Polyposis of the colon and its relation to malignancy

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POLYPOSIS OF THE COLON
AND ITS RELATION TO MALIGNANCY

Senior Thesis
by
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INTRODUCTION

During the past twenty five or thirty years great changes have taken place with the respect to the treatment of diseases of the gastro-intestinal tract. It was considered before that time, that an operation upon the bowel was usually fatal, as the procedure was necessarily dirty, and that aseptic healing was not even expected.

With respect to the colon very little work has been done before the last ten years. Diseases of the rectum were first considered as this region was more easily examined and treated than the portion of the bowel farther away from the surface of the body. Diseases of the colon are assuming an increased importance, due largely to the fact that they are becoming more common, and they are now more commonly recognized. The modern dietary may also be a factor. Among uncivilized races the alimentary tract has to digest and deal with food in which digestible and undigestible foods are about evenly mixed. Under our present civilization, however, foods, both animal and vegetable, are specially grown. The animals which supply our meats are specially bred and cared for to render meat free from gristle, and the vegetables we eat are cultivated to contain but little cellulose, and are further prepared to reduce this ingredient to a very minimum. Under these conditions to which must often be added other forms of preparation the normal stimuli to peristalsis and digestion are to a large extent absent.

Polyposis of the colon has been recorded as early as 1721, (17) at which time Menzel reported a case which simulated that of a congenital type of polyposis in a boy 15 years of age. In 1832
Wagner, and in 1839 Rolsitansky, both reported cases of multiple polyposis. Occasional cases were reported before this time, but the first serious thought along this line began in the early part of the last century. It is only in the present century, however, that prevalence of this disease has been generally recognized. Even now a great deal of confusion exists in the literature as to the exact meaning of the term "polyposis of the intestine", some authors being inclined to regard it as designating a particular type of tumor, which, however, is never well differentiated from adenomata or inflammatory hyperplasia; but on the whole it would seem that it was more commonly and rightly, used in a broader sense as the general term for any pedunculated or sessile growth projecting into the lumen of the bowel, either the result of hypertrophy or hyperplasia of mucus membrane, or a benign true tumor.

It has been the foremost thought in the mind of every research man in the field of cancer as to what the etiological factor, for its development might be, and what can be done to prevent its development.

As a large percentage of the malignancies of the body are in the gastro-intestinal tract, this area of the body, in the last few years has been a field of study for many investigators. Lockhart-Mummery and Dukes of London are perhaps the greatest authorities on the subject and have done more work than anyone else. However, a great deal of work has been done on the investigation of polyposis in the United States recently, especially at the Mayo Clinic. The disease, polyposis, is not sufficiently severe in itself to demand so great a consideration, but it has been observ-
ed for several years that it has in certain cases an apparent relation­ship to the development of malignancy, usually carcinoma, which is one of the most, if not the most, dreaded disease of man­kind. For this reason I feel it is a most important subject, and is one which will become more and more important and is worth a great deal of study and investigation.
ANATOMY OF THE COLON

The colon is subdivided in sections which have been named according to the generally accepted ideas of their locations and special functions. The five sections thus designated may be classified into two main groups. Group 1—the cecum and ascending colon to the mid-transverse colon. Group 2—the left half of the transverse colon, and the descending colon and the iliac and pelvic colon.

The actual length of the entire colon varies greatly in different individuals. The most generally accepted length is from 3 to 5 feet, although some authorities give it as from 5 to 9 feet. The iliac and pelvic portions collectively are known as the sigmoid and it may be anywhere from 9 to 15 inches long; because of the action of the taenia coli bands the colon may vary in length, from time to time, even in the same subject. This question of length is of particular importance in the administration of colonic therapy or operative attack.

The cecum is about 2½ inches in length, and its diameter is about 3 inches. According to the teaching of most text books, at the outset, the ascending colon is the same diameter as the lumen of the cecum, that is approximately 3 inches--but thenceforward, the lumen of the colon is gradually reduced in size until at the termination of the third section, or descending colon, it is barely 1½ inches in diameter. As a matter of fact there can be no dogmatic assertion in regard to this, for the colon contracts to such an extent that its lumen is obliterated. At any time the width of the lumen may be anywhere from ¼" to 6".
BLOOD SUPPLY:—The cecum and vermiform processes are supplied with blood from the ileocolic artery: the circulation of the ascending colon is from the right colic artery. That of the transverse colon comes from the middle colic artery, a vessel which lies in the transverse meso-colon. All these arteries are branches arising from the superior mesenteric. The blood supply of the descending colon comes from the left colic artery, while the iliac and pelvic portions are supplied from the branches of the inferior mesenteric, which are known as the sigmoid arteries. The veins corresponding in general to the arteries named, join the superior and inferior mesenteric vessels, but their content is conveyed to the portal vein.

LYMPHATIC SYSTEM:—The lymphatic system of the intestinal tract is of major importance in studies of intestinal tumors, because in case these tumors are of a malignant nature, metastasis of the carcinomatous cells is carried on very rapidly through these channels.

The lymph vessels of the colon are divided into four groups: First, the epicolic; Second, the pericolic; Third, the Intermediary; and Fourth, the main group.

