THE SURGICAL PATHOLOGY OF ULCERATIVE COLITIS*

by

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A RECENT ARTICLE in the *Lancet* (Brooke 1954) entitled " What is Ulcerative Colitis ? " was followed by a protracted and animated correspondence which proved at any rate that this simple question has more than one answer ! " Ulcerative colitis " to some includes almost any inflammatory process of uncertain aetiology in the colon whether localized or diffuse, mild or severe : whereas others restrict it to a severe non-specific inflammation of the whole colon accompanied by varying degrees of ulceration. Wells (1952) has suggested that for the present it is best to group cases simply on a basis of descriptive pathology. I agree with this but find it difficult to follow his example of including as idiopathic ulcerative colitis only those cases in which the inflammatory process affects the whole colon in continuity, because often some portion of the large bowel remains unaffected.

Ulcerative colitis seems to start most commonly in the rectum and pelvic colon, spreading back gradually towards the caecum. In operation specimens removed by total colectomy it is not unusual to find severe ulceration of the left half of the colon and relatively little if any inflammation of the ascending colon or caecum. Sometimes indeed ulceration ceases abruptly at some point in the transverse or descending colon. Proximal to this sharp line of demarcation the bowel appears healthy whereas distally it is obviously diseased. When only a short region of the colon is affected this is sometimes described as regional or segmental colitis, but it has yet to be proved that this is any more than a localized manifestation of a pathological process which more commonly affects a larger area.

The modern surgical treatment of ulcerative colitis by colectomy has provided a new opportunity for the study of the lesions present in severe cases and during the last four years I have examined colectomy specimens from 120 patients. These were all patients in whom medical treatment had failed to arrest the progress of the disease, so that colectomy was eventually resorted to as a life-saving operation. In a sense colectomy must always be regarded as a " confession of failure " but in the type of case to which I am referring it was the only known way of saving life and restoring health.

Before describing the lesions found in these severe cases I should like first to recall the very clear description given by Corbett (1945) of the earlier stages of the disease as seen by a surgeon through the sigmoidoscope. I quote from his Presidential Address to the Section of Proctology of the Royal Society of Medicine. " First the bowel is seen to be hyperaemic and later there is oedema and thickening of the mucous membrane

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which bleeds easily. A further step is the formation of miliary abscesses in the mucosa which rupture and result in ulcers resembling yellow spots scattered over the wall of the gut."

Gross Characters of Lesions in Colon

The view obtained through the sigmoidoscope can provide only an approximate estimate of the severity and extent of the disease and much that was unexpected may be revealed when the colon is removed and examined more completely. But perhaps I may be allowed to add that this examination of an operation specimen should not be attempted immediately. Surgeons will find it worth while to restrain their curiosity in the operating theatre and to send the colon to the laboratory intact and unopened so that it may first be distended with formalin. The best time for a surgeon to examine the colon he has removed is a few days later when it has been fixed, washed clean and made presentable.

The first noticeable abnormality in a colectomy specimen from a severe case of ulcerative colitis is that the colon is contracted down, both in length and diameter. In most cases also its wall is thickened and rigid, having lost its normal elasticity. The left half of the colon is generally more affected than the right. The disease generally ends abruptly at the ileo-caecal valve but extension of the inflammation into the terminal ileum may occur if the valve is ulcerated or fibrotic (Inberg 1953).

When colectomy has been carried out during an active phase of the disease the whole mucosa is usually deep red or purple in colour with petechial haemorrhages scattered over the surface. The ulcers may be obvious and widespread or few in number and revealed only by careful inspection. If severe the ulceration may cause narrow gutter-like depressions extending longitudinally and separated by ridges of surviving mucosa. The fact that stretches of bowel are completely denuded of epithelium may not be appreciated at first glance because bare patches, when washed clean and freed from blood and mucus, may appear shiny and pale grey, as if covered with atrophic mucosa. During the quiescent phases of the disease no ulceration may be noticed when an operation specimen is first inspected, the mucosa being brown, smooth or granular, but none the less tiny pin-point ulcers may be found with the aid of the microscope or even with a magnifying glass.

