cancer in the colon was not noted in any of this group of patients.

b) Direct results of polyps removal and patient follow-up.

The results of follow-up of 2079 patients in whom solitary - 613 (29.5%) and multiple colon polyps - 1466 (70.5%) were removed, as it turned out, significantly depended on the nature of the initial changes. In total, 7373 polyps of various anatomical types were removed from these patients, the sizes of which most often ranged from 0.6 to 3.0 cm. Of the 3211, as a rule, the largest polyps extracted from the intestinal lumen for histological examination, 2964 were benign, including 458 with severe dysplastic changes in the epithelium and 247 polyps (in 232 patients) - with malignancy.

During the follow-up, no significant changes in the colon were detected in 1000 patients (46.1%). Various changes were found in 1079 patients (51.9%). Of these, 1,021 showed growth and recurrence of polyps, which were observed more often, the more polyps were removed, their size and the severity of epithelial dysplasia were large; 12 had malignancy of recurrent adenomas; in 46 patients (2.2%), the appearance of cancerous tumors was not the result of continued polyps growth.

Cancer development in the colon (in cases where this process was difficult to associate with malignancy of polyps) nevertheless, it was observed more often in patients after removal of large glandular-villous and villous adenomas with moderate epithelial dysplasia (4.0%) and malignant polyps (4.7%), relatively less often after removal of small glandular polyps with moderate (0.9%) and generally large polyps with marked epithelial dysplasia (2.0%).

c) The nature of the initial changes in the colon in those operated on for cancer and the results of observation of this group of patients.

Long-term follow-up of 1816 patients who underwent various types of operations for colon cancer, in which during this period there were no signs of generalization of the process, made it possible to establish that the nature of the initial changes in the colon did not significantly affect the process of appearance and growth of (new) metachronous tumors. Most of the patients - 1072 (59.0%) were observed after operations for rectal cancer, in 692 (38.1%) - cancer was localized in the colon and 52 patients (2.9%) were operated on for synchronous primary multiple colon cancers. In most patients, cancer tumors had the structure of adenocarcinoma: in 1441 (79.3%) - highly and moderately differentiated and in 222 (12.2%) - poorly differentiated, other morphological forms of cancer were noted in 8.5% of patients. In 1167 patients (64.3%), cancer tumors were solitary, and 609 (33.5%) also had solitary and multiple adenomas synchronous with cancer tumors; only 40 patients (2.2%) did not have accurate data at the time of surgery. In 62 patients, synchronous polyps were removed along with the resected segment

of the intestine, and in 436, solitary and multiple polyps were removed through the colonoscope simultaneously with the operation.

A total of 1,162 polyps were removed from 479 patients. Morphologically, 821 polyps were studied: most of the polyps - 734 (89.4%) differed in moderate epithelial dysplasia, 71 showed pronounced dysplastic changes, 16 adenomas in 15 patients had signs of malignancy. In 109 patients, small synchronous polyps were not removed.

Of the total number of patients observed, 444 (24.5%) showed no significant changes in the colon. In 1053 (58.0%), there was an increase and recurrence of polyps, and 93 patients (5.1%) developed (new) metachronous cancer tumors. The growth of new polyps was more often observed in patients with synchronous polyps (67.8%) compared to patients whose cancers were solitary (52.9%). The development of metachronous cancer was also more common in patients operated on for cancer with synchronous polyps (5.7%), compared with those in whom polyps did not accompany cancerous tumors (4.6%). In both cases, these differences were not statistically significant. Nevertheless, the data obtained indicate a more frequent development of metachronous benign and malignant tumors in patients operated on for cancer and synchronous polyps.