The epicolic group consists of small nodules which are formed in the appendices epiploicae—tiny sacs of peritoneum, which project from the outer or serous coat of the wall of the colon. The pericolic group lay along the medial borders of the colon. Between the branches of the colic artery are found glands and vessels making up the intermediate group, while the main glands lay around the arterial branches, from which the arteries supplying the colon are derived.
In studying the physiology of the colon, it is best to consider it in two anatomical divisions, making the mid-transverse as our area of separation. On the right we have the transverse colon, ascending colon and cecum; on the left, the transverse and the descending colon, the iliac, and the pelvic portions of the colon. These have been designated as Groups 1 and 2 respectively. It has also been mentioned that the last named portions of Group 2 are collectively known as the sigmoid. The portion of the colon to the left of the mid-transverse has chiefly a motor function, therefore, it may be designated as the motor colon. The portion to the right of the division point, or Group 1, has more power of absorption than any other part of the intestinal canal, so it may properly be called the absorptive colon. The whole colon is largely under the influence of taenia coli bands; in the motor portion they have entire control. These bands have properties peculiar to themselves which are not shared by any other similar structures of the body. They not only have ability--common to muscular tissue--to contract when stimulated; they likewise have power of expansion, this expansion being a definite response to stimulation, and not a reflex following contraction. The contraction and expansion of these bands are believed to depend upon chemical activity in the bowel content. Gas probably also plays an important role in their stimulation. Every fecal movement is followed by gas which brings pressure to bear and acts with gravity in promoting activity of the motor portion of the colon and assisting the downward and onward passage of the residue.
These facts regarding the physiology of the colon just set forth, as well as some to be detailed further on are a distinct addition to anything heretofore found in the literature.

The movement of the colon, known as peristalsis, is a result of the action of circular muscle which, by contraction and relaxation, compress or constrict the colon, thus lessening the size of its lumen. In the same way the colon is shortened by the action of the longitudinal muscle fibres. The mechanism by which peristalsis is produced is inherent in the walls of the intestine and is highly autonomous. By the peristolic waves of the ileum, the cecum is stimulated. The ileac waves are the termination of those of the stomach.

The taenia colic bands can, by a single convulsive contraction, empty the colon of its entire content. In order to empty the cecum, the sigmoid portion coils upon itself, thus lifting the cecum up as high as the liver and forcing the colon content to the left. By peristolic action, the content of the colon Group 1 -- the absorptive colon -- is churned back and forth until all suitable material has been digested, at the same time the absorption of liquids is taking place, with the resultant drying of the residue, as it is being passed to the left colon and it is shaping into the characteristic cylindrical form of the normal feces -- to which more particular reference will be had later on. A large loop of bowel forms to the left of the splenic flexure, and as the loop descends, the saculations of the gut disappear and its contents are emptied into the rectum.

The muscular activity of the colon is greatly enhanced by the formation of carbonic acid gas and other gases which arise largely
from the action of bacteria on food material.

In the process of elimination we find that the impulse which sets up intestinal action is not mechanical, but chemical and without this chemical stimulation normal metabolism is interfered with.

The anatomy and physiology of any organ must first be studied before any pathology can be understood. It will be found as we go further into the study of polyposis of the colon and its relation to malignancy is that all theories on the etiology of the disease are based on either anatomy, physiology, or both.

ETIOLOGY OF POLYPOSIS

It has been noticed, since the first cases of polyposis of the colon were diagnosed, that there was a tendency for the disease to occur in families, giving some indication as to a hereditary background. It is also known that the condition occurs at all ages and is about equal in both sexes. Doring who collected about 52 cases from various sources, found it was most common in children, but some authorities have not had the same experience. It is most probable that it arises from chronic irritation. The condition has been noted in young children and thought to be a result of worms.

The malignant transformation brings into account the whole question of the formation of a malignant neoplasm from one which was formerly benign. Regarding the etiology, there are many outstanding theories, two being most important. The first assumes that these tumors develop from areas of the intestine, which are chronically irritated. To substantiate this theory, it is found upon examination that these polypi usually appear near or are
found in areas of chronic inflammation and at the bases of them the ova of pin worms have been discovered. The presence of mono-nuclear leucocytes and other inflammatory cells point to a chronic irritative basis. Cases of Schistosomiasis with malignancy have been seen wherein the parasite was apparently the irritative factor. These tumors are found to appear in areas of the colon or rectum which are the areas most subject to irritation, the cecum and sigmoid being the two most common sites in the colon. The development of these tumors in long standing cases of ulcerative colitis suggests them to have an inflammatory origin.

The second theory which is held states that there is a primary change in the epithelium and that the inflammatory features are secondary. This is suggested by the fact that the mucosa adjacent to the tumors often shows no inflammatory change. From a histological standpoint it is frequently easy to demonstrate the transition from normal tissue to tissue which shows adenomatous hyperplasia.

Saint, states that he believes, as do most others, that the adenomata are merely a stage in the development of true carcinomata and considers them all pre-cancerous. Many investigators have found definite malignant transformations in grossly benign tumors.

Hewitt and Howard also Struthers explain the development of the polypi on the basis that polyposis results from colitis dysentary and form resulting undermining ulcers in some such manner as the following--where the blood supply is good (near the arterioles) the mucosa is preserved, hyperplasia and regeneration
of the glands and sub mucus connective tissue takes place with the amelioration of the ulcerative process. The margins are smooth and rounded off, causing rounded sessile projections. The mucosa regenerates about and over these elevated parts, even over surrounding submucosa and muscle layer. As healing takes place, fibroblasts contract, leading to the acclusion of the orifices of the tubercles situated in the elevations. Retention cysts are formed if there are secreting cells in the walls. It has been found that there are more gland cells over the surface of the polyp than over the surrounding mucosa, therefore, it may be concluded that the polyp is a collection of small cysts. Pedicle formation may be explained on the basis that the submucosa is loose and that the drag on the tumor due to peristaltic pull causes a constriction near the base of the polyp. If the blood supply theory be true, the polypi should be found at the side of the colon and the rectum where the principle blood supply comes in.

The theory known as the Cohnheim-Ribbert theory, that all neoplasms are of a congenital origin, is in dispute. It has been thought, by some investigators, that a tumor is the result of misplaced embryonic tissue. Most authorities, however, believe that the neoplasms arise on a basis of chronic inflammation through mechanical or chemical stimuli. Most of the evidence, at the present time, favors the latter view. Those who favor the former view, or that of the embryonic tissue misplacement, base their arguments upon the outspoken heredofamilial disposition and upon the fact that the disease may occur in early youth. The arguments against this point are that disposition alone will hardly be sufficient
to explain the origin of the disease; but there must also be releasing factors, which are obliterative. There is no doubt but that a conditional factor is concerned, for otherwise the heredo-familial history would not be so common. The releasing factors which are common to a large number of these cases seem to consist of local irritations. The view which accords best with the known facts of the case, is that which assumes an inherited disposition to the pathologic response to irritation combined with long continued irritation from mechanical and chemical irritants that pass through the gastro-intestinal tract. It would appear that people who are constitutionally pre-disposed to the disease, even though they take every pre-caution possible cannot bear even the natural stimuli of food residues that pass through the gastro-intestinal canal without responding in a pathologic way.