Histology

Microscopic examination nearly always proves that ulcerative colitis is more widespread and severe than the naked-eye appearance of the colon had led one to suppose (Fig. 1). In most regions the mucosa and submucosa are congested, often to an astonishing degree, this being accompanied by a dense infiltration of the mucous membrane with lymphocytes and plasma cells and occasional eosinophils. Polymorphs are seldom much in evidence except in the tiny abscesses buried deep in the mucosa, the so-called " crypt abscesses," one of the most characteristic lesions of the disease. Most crypt abscesses eventually discharge into the bowel,

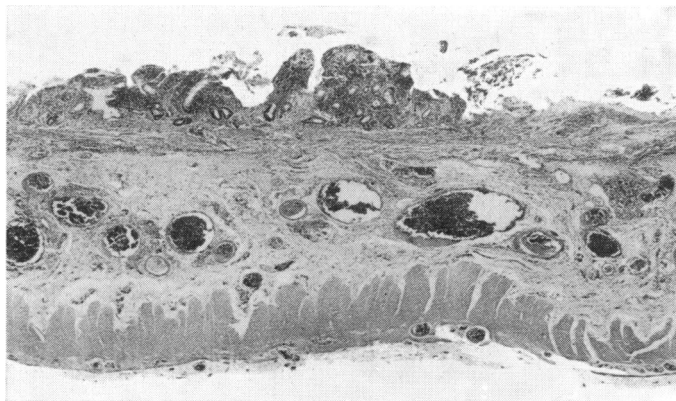


Fig. 1. Portion of transverse colon from case of ulcerative colitis at the acute phase showing destruction of mucosa and intense congestion within the submucosa. The surface of the bowel was dark red in appearance and there did not appear to be much obvious ulceration but microscopic examination showed that most of the bowel was bare, there being only a few clusters of mucus secreting glands scattered here and there. (x 15).

becoming the source of the large quantities of pus and blood evacuated with the faeces, but others may rupture into the spaces between the crypts of the mucosa thus undermining the surface epithelium. This seems to be the way in which ulcers most commonly form, though it has been suggested also that they may be due to a primary ischaemic necrosis resulting from vascular lesions or vasculitis (Warren and Sommers 1949). In most cases the ulceration is remarkably superficial in character, the only indication of inflammation in the deeper layers of the submucosa and muscle coat being a few collections of lymphoid cells in the perivascular and perineural lymph spaces.

Strictures

If however ulceration extends more deeply reaching through the submucosa to the muscle coat it may cause a local reflex muscle spasm thus giving rise to a stricture. It was Mr. H. E. Lockhart-Mummery who first pointed out to me that strictures are more commonly due to muscle spasm than to fibrous tissue overgrowth and I can confirm this and add that they are usually the result of exceptionally deep ulceration. The fact that strictures may be due to muscular spasm and not to fibrosis explains why the rigid tube-like strictures seen by X-rays may sometimes disappear in a fashion which has often puzzled radiologists (Kirsner *et al.*, 1951 ; Kern *et al.*, 1951 ; McEwen *et al.*, 1952). Eventually, of course, a long standing deep ulcer may give rise to fibrotic scarring and so cause a permanent stricture but this is not such a common complication as is usually supposed.

Polyps

The mucosa at the margin of an ulcer may become undermined and loose in its attachment, thus giving rise to polypoid mucosal tags. These

are rarely noticed in the earlier stages of the disease but are found in about 10 per cent. of long standing cases. The initial ragged mucosal tags become replaced later by rounded and pedunculated polyps composed of mucous membrane and granulation tissue. At a still later stage these inflammatory or pseudopolyps come to be composed only of a compact core of connective tissue covered by fairly normal looking glandular epithelium.

The inflammatory polyps of ulcerative colitis are not in themselves pre-cancerous. It is well known that adenomatous polyps, such as occur in familial polyposis, are definitely pre-cancerous, using this word to mean that cancer often develops within them. But true adenomas are rare in ulcerative colitis. Most of the polyps found in this disease are nothing more than ragged tags of mucosa and granulation tissue: they are inflammatory and not neoplastic in origin. Cancer is more commonly found in colons with inflammatory polyps than in those without polyps but the chief reason for this is because cases with polyps are more severe and have lasted longer than those without polyps.