2. Results of observation of the features of the appearance and growth of polyps.

Due to the lack of clear criteria for the potential malignancy of adenomas, a study of the dynamic characteristics of their appearance and growth showed that the appearance of new polyps is the predominant form of polyps growth in frequency (80.6%) over recurrence (6.6%) and an increase in the size of previously detected polyps (12.8%) regardless of their number and location in the colon. As the follow-up time and, accordingly, the age of the patients increased, the relative number of patients with polyp growth also increased. During the entire follow-up period, a total of 4,587 polyps from all parts of the colon were removed from 1,363 patients. Polyps larger than 1 cm were removed 2 times less often compared to the

first-time interventions, despite the fact that the largest polyps were most often recurrent. Severe epithelial dysplasia in repeatedly removed polyps was noted in 2.4% of cases, a significant part of which were recurrent adenomas. Malignant polyps identified in 1.2% of observations in 13 of 14 cases were also recurrent. These data certainly confirm the view that periodic removal of polyps significantly contributes to a decrease in their malignant potential, since in only one observation the newly detected neoplasm could be attributed to the category of malignant adenomas, as well as to cancer containing adenoma tissue.

A study of the growth process of adenomas, performed with restrictions due to the observation method, showed that the relative uniformity of the growth process of polyps was observed only in 6.3% of patients. Uneven growth of polyps was observed in the majority of patients (93.7%). These data convincingly showed the conventionality of the division of adenomas into slow and fast growing ones. At the same time, the growth pattern of various adenomas, even in the same patients, was different. It was also found that the relatively more or less high growth rate of adenomas is by no means correlated with the correspondingly greater or lesser severity of dysplastic epithelial changes in these adenomas.

A comparison of the nature of the clinical symptoms encountered in patients before the first removal of polyps and during the observation process showed that the symptoms that existed before polypectomy practically did not appear again in most patients who had an increase in metachronous polyps. The exception was patients with large recurrent adenomas, who periodically complained of mucus and blood secretion.

A study of the nature of the growth of polyps in patients who developed cancer in the colon (72 observations) showed that in 30 observations (52.8%) there was an acceleration of the growth of polyps in the period preceding the development of cancer, in 14 patients (19.4%) there was no acceleration of the growth of polyps, in 20 people (27.8%) there was no growth of polyps during the appearance of cancerous tumors.

In our opinion, the results of our observation turned out to be very important, showing that the number of patients with new polyps with severe epithelial dysplasia (28) or malignant polyps (1), which are considered to be a transitional form between tubular adenomas and cancer, did not fully correspond to the number of patients (more than 120 people) who developed infiltrative cancer tumors in the colon in a short time. These data call into question the universal nature of the growth process of adenomas with their subsequent long-term malignancy as the most commonly implemented mechanism of carcinogenesis in the colon.

3. Results of follow-up of features of colon cancer development.

Clinical and endoscopic assessment of the circumstances associated with the development of colon cancer in 139 patients, which amounted to 3.4% of the total number of patients observed, showed that the detection of cancerous tumors in most cases was unexpected. This was the reason for an in-depth study of the circumstances of the development of cancer. In 46 patients (2.2%), primary cancer tumors were detected at various times after the removal of most often benign adenomas, 93 patients from among those previously operated on for cancer (5.1%) were diagnosed with metachronous (new) primary multiple cancers. In 82.7% of patients, primary cancer tumors were detected within a period exceeding 1 year after operations or polypectomy, and in a smaller, but still significant part - (17.3%) up to 1 year. More often, the development of cancer was noted in patients after the removal of polyps with severe dysplasia, as well as malignant polyps.

A study of clinical symptoms showed that in 44.6% of the patients observed, the development of cancer was not accompanied by any pronounced disorders of general well-being, in 39.6% of patients various disorders appeared less than 6 months before the detection of tumors, and in 15.8% they had a long duration, but, as a rule, did not exceed 12 months. Most often, patients complained of blood secretion from the rectum, other changes in well-being were

relatively less common. The duration and intensity of clinical manifestations were the greater the larger the size of the detected tumors. At the same time, despite the short intervals between observations, 77.8% of patients were diagnosed with advanced forms of cancer. These data indicate a high rate of colon cancer development in most observations, which did not appear to exceed 12 months.

A retrospective study of the nature of local changes in the mucous membrane in the zone of subsequently detected cancerous tumors was possible only in 99 patients. In most of them - 46 (46.1%), based on endoscopic and radiological data, a visible relationship between the development of cancer and previous adenomas was not established. In 26 patients (26.3%), the absence of changes (according to X-ray examination) at the site of subsequently diagnosed cancerous tumors does not allow us to assert with sufficient certainty that in each of these observations there were no changes in the epithelium at the site of the appearance of cancerous tumors. Less frequently, in 27 observations (27.3%), cancerous tumors were found in the area of adenomas, and in 11 observations, cancerous tumors appeared in the area of small polyps (less than 0.5 cm), some of which had the structure of tubular adenomas with moderate dysplasia of the epithelium of the glands, the rest did not differ from them in visual signs.