The stages noted in the development of malignancy associated with polyposis are, first, gastro enteritis, later there is proliferative inflammation, then adenomata formation and finally carcinomatous development.

MICROSCOPICAL APPEARANCES AND CLASSIFICATIONS

A typical polyp on microscopic examination seems to consist of a central mass of typical adenoid tissue and is covered outside with the ordinary columnar celled epithelium of the colon. These tumors are not simple outgrowths of the mucus membrane, however, as the sub-mucus coat is represented. Upon careful examination it may be noted that they originate beneath the mucus membrane, they may be solitary follicles, and, as they protrude into the colon,
they become covered by mucus membrane which becomes adherent and forms the typical finger-like projection from the intestinal wall. In the pedunculated variety, there is, as a rule, no adenoid tissue in the pedicle. The pedicle consists of a tube of mucus membrane inclosing the connective tissue continuous with the submucous membrane layer of the intestinal wall.

Due to the many disputes as to whether the polypi are of a pre-cancerous nature, being originally benign, and after a time becoming malignant, or whether they are merely stages in the development of a malignancy, has lead to a study in attempted classification by Lockhart-Mummery and Dukes of London in 1928, and later by Fitzgibbon of the Mayo Clinic in 1931. Fitzgibbon, in the study of histogenesis carcinoma of the colon attempts to classify the polypi as to histopathological characteristics. He divides the tumors into three groups. Group 1, including only those growths in which the epithelium retains its normal characteristic. The tumors are usually roughly nodular, in this group, although the surface of them is smooth and regular. The polyps vary in size from tiny club shaped nodules 3 mm. or so in diameter to masses 2 cm. or more in cross section. A loose connective tissue derived from the sub-mucosa forms the tissue which makes up the pedicle and this tissue expands to sustain the nodular polyp. In this type of polyp there is no tendency to branching or papillary forms in growth. It is conceivable that whatever factor stimulates the cancerous change in the polyps could find its expression in epithelium of this group. There is, however, nothing about the polyps to indicate that they are more liable to malignant change than normal intestinal mucosa. For this reason it can be
said that the growth of group 1 are destined for a long benign
career, but no such pronouncement can be made for the polypi of
group 2.

The polypi of group 2 are easily distinguished from group
#1, but the abrupt and striking structural changes that appear
within the tumors, changes that are established in both epithe­
lial are connective tissue elements. The epithelial cells in
these polyps show less differentiation and specialization than
do the cells of the normal intestinal mucosa. These partially
differentiated epithelial cells of the polyps are elongated,
and by their increased bulk are compressed from side to side.
The cell arrangement may be in single rows, but in a great many
places the press of the outgrowing tissue cells tends to cause
them to pile up in multi-layered buds which project into the
lumens of the tubules, but frequently into the connective tissue
matrix as well. The nuclei of these cells are also elongated
and on staining they take the dye more deeply and thus give
to the tissue of proliferation a darker and easily recognized
color. As the process of epithelial proliferation goes on there
is also a proliferation of the connective tissue of the sub­
mucosa and the tug of the tumor soon pulls the muscularous mucosa
and fibriles of the submucosa upward to form a stalk. If the
rate of growth of the polyp is not too rapid, the connective
tissue elements are drawn out into the branching divisions to
form the tree-like supporting structures of the epithelial tissue.
Formation of pedicles is largely a matter of parallel growth in
the connective tissue in the polyps of group 2. The polyps of
group 1 having a slower rate of growth, the pedicle may be greatly influenced by factors outside the tumors themselves, particularly the force of peristaltic action.

From these studies one would assume that the development of carcinoma in polyps is a function of the rate at which tumors grow. In the slow rate of formation of Group 1, there is little, if any, likelihood of cancerous change. In the markedly more rapidly growth of polyps of Group 2, there is a question only of time when carcinoma appears. The conclusion to be drawn from this is that epithelium cannot proliferate indefinitely at the moderate rate without losing its bearings.

The third group of polyps are those in the epithelium of which the process of differentiation have been arrested at such an early stage that the cells have received only the most rudimentary characteristics of normal intestinal tissue. Group 3 is an accentuated form of group 2. However, the two groups remain distinct and can be readily separated by microscopic examination. In the epithelial cells of group 3, it may be noted that the rate of growth is so much more rapid than the surrounding connective tissue that the connective tissue elements cannot keep pace with them. For this reason, the resulting polyp is a mass of epithelial complexes and tangled skeins of disorganized gland tubules. Although the polyps of Group 2 may get very large and remain a long time, those of group 3 never exceed 1 cm. diameter in cross section. Due to the great undifferentiation of these cells they approach those described as malignant, and the rapid proliferation of these complexes must soon break down the barrier of the
muscular coat of the intestine and become infiltrated into the deeper tissues.

Lockhart-Mummery and Dukes classify the polyp formation into stages rather than types, in the belief that they are all pre-cancerous. The first stage, being that of localized patches of hyperplasia invisible to the naked eye, but discoverable with the microscope, affecting an extensive area of the bowel. The second stage, the appearance of a crop of sessile adenomata as wide an area as was affected by the initial hyperplasia. The third stage, the development of cancer, either in one of these pre-existing adenomata or in the neighboring epithelium. The fourth stage, the progressive enlargement and dissemination of the malignant tumor accompanied by a retrogression of the hyperplastic changes and benign tumors surrounding the benign growth.
Symptoms and Diagnosis

The most marked symptom of polyposis of the colon is diarrhea. This is severe and intraceable. The patient rapidly wastes and becomes emaciated due to the loss of fluid from the body tissues and there is not infrequently tenesmus. Stools are liquid and contain much slimy mucus. Blood is frequently present in stools and is immediately mixed with them, blood being a more common symptom in cases which have undergone malignant change. The symptoms in nearly all cases of polyposis resemble those of cancer or ulceration of the colon; but the diarrhea is, as a rule, more severe. Abdominal pain is usually present and in most cases there has been severe pain in the left side of the abdomen. There is, often marked anemia which is the result of bleeding over a long period of time.