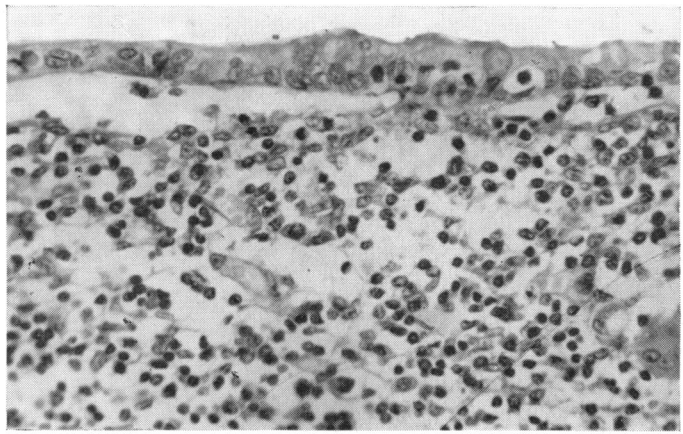
Healing and Repair

The first impression gained from a microscopic examination of a colectomy specimen of ulcerative colitis is that the damage to the mucosa is even greater than had been apparent to the naked eye, but a closer study of sections almost always also reveals some indication of healing and repair. This is of interest in relation to the possibility of natural recovery and also because it may be linked up with the threat of malignancy following ulcerative colitis, a problem to be considered later.

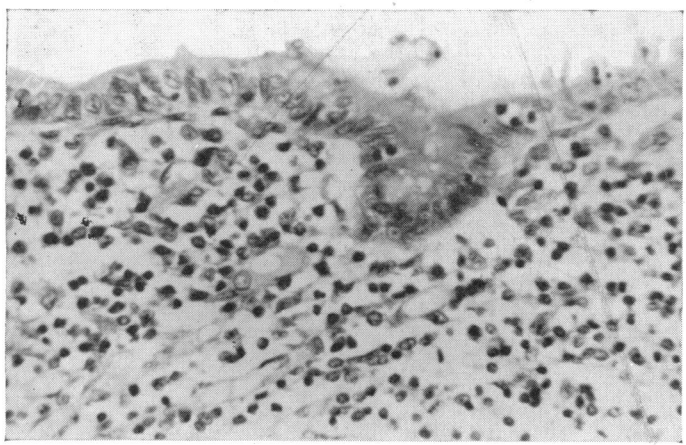
Natural healing in any organ is apt to be a complicated process in which many different tissues play a part in orderly sequence. The course of events in ulcerative colitis depends on the degree of damage to the mucosa. If only the surface layer of the mucosa has been injured healing seems to follow quickly in most cases, being brought about by proliferation of the surviving glandular epithelium at the bottom of the crypts.

Healing takes much longer if an ulcer has extended through the whole depth of the mucosa so that regeneration of epithelium has to be initiated from the mucosa surrounding the ulcer. Much now depends on the condition of the margin. In the progressive phase of ulcerative colitis the mucosa at the margin of ulcers is being constantly undermined, and as long as this continues an ulcer cannot heal, but in the more quiescent phases of the disease an ulcer may develop a more healthy edge and this may become the growing point of epithelial regeneration and repair.

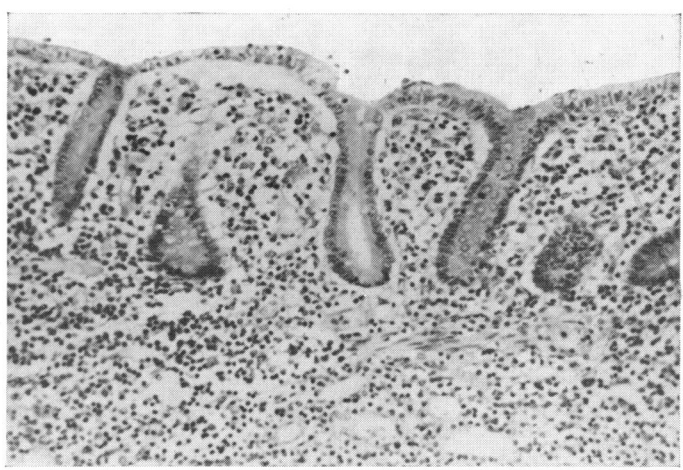
The first visible evidence of the healing of an ulcer is the appearance of a thin film of epithelium creeping across the floor from the margin (Fig. 2*a*). The spearhead of the advance consists of flat pavement-like epithelium but this later gives place to cuboidal and columnar epithelial cells, and finally, as differentiation proceeds, to mucus-secreting epithelium of the familiar " goblet-cell " type.