Fragments of polypoid tissue were more often found in cancerous tumors detected in the area of polyps (25.9%) compared to tumors that appeared against the background of macroscopically unchanged mucous membrane (13%).

The data obtained allow us to unconditionally confirm the concept of the phased development of colon cancer mainly from polyps in only 16.2% of our observations, however, in most cases (83.3%), sufficiently convincing evidence of the origin of cancer tumors from adenomas was not obtained. The role of small adenomas with moderate epithelial dysplasia in the development of cancer also remained unclear. Thus, we can see that the high rates of cancer development and the lack of practical ability to predict the

timing of their appearance, localization and specific patients in whom the appearance of cancer tumors may occur, we noted in 83.8% of our observations. In this regard, there does not seem to be sufficient reason to hope for a significant reduction in the incidence of colon cancer due to prophylactic removal of polyps. This view is also partly explained by other findings in our study. So, in some cases, polyps, having reached a fairly large size, retained their belonging to benign adenomas, while the detection of small neoplasms, which are infiltrative cancerous tumors, suggests significant qualitative differences between the development of adenomas and cancer. This is probably why, by removing adenomas, as it was shown, we were unable to prevent the rapid development of infiltrative forms of cancer in a significant number of patients. To a greater extent, it was possible to reduce the potential malignancy of adenomas. These data indirectly indicate a high probability that, despite morphological similarities, there are at least two varieties of colon cancer that differ in the nature of previous changes, the speed of development, potential malignancy and, apparently, qualitative features of the mechanism of malignancy of epithelial cells. All this does not allow us to consider most cases of cancer in the colon as a result of evolutionary changes in adenomas.

4. Results of the study of the mucosal microstructure of the colon in patients with colon tumors and in the control group.

Chromo- and colonomicroscopy according to the developed methods in 270 patients made it possible to differentiate and identify the main types of epithelial tumors, hyperplastic polyps and microformations in the mucous membrane of the colon by the nature of intravital color. It turned out that the tissue of adenomas and cancerous tumors does not perceive intravital color well, hyperplastic polyps and microscopic foci of hyperplasia are intensively stained.

Chromo- and colonomicroscopy made it possible to establish that the epithelium of the colon has not a uniform, as the ego was previously thought, but more often a mosaic structure. There are

three main (most common) varieties of cellular architectonics of the superficial epithelium of the colon.

Studying the structure of the surface epithelium of tumors and the macroscopically unchanged mucous membrane made it possible to establish a new pattern. This pattern is that different varieties of cell architectonics of the surface epithelium correspond to certain morphological types of epithelial formations: since microadenomas and tubular adenomas are located on the epithelial surface of type I, hyperplastic foci and polyps - against the background of the epithelial surface of type II, cancerous tumors in more than 90% of observations directly touch the epithelial surface of type III, somewhat less often (up to 70% of observations) this also applies to villous tumors.

Studies of various age groups of patients made it possible to establish that certain changes - such as an increase in the size of polyps, as well as an increase in their number - occur not only in the epithelial formations themselves, but also simultaneously in the corresponding epithelial surfaces. These changes in epithelial architectonics are diffuse and to a certain extent correlated with the age of patients, which made it possible to associate them with the aging processes of the colon epithelium.

The data obtained by us also made it possible to establish that type III (variety) of the structure of the epithelial surface is diffuse hyperplasia of the mucous membrane, which has significant endomicroscopic and morphological differences from focal hyperplasia. It is characterized, as a rule, by a large prevalence, occupying large areas of the epithelium, which gave us the opportunity to classify it as a diffuse type. Endoscopically, such an epithelial surface looks wrinkled, the vascular pattern is poorly differentiated, which is often mistakenly regarded by endoscopists as inflammatory changes. The prevalence of diffuse mucosal hyperplasia was studied in the colon based on the results of a special examination of 160 patients with various tumors and a control group belonging to various age categories. The results of this study suggest

that complex changes occurring in the hyperplastic mucosa are associated with the tumor process.