There is usually a history of bleeding and diarrhea for long periods. One patient gave a history of almost continuous bleeding for ten years. In another patient the symptoms had persisted without intermission for over three years. Another very remarkable instance was that of three members of the same family all suffering from the condition.

The diagnosis, made on examination of the rectum, shows a number of polypi scattered over the mucus membrane and usually the sigmoidoscope shows a similar condition in the pelvic colon. In these cases the colon usually is tender when palpitated through the abdominal wall.
It is to be born in mind that a chronic ulcerative colitis is a potential chronic polyposis and later is a potential malignancy.

Proctoscopic and sigmoidoscopic examinations are essential. Visualization of the colon by Roentgen-ray should be made in every case of ulcerative colitis, no matter what the etiological factor might be. The radiologist should make two views of the colon, one filled with barium, and another after partial escape of the barium. (9)

According to Erdman and Morris there are two clinical types of polyposis. First the adult form, which is evidently acquired during adult life, and which shows a few scattered polypoid tumors closely associated with frank irritation of the mucus membrane, such as hemorrhages, erosions, ulcerations, strictures, etc.

Routine autopsies rapidly disclose the fact that these tumors are symptomatically silent throughout life; on the other hand these apparently innocent tumors, do at times, initiate symptoms which threaten the life of the patient unless an accurate diagnosis and efficient treatment are obtained.

The second type manifests itself early in youth by intermittent, profuse rectal bleeding and dysentery with consequent secondary anemia, presenting a definite, clear cut, and unmistakable picture which may be, in a large number of cases, supplemented by history involving other members of the family. On examination these cases show on the mucus membrane of the colon, from the ileocecal valve to the rectum, a thickly and uniformly studding with adenomatous polyps without apparent signs as to the etiology as is seen in the first group.

The contention may still be made that these two types may represent a difference in degree of the same process, that is, adenomatous hyperplasia, by the very obvious differences in their clinical pictures justifies the grouping suggested.
Dukes, who is one of the greatest English authorities on the subject of tumors of the colon, states that these adenomatous polyps arise from small areas of increased epithelial growth which can be distinguished under a microscope by the fact that the cells secrete less mucus than their neighbors, and their nuclei stain more deeply with haematoxylin. The more active growth of the epithelial coat results in a projection out into the lumen of the bowel, accompanied by a bowing of the attached coat of the muscularous mucosa.

The secreting cells of the large intestine are depicted as a folded coat closely adherent to the muscularous mucosa and the scaffolding of the reticular tissue, muscle and vessels which the muscularous mucosa supplies to the spaces between the crypts. If the epithelial layer between two points on the wall of the intestine grows more rapidly than in neighboring areas, the first result may be an increase in the depth of the crypts accompanied by an elongation of the scaffolding which arises at right angles to the muscular foundation. A greater secreting area is now noted. In case there is a stimulation to more active growth or function, the first stage of tumor formation must then occur, with a forward bending of the muscularous mucosa, in order to provide a more extensive base for the support of the growth, and a further lengthening, and branching of the scaffolding structure.

This is a mechanical description of the tumor formation which may be noted on examination, and when observed may assist a great deal in arriving at a diagnosis. This view is opposed, however, to those held by some writers, that adenomata owe their origin to some submucous structure such as lymphoid follicle, the secreting
cells in the lumen of the gut, of which Dukes found no evidence. Chronic inflammation, as has been previously stated, as a frequent factor in the tumor growth, is questioned by Dukes, as he states that in the tumors he has studied, if there has been any preceding inflammation, the tissues did not show any evidence of it.
THE RELATION OF POLYPOSIS TO MALIGNANCY

All who are familiar with the disease, now recognize that gastric and intestinal polyposis are pre-cancerous diseases. It is possible that carcinoma of the stomach and carcinoma of the rectum are much more frequently preceded by adenomata than was previously thought. Schmieden believes that most of the cases of carcinoma of the rectum and the colon arise from polyps. One must admit, however, in ordinary cases of carcinoma there is no evidence of the Mendelian dominance whereas, in the carcinomata that develop upon a polypoid basis, Mendelian dominance is often very striking in the family history.

The growing frequency and prominence in the literature on the subject of polyposis is indicative of the increasing interest which a developing knowledge of this condition has stimulated. The occurrence of simple benign intra-luminary tumors of the gastro-intestinal tract has been a matter of such common observation that their appearance has ceased to cause more than passing interest. Intussusception, intestinal obstruction and vague abdominal pains have been recognized frequently associated with intestinal polyposis.

The frequency of occurrence of single and multiple polyps of the large bowel and rectum is in direct proportion to the care in observation in the examination of these cases. Polyps are most always demonstrable in resected specimens in the mortuary or, by proctoscopic examinations. Their size and numbers are so variable that one may frequently experience difficulty in satisfactorily demonstrating the tumor and yet in most instances, one readily makes out single or multiple polyps, varying in size and form,
from small protuberances of the mucus membrane, which histologically are of true polyp formation, to the diffuse lesions commonly recognized as polyadenomas or polypoidosis.

As late as 1902 and 1903 the disease was considered rare, but it has been repeatedly noticed that there is a tendency for these cases to undergo malignant degeneration.

Lockhart-Mummery divides multiple polypi of the colon into four classes. (One) true multiple adenomata; (two) polypi found in association with hyperplastic tuberculosis; (three) multiple polypi found in association with an old stricture of the colon; and, (four) the polypoid condition of the mucosa which sometimes results from ulcerative colitis.