A. Formation of surface film of flattened and cuboidal epithelium. (x 315).



B. Commencing formation of tubular glands. (x 315).



C. Restoration of crypts in mucous membrane. (x 153).

Fig. 2. Three stages in healing of ulcer in Colitis.

I have spoken of this as the first visible evidence of repair but it is preceded by important changes in the underlying connective tissue which literally pave the way for the advancing epithelial film. These initial preparations consist in a condensation of the reticular fibrils formed by fibroblasts, thus welding together a basement membrane over which the delicate film of advancing epithelium can glide and to which it eventually becomes anchored. This film of epithelium is a fragile structure and has a tenuous and uncertain hold until successfully linked up on all sides, so that the whole floor of the ulcer is covered.

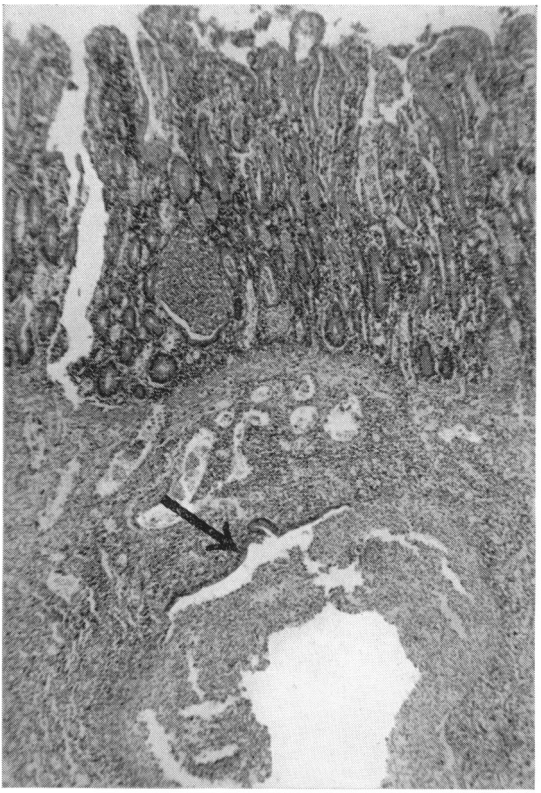
So far we have considered only the regeneration of the surface glandular epithelium. The complete restoration of the mucosa requires that this surface epithelium should dip down to form crypts to be supported and nourished by a loose vascular connective tissue stroma. In some superficial healing ulcers the appearances suggest that a spongy layer of granulation tissue is being built up beneath the newly-formed epithelial film, thus raising it from the base line of the floor of the ulcer to the level of the mouth of the crypts in the surrounding mucosa. Once this supporting stroma has been provided the covering epithelium may begin to dip down, forming little pits and later tubular glands (Figs. 2*a* and 2*b*). Reconstruction of mucosal pattern such as this is only seen in small and shallow ulcers. If ulceration has extended more deeply and reached the submucosa or muscle coat it is very rare to find any indication of mucosal regeneration even after the bowel has been rested and defunctioned.

I have dealt in some detail with the question of natural healing because it has a bearing on the possibility of anastomosing the ileum to the rectum after subtotal colectomy, so avoiding a permanent ileostomy. In recent years several cases of ulcerative colitis have been treated in this way (Corbett 1945 ; Aylett 1953). The question as to whether or not this is good surgical practice will be decided eventually by observing what happens to these patients. In the meantime, whilst this form of treatment is still *sub judice*, there is a little piece of evidence which may provide encouragement for the further trial of restorative resections in selected cases.

