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Polyps and Cancer of the Large Bowel

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MORTALITY STATISTICS tell us that cancer of the colon and rectum is second only to lung cancer as a cause of death in the general population of England and Wales[1] but when its relatively much higher cure rate is taken into consideration then the incidence rates of lung and bowel cancer may be very similar. Statistics from the United States have shown that large bowel cancer is becoming commoner and now has a higher incidence in the total population than any other type of cancer except cancer of the skin.[2] Cancer of the colon and rectum is therefore an important public health problem.

It is well recognized that the identification of precancerous conditions is the basis of cancer prevention. At the present time isolated adenomas, familial polyposis and ulcerative colitis are the conditions that are known to predispose to cancer of the large bowel. The concept that most cancers of the colon and rectum evolve from isolated adenomatous polyps and villous adenomas is sometimes known as the polyp-cancer or adenoma-carcinoma sequence.

Granted that a substantial body of evidence in support of the polyp-cancer sequence is already available[3,4] the following questions require to be answered in detail:

(1) Do all adenomatous polyps and villous adenomas inevitably become cancerous? (2) Does all cancer of the colon or rectum evolve from preexisting adenomatous polyps and villous adenomas? (3) How long does it take for the adenoma-carcinoma sequence to evolve? (4) If some cancer does not arise from preexisting adenomas, what is the alternative mechanism of histogenesis?

Aspects of the morphology of the adenoma-carcinoma sequence will be described here, together with some statistics from St. Mark's Hospital, London, about the malignant potential of isolated adenomatous polyps and villous adenomas. Other evidence will also be presented which gives some idea of the life history of the adenoma-carcinoma sequence.

Morphology of the Adenoma-Carcinoma Sequence

It is common to see neoplastic tumors in the colon and rectum that are partly benign and partly malignant. This can be obvious on gross examination. Sometimes, however, the benign or malignant component may only be apparent as a result of microscopic studies. A macroscopically benign adenomatous polyp or villous adenoma should always be carefully examined for evidence of invasive cancer because the latter may be limited to small microscopic foci. Occasionally, what appears to be a benign adenomatous polyp is found to be entirely composed of cancer on microscopic examination (so-called polypoid carcinoma). Whatever their relative proportions the presence of contiguous benign and malignant tissue is some evidence that the carcinoma arose from a previously benign adenoma.

In a series of 1,961 malignant tumors in patients seen at St. Mark's Hospital from 1957 to 1968, there were 278 (14.2 percent) in which there was evidence of contiguous benign tumor, either adenomatous polyp or villous adenoma. The frequency with which benign adenoma is found in continuity with cancer varies with the extent of spread of the malignant component. If the latter shows spread into the extramural tissues of the wall of the colon or rectum the frequency with which benign tumor is found is only 7 percent. With spread in continuity limited to the wall