The true multiple adenomata is a condition in which there are small adenomata growing from the mucus membrane of the colon. This condition was first described in 1863 by Virchow. The number and size of these polypi vary a great deal in different cases. They may be very small and numerous in some cases, and the entire colon be completely covered with them, or they may be large and in smaller numbers. These polypi appear in two distinct types, one in which the entire colon is covered with small semi-pedunculated polyps in such great numbers that the normal intestinal mucosa is almost hidden.

In the other type, which is the more common, there are numerous polypi of all sizes and shapes, some of them sessile, but the majority pedunculated. The sessile polypi appear to be only the early condition of the large pedunculated ones. They are often large and their pedicles may be an inch or more in length. Along with the larger tumors there are usually a great many small unde-
veloped polypi, and if they are examined they will be found to be growing from the free edges of the valvulai connuientes. After examining a great many specimens it seems probable that the polypi all originate as outgrowths from the edges of these folds.

These polypi, as a rule are most numerous in the pelvic and descending colon. The rectum is also commonly involved. The polypi in the rectum are naturally the most easily detected and in several instances the condition is described as multiple polyposis of the rectum. Seldom, however, is a case confined merely to the rectum, although in many cases the colon may be involved without any rectal involvement. In most cases the polypi extend throughout the colon, but the cecum seems to be less effected than the remainder of the large bowel.

The larger polypi, especially those near the end of the pelvic colon, tend to become ulcerated from the traumatism to which they are subjected by the passage of the feces.

The most important factor here, however, is the fact that there is a marked tendency for the polypi to become malignant, as has been stated before, and cause a carcinomatous stricture. This is more liable to occur in parts of the colon where the polypi are the most numerous, such as the sigmoid flexure, and rectum.

In several case studies by Lockhart-Mummery carcinomatous strictures were found in the sigmoid flexures. In a solitary case there was evidence of cancer associated with polyposis of the colon a few months after the case was first seen. In this case numerous polypi could be seen with a sigmoidoscope in the sigmoid flexure and the rectum. All of the polypi in the rectum that could be reached were removed. On examination of these tissues the typical struc-
ture of simple benign adenoma was seen. The patient, however, died some months later after developing symptoms of cancer in the sigmoid flexure.

In another case there was a carcinomatous stricture in the sigmoid, which was resected. On examination it was evident that the growth had arisen in one of the polypi. Two of the polypi at some distance from the growth were examined; while one was a simple benign adenomata, the other showed signs of commencing malignancy. In another of Mummery's cases, the patient was operated on for cancer of the sigmoid, and the bowel resected. No polypi were seen in the resected portion, but a year later the patient returned with recurrent symptoms and upon examination several pedunculated polypi were seen some six inches above the old line of anastomosis. The patient died after a second operation and at post mortem there were some six or seven polypi, the highest of which were eight inches above the original line of anastomosis. There was no recurrence at the original site; but on examination, several of the polypi were found to be malignant.

Another case which was seen by Lockhart-Mummery showed on examination that the whole bowel was crowded with adenomatous polyps as large as grapes and in one place there was a typical carcinoma which had spread through the rectal wall and become fixed to the pelvic wall. The carcinoma, in this case, was clearly secondary.

As cancer claims about one out of twelve of the human race, one out of every thirty lethal cancers occurs in the rectum. Carcinoma of the intestinal tract comprises 45% of all cancers of the body, and 13% of all are in the colon and rectum. Lockhart-Mummery, after a study of 200 cases of carcinoma of the rectum, believes that the
most important pre-disposing cause of cancer apart from age, is the presence of these benign polyps in the colon. In a large majority of his cases, in which a segment of the bowel had been resected for carcinoma, the associated adenomata were present. Verse asserts that most gastro-intestinal cancers arise from these simple adenomata, themselves a result of inflammatory hyperplasia.

In a series of 127 cases of multiple polyposis collected from the literature by Hullsiek (15) in 1928, the non-malignancy incidents was 34.6% and an additional 31 of these patients died after having suffered symptoms suggestive of malignancy, so that it is reasonable to suppose that the index is consequently higher than the figures show. Jones says, in speaking of the polypi, that they are "---a condition which we have become to believe more and more of great importance, of even greater importance, than carcinoma itself, for polyps frequently become carcinoma and proper treatment before they become malignant means permanent cure." Yeoman says, in speaking of single benign polyps, "unless thoroughly removed at the base they are likely to re-occur and are prone to malignant degeneration."

Nowhere, according to Ewing, can more clearly be demonstrated the logical transition from simple inflammatory hyperplasia to tumors which are morphologically, pathologically, and clinically adenomata and carcinomata. The foregoing remarks and quotations should be sufficient to emphasize the necessity of a keen appreciation of the potential dangers of the benign tumors of the bowel.

Ewing defines a tumor as "an autonomous new growth of tissue", and may be classified according to one of three plans - regional, etiological, and histological. The tumors under consideration have
been discussed previously from the histological standpoint, yet at times one must consider them as to their morphological factors.

In a collection of 46,379 of rectal diseases of all types, benign tumors were found in 554 instances. Dewis collected in 1904 reports of 219 cases of benign tumors of the intestinal tract on each of which a microscopical diagnosis was available. Leichenstern collected from the literature 128 intestinal polyposis cases. Of the total, 247 cases in the two series, 243 tumors were in the rectum and colon, and 202 of these were adenomata. One is able to state with a reasonable degree of assurance that about 50% of all benign growths in the intestine are in the rectum, hence are in reach of the examining finger. Tumors of the colon may be listed as angiomata, fibromata, myomata, lypomata, adenomata, and papillomata (or villous tumors), the latter being extremely rare. The distribution of the various tumors is shown by a table of Dewis' and Leichenstern's 347 cases. A greater number of adenomata in the intestine tract is noted in all parts.