Analysis of the results of endoscopic, endomicroscopic and morphological studies of microformations, diffuse hyperplasia, as well as data on the features of cellular kinetics, allowed us to suggest that the appearance of cancerous tumors, the origin of which turned out to be impossible to associate with sufficiently large long-term adenomas, may be due to disruption of normal intercellular interactions in the mucosa, leading to changes in the genome of epithelial cells characteristic of cancer.

In order to further study the data of colonomicroscopy and more accurately establish changes in the epithelium preceding the appearance of tumors, we analyzed the results of observation within 5 to 8 years for 105 patients after they underwent colonomicroscopy. This group of patients included 59 people operated on for cancer, in whom the segment of the intestine examined with a colon microscope was not resected, 26 patients after endoscopic removal of polyps and 20 patients of the control group who did not have macroscopic changes in the colon. Most of the patients - 78 (74.3%) did not show any macroscopic changes, and 27 people (25.7%) had tumor growth. In 24 patients, there was an increase in polyps, including in 19 patients operated on for cancer, in 2 - after endoscopic polypectomy and in 3 in the control group. In 3 patients operated on for cancer, metachronous primary multiple cancer tumors developed in the remaining sections of the intestine.

Baseline changes in the epithelium of the endomicroscopically examined segment of the distal part of the sigmoid intestine, including polyps, microformations, as well as the types of structure of the epithelial surface, were compared with the nature of the changes that occurred during observation within this segment of the intestine. In almost half of the observations (6 out of 13), the appearance of adenomas was preceded by the detection of microadenomas during endomicroscopy, located on the corresponding epithelial surface (type I); in 1 of 3 observations, the appearance of hyperplastic polyps was preceded by microscopic

adenomas and foci of hyperplasia, the structure of the epithelium (I and II). In the remaining observations, the appearance of adenomas (7) and hyperplastic polyps was associated only with the identification of the corresponding types of epithelial surface, which more often had a combined character within the endomicroscopically examined segments of the intestine. In most patients (12 out of 18), no polyps were subsequently detected after the detection of microadenomas. The appearance of hyperplastic polyps was noted in only 1 out of 16 cases of detection of microscopic foci of hyperplasia.

In 16.2% of observations, the development of colon cancer occurred at the site of recurrent adenomas, usually as the epithelial dysplasia increased for a long time. We were unable to obtain reliable data on the development of cancerous tumors, the origin of which was not associated with recurrent adenomas (83.9%), at the site of previously detected focal changes in the mucous membrane - microadenomas and foci of hyperplasia. The development of cancer in the region of endomicroscopically examined segments of the intestine in both (2) observations was preceded by moderately pronounced diffuse hyperplasia of the mucosal epithelium: in one of them, the entire mucosal surface was hyperplasized, in the other, in combination with other types of epithelial structure (I and II). In the last observation, it was not possible to reliably associate the development of cancer with diffuse hyperplasia. At the same time, the direct contact of the site of diffusely hyperplastic mucosa with the developed cancerous tumor seems to confirm the connection between hyperplasia and the development of cancer in this observation. At the same time, the detection of small tubular and glandular villous adenomas with moderate epithelial dysplasia shortly (3.5 months) before the appearance of cancerous tumors indicates with a significant degree of probability that the development of cancerous tumors took place with the participation of both diffuse hyperplasia and adenomas. This assumption is based on the fact that both small adenomas and diffuse hyperplasia themselves can hardly be seriously considered a source of cancer

development in a significant number of cases due to the absence of pronounced dysplastic changes in each of these types of mucosal changes.

Most of the observations of the rapid development of cancer also provide certain grounds for this interpretation of the causes of its appearance, since cancer tumors, as we could see, often contained adenoma tissue and had direct contact with areas of diffuse epithelial hyperplasia. These data are partly confirmed by the results of a study on the prevalence of diffuse hyperplasia. Of the 40 patients with infiltrative cancerous tumors of the colon, such contact was noted in 38 cases (95%). On the other hand, the localization pattern of diffuse mucosal hyperplasia sites largely coincides with the localization pattern of cancerous tumors.