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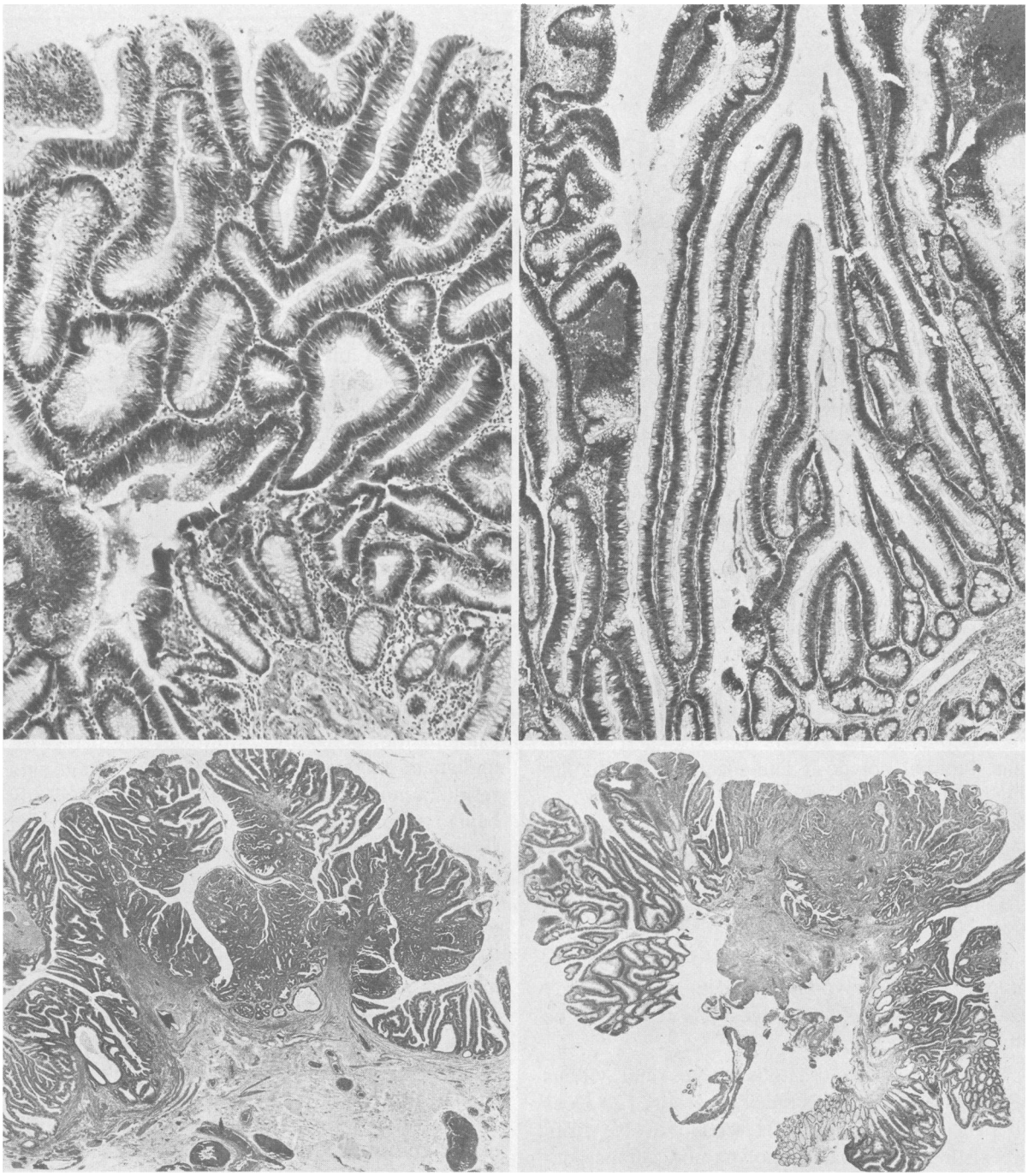

Figure 1.—Upper Left, detail of benign adenomatous polyp showing mild epithelial atypia (reduced from H & E× 126); **Upper Right,** detail of benign villous adenoma showing mild epithelial atypia (reduced from H & E×50); **Lower Left,** tubulovillous (villoglandular) adenoma. In the central part of the photograph there is severe epithelial atypia but the neoplastic glands have not actually crossed the line of the muscularis mucosae (reduced from H & E×15); **Lower Right,** tubulovillous adenoma. In the central part of the specimen there is severe epithelial atypia with invasion by adenocarcinoma across the line of the muscularis mucosae into the submucosal tissues. The adenoma is in continuity with the adenocarcinoma (polyp-cancer sequence) (reduced from H & E ×15).

of the bowel it rises to nearly 20 percent, but if there is invasion of the submucosal tissues only it is nearly 60 percent. This approach to the study of the adenoma-carcinoma sequence suggests that certainly about half and probably nearer two thirds of all cancer of the colon and rectum arises from previously benign adenomatous polyps or villous adenomas. It is probable that as cancer spreads through the bowel wall so it expands on the mucosal surface and tends to destroy surviving benign tumor.