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New growths of the colon may or may not be polypoid in shape. The word polyp has a purely morphological application and bears no relation to histological character. A polyp is merely a new growth with a pedicle and according to Hullsiek, who differs from a great many other authorities, may be adenomata, fibromata or lypomata and may be either benign or malignant. He states that the numerous attempts at classification of the polyps either clinical or pathological is unsatisfactory. The only satisfactory classification which has been given before is the one used by Lockhart-Mummery. The adenomatous polyp is some cases is not a true adenoma, but merely a polyp covered with more or less normal mucosa. Some of these tumors have been reported to attain the size of an orange. These tumors bleed easily and as has been stated before exhibit as one of their early symptoms a streaking of blood in the stool.

In considering the question of malignancy in single polyps we must remember that these tumors are usually promptly removed as soon as they are discovered, thus ending for once and for all any chance of becoming malignant. This applies mainly to the rectum, however. Those of the colon being less accessible and more difficult to remove makes the chance of their becoming malignant comparatively greater than that of the rectum.

In a series of single polyps, Hullsiek reports malignant degeneration in 24%. Due to the fact that benign solitary adenomata are frequently seen in children one would feel that carcinoma of the rectum and colon in childhood should be higher than is actually the case, if these cases have such a high malignancy index. We have no satisfactory way of knowing the length of time the tumors may be present before carcinomatous change takes place, but appar-
ently it may be years.

According to studies made by Kenedey and Webber the early age of the onset noted in most of these cases, and a lack of other etiological factors, has lead to the belief that the lesions are congenital. They found that the polyps tend to undergo malignant change early, such change has been found frequently when patients are in their early 20's or 30's, although it has even been found when patients were in their late teens.

Even though the condition is discovered early in life before malignant degeneration of the polyps has occurred, the prognosis is not materially changed. The only treatment which offers a prospect of cure is colectomy as is described later and, as is well known, this procedure carries a high rate of mortality. In addition the prospect of cure by colectomy becomes less, because of the possibility of lesions in the small bowel which if present may be expected to pursue the same course as those in the large bowel and which may not be very easily removed. Single adenomata should be considered as pre-malignant growths in all cases and, as such, should be promptly and completely removed, when found. These adenomatas of the colon in some cases, however, may persist for years without undergoing malignant change, but the majority, as has been noted before, turn into cancer in from one to seven years, depending upon the patients vitality, the degree of irritation, and the character of the tumor. According to Levin soft polyps more often undergo malignant change than dense or fibro-adenomata. There may be periods, in the course of the disease, of improvement, but sooner or later the result is a progressive anemia, depletion, emaciation, intestinal malignancy or intestinal obstruction.
It is assumed by Wheeler that the beginning of the disease is an ulcerative colitis. The ulcerative process is of such a character that portions of the mucosa and sub-mucosa adjacent to the primary arterial branches is preserved and these portions remain as ragged tags scattered over the surface of the colon. As these ulcers heal, the tags become smoothed off, and remain as rounded sessile elevations, or as polypoid projections of the mucus surface. Later on, as cicatrization proceeds, the orifices of certain of the tubules situated in and between the polyps may become occluded and retention cysts form, giving rise to what Virchow called "Colitis polyposa cystica." It is the end-stage of colitis polyposa. By some authorities a subtle distinction is made between adenomata, papillomata, and true polypi; but it appears likely that one is but a stage in the development of the other.

In thirty-three consecutive cases of carcinoma of the rectum and colon, at St. Mark's Hospital, Dukes made special search for adenomata in portions of the bowel removed at operation, and found these tumors in twenty-five cases. These little tumors were easily seen before the piece of bowel was hardened in a fixative solution, but the shrinkage and distortion caused by the formalin made them less easy to find. These tumors can be demonstrated most clearly if in fresh specimen. Both the large and small types, which have been described before, have been found.

In a series of cases of carcinoma of the large bowel, Dukes found in 75% of cases that within a radius of 3 inches from the cancer there appeared a few of the larger type of adenomatous tumors.
To gain more light on the relationship between carcinoma and adenoma, serial sections were cut through the cancers, through the neighboring mucus membrane and through the adenomata close to the margin of the cancer. One large adenoma on section, which was separated from the carcinoma by an inch of normal mucus membrane, showed evidence of being carcinomatous at the tip, but the mucus membrane covering the neck of the polyp showed no evidence of malignancy. The conclusion drawn here, was, that this was an instance of malignancy developing in an established adenoma which was originally benign.

Saint states that he bases his belief, that polyposis has a direct bearing on malignancy, by the fact that with the growth of these adenomata the cells become less differentiated. This fact has also been observed by Dukes and Lockhart-Mummery. The question then arises, can this process be so pronounced that these cells can so readily be called malignant before any direct indication of malignancy is noted. These cells are apparently not serving any purpose as to physiological function but are primarily concerned with proliferation.

Saint also states that in thirty-six cases in his series of observations of multiple polyposis of the colon, carcinomata occurred in thirteen. None of the adenomata present showed carcinomatous change in the thirteen cases. However, it must be stated that none of them had grown to a very large size.

Considering the large number of carcinoma of the large bowel encountered without adenomatous polypi being present, the association of the two conditions in the same intestine is not very frequent, according to Saint (who seems to be one of the very few to believe this), and it would seem that although carcinomata occur which are
undoubtedly the outcome of malignant change taking place in adenomata yet the majority arise as cancer per se. It was found to be true, in the observations of Saint, that no malignant change had taken place in any polyp which was smaller than the size of a walnut.
TREATMENT

Robert C. Coffey states that there is probably no benign process in which there is a higher incidence of mortality and it must be conceded that every disease should be treated on the basis of its pathology. In considering treatment one must consider the degree of pathology and the amount of treatment or operative procedure which must be made in the individual case. Treatment of gastric and intestinal polyposis has been most unsatisfactory in the past. Irrigation has been tried with and without colostomy; and wide resections have been made. Recently another method of treatment has been introduced, which is that of deep X-ray therapy.