It is quite obvious that this interpretation of events in most of the cases of colon cancer that we have observed, the appearance of which was not associated with previous adenomas, should be considered hypothetical. However, it is necessary, along with the well-known arguments that currently determine the attitude towards the development of cancer in the colon, to take into account a number of newly identified circumstances that could confirm this hypothesis in a certain sea:

a) as shown by the analysis of clinical observations, most adenomas, even reaching significant sizes, retain all signs of benign tumors. At the same time, the appearance within the same time frame of infiltrative small-sized cancer tumors containing fragments of polypoid tissue suggests that the differences between the growth of adenomas and the development of cancer are by no means due only to the different rate of evolution of adenomas, as was previously thought. More likely, given the results of the observation, is the position that adenomas of even small size may be a component contributing to the initiation of rock in the colon;

b) the revealed correspondence between the structure of the epithelial surface and morphological types of microformations, polyps and tumors of the colon, as well as the synchronous nature of changes in each type of epithelial surface together with tumors

located within them as the age of patients increases and the growth of these tumors intensifies, most likely indicates relatively independent growth and development of various morphological types of tumors. Less likely in this regard is the modern concept of the phased transformation of tumors from one morphological type to another, despite the fact that the existence of tumors with a combined structure is convincingly proven;

c) there is a high degree of overlap between the spread of cancer tumors in the folds and physiological sphincters, in the intestinal sections and diffuse hyperplasia of the colon mucosa, which suggests a close relationship between diffuse hyperplastic changes and the development of cancer;

d) in addition, our data showed that the appearance of cancer resembles the appearance of adenoma, and the spread is similar to the spread of diffuse hyperplasia, i.e. cancer tumors tend to circulate the intestinal wall in the area of folds, thus detecting signs characteristic of both adenomas and diffuse hyperplasia;

e) the identified various changes in the epithelium lead, as we have shown, to a special kind of violation of cellular kinetics in the superficial epithelium of the mucous membrane, especially between adenomas and diffuse hyperplasia. Such processes should in some cases lead to disturbances of normal cell-cell interactions in the epithelium, which under certain circumstances can probably lead to damage to the genome characteristic of cancer simultaneously in a large number of epithelial cells. As can be realistically observed, colon cancers differ in cell polymorphism and consist of a large number of cell clones. This seems to be caused not only by pathological mitoses, but also by the simultaneous formation of multiple clones at the time of tumor initiation.

Unilateral consideration of the facts indicating the likelihood of colon cancer initiation in a significant part of the observations involving hyperplastic and dysplastic epithelium would not contribute to the objectivity of our analysis. In this regard, we also considered it appropriate to list those data from our observations that

may contradict this hypothesis. Among those, first of all, it is necessary to indicate:

a) the absence of polypoid tissue in a significant part of tumors, the development of which was not associated with large adenomas;

b) certain doubts about the possibilities of cancer initiation through the alleged mechanism are caused by the fact that microadenomas and small adenomas practically do not occur within the diffusely hyperplastic epithelial surface, only adenomas larger than 1 cm sometimes come into contact with areas of diffuse hyperplasia;

c) as we have indicated previously, the presence or absence of polypoid tissue in cancerous tumors is not conclusive evidence of their origin from adenomas or macroscopically unaltered epithelium;

d) in addition, diffuse hyperplasia was not accompanied by all, without exception, colon tumors; there is also no way to argue, based on our observations, that diffusehyperplasia preceded the development of all cancerous tumors. On the other hand, given the nature of changes in the epithelium in diffuse hyperplasia, the possibility of developing cancer against its background cannot be completely ruled out. The implementation of such a scheme is difficult, however, to recognize as quite likely, since the observation data indicate that the development of cancer in most cases was preceded only by moderate diffuse epithelial hyperplasia.

In conclusion, I would like to emphasize once again that each of the arguments we have given, both in support of the point of view about the possibility of initiating cancer tumors with the participation of hyperplastic and dysplastic epithelium, and against it, are indirect and can be challenged as well as the arguments put forward by the founders of the concept of phased development of cancer mainly from adenomas or the development of cancer "de novo." At the same time, with the help of this hypothesis, it turned out to be much easier to explain all the variety of circumstances that accompanied the development of colon cancer, not only from the

materials of most of our observations, but also from the literature, no matter how contradictory they might sometimes seem.