Malignant Potential of Adenomatous Polyps and Villous Adenomas

Adenomatous polyps, villous adenomas and their synonyms are names given to describe different histological types of benign neoplastic polyp (see Figure 1). There is a histological spectrum with the typical adenomatous polyp (tubular adenoma) at one end and the typical villous adenoma (villous papilloma) at the other. The intermediate histological type has been called "papillary" adenoma, "villoglandular" or "tubulovillous" adenoma. Whatever the name used, the histological structure is intermediate between adenomatous polyp and villous adenoma and will be described as such here.

The adenomatous polyp (75 percent) is far more common than the typical villous adenoma (10 percent) and about 15 percent of tumors have an intermediate structure. The malignancy rate for the different histological types of polyp can be assessed by an analysis of the frequency with which cancer is found in a series of tumors that are either wholly or partly benign. *In this context "cancer" is defined as invasion across the line of the muscularis mucosae.* The general malignancy rate for the common adenomatous polyp is only 5 percent compared with 40 percent for villous adenomas. The intermediate type of polyp (usually called villoglandular adenoma in the United States) at 22 percent seems to behave more like the villous growth pattern than the adenomatous polyp. These figures emphasize that villous adenomas have much the greatest malignant potential. How can this be explained?

It has been clear for many years that there is a close relationship between the size of adenomas and their malignant potential. The St. Mark's experience shows that the malignant potential of adenomatous polyps and villous adenomas (including the intermediate type) is very low indeed for tumors under 1 cm in diameter; between 1 and 2 cm in diameter the malignancy rate increases to one in ten, but nearly half of all polyps over 2 cm in diameter contain evidence of invasive cancer. These figures obviously have great practical importance for radiologists, surgeons and pathologists.

The common adenomatous polyp is usually small and very rarely contains invasive cancer.[5] As they grow, however, so the malignant potential increases and about a third of them over 2 cm in size are malignant. But, even small villous adenomas have a malignancy rate of about 10 percent and cancer is found in about 50 percent of those over 2 cm in diameter. The malignancy rate for the intermediate histological type approaches much closer to that for villous adenomas than for adenomatous polyps. Mostly, the villous type of growth pattern presents as a larger tumor than the ordinary adenomatous polyp.

Although there are important differences in the frequency and behavior of adenomatous polyps, villous adenomas and the intermediate histological type, it must be emphasized that the cytological characteristics in all three varieties are the same. It is essential to distinguish between the histology or tissue architecture of these tumors and their cellular features. It is customary to regard the latter as an epithelial atypia or dysplasia which can be graded as mild, moderate or severe. Many histopathologists would regard severe dysplasia as synonymous with carcinoma *in situ.* However, this is an expression best avoided in the diagnostic practice of tumors of the colon and rectum because of its controversial meaning.

The grade of atypia in polyps is not always uniform and foci of severe dysplasia may be seen in a tumor which otherwise has mild or moderate dysplastic changes. The criteria for judging the degree of epithelial atypia include nuclear changes such as enlargement and pleomorphism, loss of polarity, stratification and an increase in the number of mitotic figures, some of which may be abnormal forms. With increasing severity of dysplasia there is loss of differentiation and usually, but not invariably, a decreasing amount of mucin secretion. The diagnosis of malignancy is made only by observing invasion across the line of the muscularis mucosae. Once this barrier has been breached there is potential for metastasis, although a distinction must be made between true cancer and pseudocarcinomatous invasion.[4]

The grade of epithelial atypia is valuable in the study of the malignant potential of adenomatous

polyps and villous adenomas. Mild atypia is associated with a low malignant potential, but a third of all polyps with severe atypia contain invasive cancer. In other words, there is a clear correlation of increasing epithelial atypia with increasing malignant potential. The St. Mark's figures[5] also show that small polyps very rarely show severe atypia but when they do there is a high malignant potential. But as polyps get larger the influence of the degree of atypia on malignant potential is diminished. Size seems to have paramount importance in judging the risk of cancer.