Dr. J. Rehfisch used in a case 200,000 K.U., 70 cm. distance, 35 cm. port, and 1 mm. of aluminum, and 2 mm. of copper. Shortly after the first treatment the patient reported passing many small macerated grape-like masses which on section showed only necrotic tissue, but its formation, the connective tissue framework, was like that of a polyp. With the passing of these masses the general condition of the patient showed a very marked improvement.

At the examination 26 days after the first treatment all that could be felt remaining of the abdominal masses previously felt were small ones deep in the lower left quadrant. The diarrhea which the patient had previously had ceased. The patient had gained in weight and showed corresponding improvement; within a few weeks he was able to return to work.

Roentgenograms, taken 27 days after the initial dose of deep X-ray therapy, showed a very marked retrogression of the polyposid condition. There were, however, still a few areas of an irregular outline visible suggesting persistence of a few polyps. If
this type of therapy will work in other cases of polyposis of the colon, medical science may be able to help the patients escape the fate which has seemed to await the victims of intestinal polyposis, or carcinoma as a final stage of the disease.

Dr. Barker emphasizes that the dosage of the X-ray administration be heavy. The patient, previously spoken of, when asked how he bore the treatment, stated that it was a very trying ordeal and that he was very sick temporarily after the treatment. Dr. Levin of New Orleans stresses the fact that an early diagnosis should be made and that one should yield ground to the surgeon early in order to do justice to yourself and to your patient. When you wait until the polyposis becomes disseminated, it is as hopeless as a disseminated malignancy. Then surgery, Roentgen-ray, and radium therapy will be of little assistance in this treatment.

Dr. D.C. McKenney reports a conservative type of treatment of a case of polyposis, before malignancy was noted. The patient was given mineral oil by mouth, agar agar, tincture of iodine, carbolic acid and charcoal; enemata of water were given morning and evening. In the office, at frequent intervals, there were removed with a snare through the colonoscope, from 3 to 20 polypi, a total up to the present time the article was written of 481. In about eight weeks following the institution of the treatment the patient had fairly well formed stools which were reduced in number (the patient had not had a formed stool for 10 years previous to the treatment). In about six weeks the patient gained 20 lbs. in weight but he continued to have cramps. At this time, as a result of the removal of many polypi in the lower bowel there came into view, in the angle of the pelvic colon about 12" from the anus, a polyp with a
broad base, and the size of a very large walnut. This was removed piece-meal on different days without very great damage. There was some discomfort and hemorrhage for a day or two after the operation but the cramps have disappeared without symptoms up to the time this article was written.

Some authors feel that polyposis, whether or not malignant change has taken place, colectomy is the treatment of choice. It seems wise to perform the operation in stages, and in the first stage the establishing of a permanent opening by ileostomy. (7)

Dr. C. F. Dickson advises the following procedure in these cases:– the ileum is divided between clamps 30 to 40 c.m. from the ileocecal juncture. The distal end is then closed and replaced in the abdomen to be removed at the time colectomy is performed. The proximal end of the ileum is brought out of the wound and into its lumen a large calibre catheter is placed by means of a purse string suture. If obstruction is not present, drainage from the ileal stoma does not begin usually for two to four days. The amount of drainage material gradually increases, and because of the liquid nature of the discharge, it becomes annoying and is a continuous burden to the patient for a period of about two months. The ileum apparently begins then to take on function of the right portion of the colon, to a large extent, and consequently, the ileal content becomes semi-solid in character and is managed by the patient in much the same manner as that of a permanent colonic stoma. The second stage may be well postponed for two to three months, particularly if the patients are debilitated.
Removal of the colon is best begun on the right side; it is removed in its entirety to the lower portion of the recto-sigmoid where it is cut off, and the distal end inverted and covered with the diaphragm of the pelvic peritoneum. The blood supply of the remaining portion of the rectum and of the recto-sigmoid may be injured and for this reason it seems wise to insert into the posterior cul-de-sac one end of a rubber tube, the distal end of which is brought out into the vagina posterior to the cervix by a single silkworm suture.

The third stage, which is done two to three weeks after removal of the colon, consists of a posterior resection of the remaining segment. This is carried out without making an opening into the peritoneal cavity.
Case I

Robert C. Coffey reports a case in which a woman, aged 31, noticed for nine years before what she called a running of the bowels lasting 10 days with some blood in the stools. A recurrence took place two times the next year and many recurrences with increased symptoms have been recorded since that time. Five years previous the patient had a severe hemorrhage lasting four to five days and these stools were described as clotted blood. A year later a similar hemorrhage occurred. Patient stated that her stomach had been very weak for six months. She stated that at times the intestine protruded through the rectum. Proctoscopic examination--penetration 25 cm. showed the bowel wall to be studded with soft irregular masses of tissue, varying in size from that of a pea to the size of a hen's egg. A diagnosis of polyposis was made. Several of these masses were removed and on frozen section pronounced papillo-adeno-carcinoma.

Case II

H. P. Kuhn reports a case of a man of 68 years complaining that he was unable to have good bowel movements, passing only watery mucus two to three times each day and occasionally bloody mucus. Loss of weight had been about 10 lbs. The trouble started 10 years ago he stated when he was chronically constipated. In the meantime, he had been at times symptom free. Physical examination was negative. X-ray examination showed an obstruction at the junction of the pelvic and descending colon through which the opaque media passed very slowly as a thin stream. A diagnosis of carcinoma of the sigmoid was made.
A colostomy was done and during the operation hard nodules were palpated in the descending colon. The patient died after the operation, and at autopsy showed, upon opening the lumen of the large intestine, that there were a very large number of adenomatous polypi extending from the cecum to the rectum. The tumors varied in size from 5 m.m. to 4½ c.m. The polypi showed no evidence of carcinoma in themselves, but they surrounded an area that was a hard carcinomatous ulcer. The polypi, which on section was shown to be essentially benign, the largest of them showed a rather abrupt change from normal epithelium into polypoid overgrowth. Marked epithelial proliferation and glands of large calibre were seen in many sections.