Summing up our work, it also seems quite appropriate to explain that the hypothesis put forward by us can be most useful only if direct evidence can be found to confirm it, the search for which can most likely be carried out through cooperative endoscopic and genetic studies. If our proposed interpretation of events in the development of colon tumors does not find confirmation in the future or is refuted, we nevertheless sincerely hope that the data obtained in the process of our research will be useful for specialists working on this problem.

CONCLUSIONS

1. The results of clinical and endoscopic observation conducted in accordance with the principles of modern deontology in 4134 patients with epithelial neoplasms of the colon for up to 15 years confirm the need for periodic examination of patients in this category.

2. Observation of 239 patients with small (up to 0.5 cm) solitary and multiple polyps showed that most of them (77.4%) did not have significant changes in the condition of polyps and the mucous membrane of the colon.

3. The growth and recurrence of polyps in the follow-up of 2079 patients after endoscopic polypectomy was noted in 49.7% of cases, including 0.6% of them had malignancy of recurrent adenomas; in 2.2% of patients, the development of cancer according to visual data was not associated with continued growth of polyps; in 48.1% of patients, no growth of neoplasms was recorded.

4. The results of observation of 1816 patients operated on for colon cancer showed that 58.0% of them had growth and recurrence of polyps, 5.1% had the development of metachronous primary multiple cancer tumors.

5. All observed forms of polyps growth: the appearance of new adenomas, an increase in the size of previously identified polyps and recurrence are uneven; the appearance of new polyps turned out

to be the predominant form of polyps growth in frequency (80.6%). The increased growth of polyps may indicate an increased likelihood of developing colon cancer.

6. With periodic removal of polyps from the colon, a significant decrease in the degree of dysplastic changes in newly detected adenomas is observed, which indicates the high effectiveness of endoscopic polypectomy in preventing the development of cancer from large adenomas.

7. In 83.8% of patients, the development of infiltrative cancer tumors occurred despite the periodic removal of all polyps, which does not correspond to the point of view about the predominant origin of cancer from large adenomas.

8. Most polyps, even as they reach significant sizes, are relatively benign adenomas. At the same time, the appearance within about 1 year of infiltrative cancer tumors without previous large adenomas suggests that such tumors arise in connection with alternative mechanisms of blastomogenesis.

9. With the help of intravital chromo- and colonomicroscopy, three main types of cellular architectonics of the epithelium were identified, differing in the location, number and nature of the intravital coloration of colonocytes, as a result of which the mucous membrane often has a mosaic structure. Moreover, various morphological types of epithelial neoplasms: tubular adenomas, hyperplastic polyps and cancerous tumors are located on the types of epithelial surface characteristic of them.

10. Diffuse hyperplasia of the colonic mucosa was revealed, its endoscopic, microendoscopic semiotics and prevalence in the colon were studied; histological and electron microscopic identification of hyperplasia of this type was carried out. This made it possible to consider diffuse hyperplasia as one of the factors that can affect the possibility of developing cancer.

11. The appearance of cancerous tumors is often preceded by moderate diffuse mucosal hyperplasia without focal changes, in some cases in combination with other types of cellular architectonics of the epithelial surface. Against the background of hyperplastic

epithelium, sometimes for 3-3. 5 months before the detection of cancer, small adenomas with moderate dysplasia of the epithelium of the glands are detected, which suggests the complicity of these structures in the development of cancer. These data do not coincide with the point of view about the possibility of cancer on the unchanged mucous membrane.

12. The appearance of adenomas, especially rapidly growing ones, against the background of hyperplastic epithelium should be considered potentially more dangerous from the point of view of the possibility of cancer development in comparison with adenomas located on the epithelial surface characteristic of this type of neoplasm.

13. In most patients, the appearance of infiltrative cancerous tumors is almost asymptomatic. In the presence of clinical manifestations, among which blood and mucus secretions predominate, their duration does not exceed 6-8 months and, apparently, corresponds to the timing of cancer development. These data contradict ideas about the predominantly slow rate of development of colon cancers.

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