The relationship of grade of atypia to histological type of polyp is also interesting.[5] The malignancy rate for all adenomatous polyps with mild or moderate atypia, which are the great majority, is low. Severe atypia in adenomatous polyps is uncommon but is associated with a relatively high malignant potential (about 25 percent). Villous adenomas, on the other hand, often show severe atypia and this may be one important explanation for their high malignant potential compared with that of adenomatous polyps.

Multiple Benign and Malignant Tumors

There is abundant evidence that most cancers of the colon and rectum arise from previously benign adenomatous polyps and villous adenomas.[3,6-8] Granted the importance of this relationship, a study of multiple benign and malignant tumors gives useful information about groups of patients who are at increased risk from neoplastic disease of the large bowel. Of a total of 3,002 patients at St. Mark's there were 2,412 who had one tumor only and 590 (19.7 percent) who had multiple synchronous tumors, either benign or malignant. This means that one in five of all patients with neoplastic disease of the large bowel have more than one benign or malignant tumor somewhere in the colon or rectum. This fact has important clinical implications. It means that meticulous examination of the whole large intestine is essential for patients who have presented with a tumor in one part of it.

In the same series of 3,002 patients there were 210 (7 percent) in whom a second or metachronous benign or malignant tumor was found to have developed when subsequent follow-up examinations were made. It is probable that this figure is an underestimate because this study covers a period of time before the introduction of colonoscopy. Moreover, in not all the patients were sufficiently meticulous follow-up examinations by air contrast barium enema carried out—which is essential for proper investigation of the whole colon. It is likely that the risk of a second tumor developing is at least one in ten and probably greater. This also illustrates the importance of follow-up of all patients who have had an adenomatous polyp, a villous adenoma or a cancer removed from any part of the large intestine. Studies at St. Mark's have also shown that the risk of developing cancer increases with the number of benign adenomatous polyps or villous adenomas. At this point, the important distinction between polyps that are genuine adenomas and those that a histopathologist can recognize as hyperplastic or metaplastic polyps must be emphasized. The latter have no relationship to cancer.

Metachronous Cancer of the Colon and Rectum

Patients in whom a malignant tumor has been removed from one part of the large bowel are at risk for a further malignant tumor developing in any remaining large intestine.[9,10] The interval between the first and second malignant tumor varies from 2 to 31 years in the St. Mark's series, with an average of 13.5 years. The cumulative risk of developing a second malignant tumor increases with the length of follow-up, reaching about 5 percent after 25 years, but the risk varies according to whether or not adenomatous polyps or villous adenomas were present in the first operation specimen. If they were present then the risk of a second malignant tumor rises steeply with time to reach 10 percent at about 25 years. In the absence of such polyps in the first specimen the curve flattens off to a metachronous cancer rate at 25 years of only about 4 percent. This is evidence, first, that there is an important relationship between adenomas and cancer, but, second, it suggests that the adenoma-carcinoma sequence is probably a process that evolves for many years.

Life History of the Adenoma-Carcinoma Cancer Sequence

The actual time it takes for the adenoma-carcinoma sequence to evolve can be measured by a study of the age distribution curves of patients with adenomas and cancer. These show that adenomas appear on the average about four years before cancers. This figure must be a considerable

underestimate because whereas the age at diagnosis of cancer may be fairly accurate, the age at diagnosis of a polyp is likely to be very approximate because usually there are no symptoms. Further comment about the value of age distribution curves as applied to the adenoma-carcinoma sequence is given below under the heading of Familial Polyposis.

It is rarely possible to make direct observations on the adenoma-carcinoma sequence because polyps are usually removed by local excision. The fate of four patients with adenomatous polyps in the rectum who refused treatment has been studied. In the first two cases the diagnosis of cancer was made about five years later. In the third case the polyp-cancer sequence took longer than 12 years to evolve. The case of the fourth patient illustrates the observation that a histologically proven adenomatous polyp may remain benign for at least 10 years without becoming malignant. It has already been shown that the malignancy rate for all adenomatous polyps is only about 5 percent, which of course suggests that many, and probably most, adenomatous polyps never evolve into cancer.