Case III (7)

C. F. Dickson reports a case of a woman, age 25, who came to the clinic October 9, 1929, because of bloody diarrhea which had persisted for three years. As much as 100 to 200 cc. of blood had been passed by the rectum with one intestinal evacuation. Stools had not been formed for 15 years. Seven months previously she had noticed a mass protruding from the rectum which was removed by her physician at home. A second mass similar to the first was noticed three months later. The patient's general condition had been good with no loss of weight, and she had complained of no pain or cramps.

On rectal examination a nodular mucus membrane was revealed. Roentgenograms of the colon were made which gave evidence of a polyposis of a malignant appearance in the region of the recto-sigmoid. Proctoscopic examination revealed multiple polypi beginning just above the anus and involving the bowel as far as could be seen,
which was 24 cm. One region 3 to 4 cm. above the anus appeared to be malignant. Biopsy showed adeno-carcinoma and operation was advised.

The material removed at operation revealed an adeno-carcinoma graded 2 of the recto-sigmoid. The growth measured 3.5 x 2.5 x 1.5 cm. The patient made an uneventful post-operative recovery, after the colectomy, and in one years time had gained 30 lbs. in weight, and for seven months previous to the time this article was written she had been able to attend to her household duties. This indicates that even though a diffuse and extensive malignant degeneration has taken place, colectomy is indicated. Apparently in this case metastasis to surrounding structures had not been marked, and that by removal of the colon the patients life had been saved.

Case IV

A patient aged 58, male, was reported by Lockhart-Mummery and Dukes to have come to the clinic to have a large pedunculated adenomata removed from the rectum. At operation and adenomata the size of an orange was removed. It had a long pedicle attached about 4 inches above the anus. It was then discovered that there was another adenoma nearly as large as the first impacted in the upper part of the rectum. This was removed with considerable difficulty. After the removal of the second polyp, a sigmoidoscope was passed and a third adenoma, as large as the others, was seen in the sigmoid flexure. The abdomen had to be opened so this adenoma could be removed, it was situated in the lower third of the sigmoid colon and part of it had undergone malignant change and involved the bladder wall.
Case V

A male patient, age 52, was referred to the University of Nebr. Hospital by the Dispensary and admitted November 21, 1931. He complained at that time of sharp epigastric pains and upper right abdominal pains since August 1931. The pains were associated with nausea and vomiting. He had lost 15 lbs. in weight since the onset and has had spells of severe diarrhea at times, but has never noticed any bloody or tarry stools at any time. Just before entering the hospital he had been jaundiced, and with the symptoms of pain near Murphy's point a diagnosis of cholelethiasis was made.

A proctoscopic and sigmoidoscopic examination was made because of the persistent diarrhea, and about 2 inches above the anus an irregularity of the rectal wall was noted which seemed to be polypoid in character. Marked scar tissue formation with bleeding and a discharge of pus were present.

A biopsy specimen from the involved region was taken, the specimen being a polyp, and a diagnosis of carcinoma of the colon was made microscopically.

At a meeting of the cancer committee, after examination of the patient, it was decided that there was metastasis to the liver as was shown by the X-ray and that they felt that operative procedure was not indicated. The patient then left the hospital with a diagnosis of polyposis following ulcerative colitis with carcinoma of the upper part of the rectum and lower colon with metastasis to the liver.

Case VI

Leo Case, age 40, came to the University of Nebraska Dispensary February 6, 1932, complaining of generalized weakness and loss of
blood in stools which had persisted for about two years becoming progressively worse with a loss of weight of over 45 lbs. during that time. The stools have never been black, but always a bright red.

The patient was examined by Dr. Russell Best, and polypoid masses were found in the sigmoid colon.

A Roentgenogram showed multiple filling defects, which were most prominent in the sigmoid. At this time a diagnosis of multiple polyposis was made.

There was no evidence either by X-ray or clinical examination malignant degeneration, and up to the present time there has been no change in the patient's condition.
CONCLUSION

Why cancer develops is an extremely interesting but rather unanswerable question due to the apparent lack of knowledge of the subject up to the present day.

In considering cancer of the colon, there seems to be many different opinions as to its etiology but nearly all authors concede that there is a relationship between multiple polyposis and carcinoma. The question remains, what is the relationship between the two?

The first consideration is that polyposis has been known to occur in families for over thirty years indicating that some persons have an inherited predilection to the disease as many people or families do to such diseases as tuberculosis and cancer in general. If chronic irritation alone is the etiological factor it would be assumed that people living in the same districts, eating the same type of food and having somewhat the same habits, would develop the disease, but this is not found to be true. It would seem plausible then, to assume that other factors enter in. There is no question but that there is sufficient evidence to support the fact that there is an inherited tendency toward the disease by some persons.

In my opinion, by combining the two previous factors, that of chronic irritation and a pre-disposition to the disease, the etiology in most cases may be explained. The previous colitis which frequently is associated with polyposis may be the result of chronic irritation and infection. The irritation may be either chemical or mechanical.
In the classification of tumors it is almost impossible to examine enough specimens, previous to the formation of the malignancy to state which are pre-cancerous and which are not. The classification by Dukes seems to be the simplest and most applicable in that all cases of polyposis should be considered pre-cancerous, and that there is a variation in the rapidity of carcinomatous development in different cases. This would explain why some cases go for a long period of time without malignant degeneration occurring and others becoming rapidly malignant. The general condition of the patient may be a factor in the rapidity of the development of the growth.

The symptoms are rather vague and not unlike those of other diseases, but when present a complete examination should be made with a colonoscope and X-ray, as an early diagnosis and removal of the polyp may stop the growth of a potential malignancy.

In considering the relation of polyposis to malignancy it is not assumed that every polyp will become malignant or will be associated with a malignancy, but a high enough per cent of cases of this type have been reported to consider every case a potential malignancy. For this reason, when polypi are found in the large bowel, they should be immediately removed so far as possible and if to extensive a total colectomy is indicated.


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