It is easier to make direct observations over a long period of time on villous adenomas because these are usually large tumors that are prone to recurrence after local excision. Our studies have found that villous tumor, proven histologically, will remain benign for up to 20 years without becoming malignant. In one patient benign tumor only was observed for nearly 30 years before malignant change was detected. In another patient the evolution of the polyp-cancer sequence took at least ten years. In all these patients repeated local excisions for benign tumor had been done at the same site in the rectum and it is, of course, possible that this delayed the onset of malignancy. Although it has already been shown that villous adenomas have a high malignant potential it is likely that the adenoma-carcinoma sequence, as judged by this evidence, evolves over many years and as with adenomatous polyps, it is likely that some villous adenomas may never become cancerous.

The life history of the adenoma-carcinoma sequence is probably very variable. The study of metachronous cancer rates, age distribution curves and these direct, if selected, observations suggests that it is never less than 5 years and is, on the average, about 10 to 15 years, but may even cover a normal adult life span. Further support for this opinion is obtained from a study of the adenoma-carcinoma sequence in Familial Polyposis.

The Adenoma-Carcinoma Sequence in Familial Polyposis

In this genetically predetermined condition the mucous membrane of the large intestine is covered by hundreds or thousands of adenomas. Mostly these have the structure of tubular adenomas (adenomatous polyps) but it is not sufficiently well recognized that a minority are villous and others have an intermediate histological structure. In patients with familial polyposis, cancer will almost inevitably develop if left untreated and all the evidence suggests that the cancer arises from the adenomas.[11]

A study of the life history of the adenoma-carcinoma sequence in familial polyposis gives very useful information which is relevant to our ideas about the time it takes for cancer to evolve from isolated adenomatous polyps or villous adenomas. For example, the age distribution curves for polyposis and cancer show that the average age at diagnosis of polyposis without cancer is about 27 years and polyposis with cancer about 39 years. This gives a time interval of about 12 years between the diagnosis of polyposis and the later development of cancer. As with the age distribution curves for isolated adenomas and cancer, measurement of the age at onset of polyposis is inaccurate but probably much less so than for isolated lesions. In any case the figure of 12 years is likely to be an underestimate of the length of the adenoma-carcinoma sequence in these circumstances.

More information about the time it takes for cancer to develop in patients with polyposis comes from analysis of the age at onset of polyposis and cancer in 59 patients who, for one reason or another, did not have any treatment for their disease. Mostly these patients were under care at St. Mark's Hospital before the operation of total colectomy and ileorectal anastomosis was established about 25 years ago. Findings in this study have shown that out of 59 patients with polyposis observed during five years, in only seven (12 percent) did cancer develop. There were, then, 52 patients who harbored adenomas for five years without malignant change. The cancer rate between five and ten years increased to 25 percent, but there were still 29 patients who had had adenomas for ten years that remained

benign. At 10 to 15 years the cancer rate increased to just over 30 percent and there were still 13 patients who had had adenomas for 15 years without any malignant change. The cancer rate at 15 to 20 years was over 50 percent but four patients had polyposis for 20 years that remained benign. Lastly, there were three patients in whom the adenoma-carcinoma sequence took over 20 years. These figures lend support to the concept that the evolution of cancer of the colon and rectum from adenomatous polyps and villous adenomas takes at least 5 years and maybe more than 20 years, but on the average lies between 10 and 15 years. It must also be remembered that only one or a few malignant tumors develop in polyposis and that most of the adenomas in this condition do not become malignant during a normal life span. It has already been shown that the malignancy rate for adenomatous polyps is only about 5 percent, and for villous adenomas about 40 percent. This must mean that many adenomatous polyps and villous adenomas never become malignant.

For many years it has been customary at St. Mark's to treat patients with familial polyposis by total colectomy and ileorectal anastomosis. The adenomas in the rectum are removed by fulguration and recurrences of benign tumor at subsequent follow-up examinations are also treated by this method. The risk of cancer in the rectal stump after colectomy and ileorectal anastomosis has been analyzed for 86 patients followed for up to 25 years.

So far only in two patients has cancer of the rectum developed at two and seven years after colectomy. The longest follow-up is for 11 patients who have remained free of cancer for between 20 and 25 years. This low incidence of cancer of the rectum after colectomy and ileorectal anastomosis at St. Mark's is in great contrast to that reported from the Mayo Clinic[12] and requires some explanation. It may be significant that the rectal stump was kept free of adenomas by fulguration in all the St. Mark's patients. In other words, removal of adenomas means prevention of cancer. It is also possible that the operation of total colectomy and ileorectal anastomosis so changes the environment of the rectal mucosa that neoplastic activity is inhibited. Hence, perhaps, the observation of regression of adenomas in the rectum after this operation. The high cancer rate in the rectum in the Mayo Clinic series may, however, be explained by different methods of selection and management of patients with polyposis.

Conclusions

At the beginning of this discussion four questions were asked for which answers can now be attempted.

First, do all adenomatous polyps and villous adenomas inevitably become cancerous? The answer must be no, if only because the prevalence of these tumors is so much greater than the prevalence of cancer. Evidence has been presented that shows that the risk of cancer varies with the size of the adenoma, with its histological type and the degree of epithelial atypia. Generally speaking, the risk of cancer is very low indeed for tumors under 1 cm in diameter but increases to 50 percent when the adenoma is over 2 cm in diameter. Villous adenomas are usually larger than adenomatous polyps.

Villous adenomas have considerably greater malignant potential than adenomatous polyps. Apart from the important issue of size, it has been shown that the cancer rate increases with the degree of epithelial atypia and severe atypia is more common in villous adenomas than in adenomatous polyps. However, the evidence also suggests that many adenomatous polyps and villous adenomas never become malignant.

Second, does all cancer of the colon and rectum evolve from preexisting adenomatous polyps and villous adenomas? The evidence suggests that most cancer of the colon and rectum has evolved through the adenoma-carcinoma sequence. The answer to the fourth question posed at the start can be conveniently answered now. If some cancer does not arise from adenomatous polyps and villous adenomas what is the alternative mechanism of histogenesis?

The concept of cancer "de novo" is difficult to appreciate because it has never been defined in morphological terms. It must be understood that adenomas can be very flat, although clearly circumscribed lesions which are only very slightly raised up above surrounding normal mucous membrane. However, it is rare for them to adopt this form in the colon and rectum. More often they are obviously elevated to form a "polyp," sessile or pedunculated. Whatever its gross appearance adenoma is the only known precursor of cancer of the large bowel other than the more diffuse and extensive epithelial changes seen in long-standing ulcerative colitis. For pathologists,

of course, familial polyposis should be more accurately called "adenomatosis."

How long does it take for the adenoma-carcinoma sequence to evolve? It is not possible to give an accurate answer, but the study of the behavior of patients with isolated adenomas and familial polyposis suggests that the polyp-cancer sequence evolves slowly. On the average it takes 10 to 15 years; it may take as little as 5 years or as long as 25 years.

Because adenomatous polyps and villous adenomas have significant potential for malignant change every opportunity should be taken to discover and remove them. At a time when the surgical cure rate for cancer of the colon and rectum shows no sign of improvement prevention becomes an issue of great clinical importance. The introduction of the double contrast barium enema and the colonoscope means that we can now accurately examine the entire large bowel.

Patients who have had adenomas or cancers removed have a significantly increased risk of further adenomas or cancer developing in any remaining large intestine and should therefore have regular follow-up examinations by air contrast barium enema or colonoscopy, whichever is clinically appropriate. Study of the life history of the adenoma-carcinoma sequence suggests that these follow-up examinations can be done at three yearly intervals provided the patient's large bowel was tumor-free at the last examination. It is only by persistent follow-up and meticulous examination of the whole large bowel that a significant measure of cancer prevention will be achieved.

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