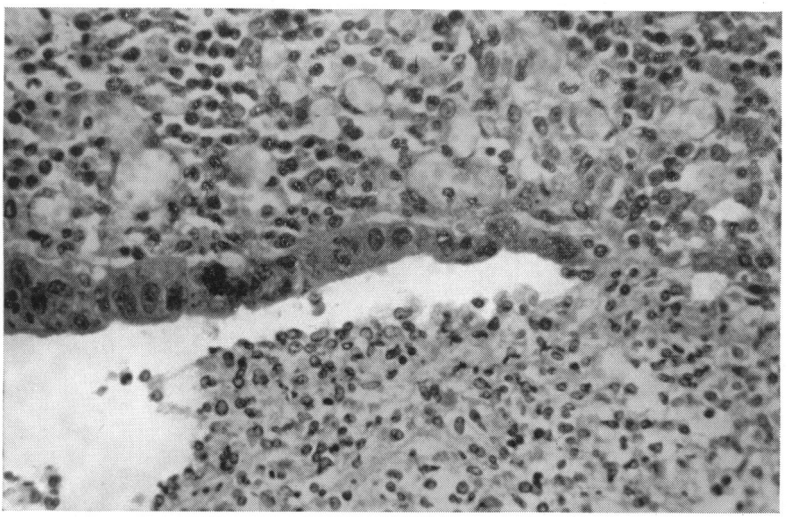
Recently in cooperation with Dr. Coghill, I have examined several biopsies taken from the recto-sigmoid region in cases of ulcerative colitis of varying degrees of severity and almost invariably found signs of epithelial regeneration in the crypts of the mucosa as shown by the presence of cells in mitosis : in fact, mitotic activity often seems to be in excess of the normal in cases of ulcerative colitis. But though these biopsies have provided a reminder of the resources of natural healing they have also indicated once more that ulcerative colitis is apt to be patchy in its distribution. Good bits and bad bits of mucosa may be separated by only a few inches.

Misplacement of Epithelium

In what I have already said I have emphasized the fact that in many cases of ulcerative colitis a careful search may reveal some indication of epithelial



A. Misplaced epithelium (marked by arrow) in wall of abscess in submucosa. (x 37).



B. Higher magnification of misplaced epithelium marked by arrow in A. (x 300).

Fig. 3. Misplacement of epithelium in healing stage of Ulcerative Colitis.

regeneration and repair, evidence that the machinery of natural healing is still at work, coping with débris, repairing breaches and attempting to restore the familiar pattern of the mucosa. Sometimes, however, whilst mucosal repair is still proceeding, fragments of glandular epithelium may become detached and buried in the submucosa or even in the muscle coat, an accident which is not so surprising when one recalls the restless, turbulent environment in which repair must proceed.

The commonest place in which to find fragments of misplaced glandular epithelium is at the margin of an abscess in the submucosa due to the fact that epithelium has grown down the track through which the contents of the abscess have been discharged (Fig. 3). An epithelialized track extending into the submucosa may remain as a permament malformation after a focus of suppuration has healed, causing mucosal bridges and tunnels, which are lined by healthy-looking mucus secreting intestinal epithelium. Occasionally, one finds clumps of intestinal epithelium buried

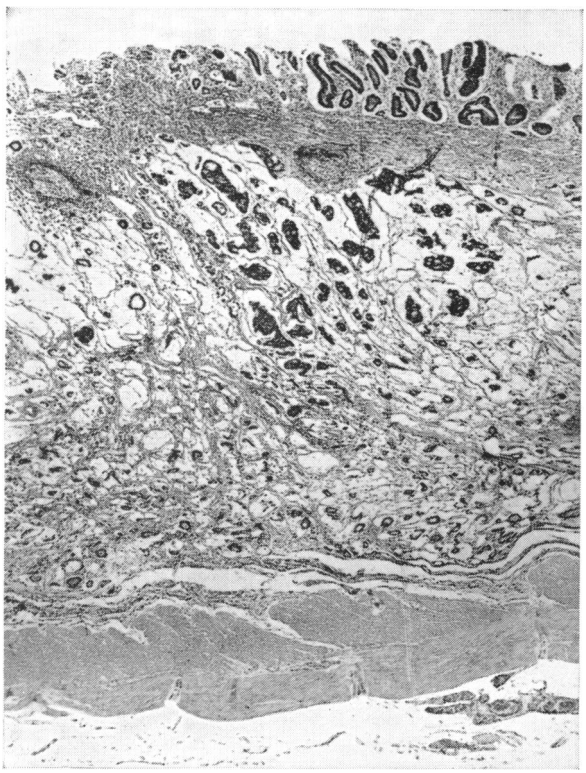


Fig. 4. Cancer following Ulcerative Colitis.
Section showing focus of carcinoma situated in submucosa : no malignant growth in mucosa. (x 24).

deep in the muscle coat. Misplacement of epithelium may be a predisposing factor in the development of carcinoma and may explain why the first focus of malignancy may be found in the submucosa, beneath intact mucous membrane (Fig. 4). Support for this hypothesis is provided by experience gained in the experimental production of gastric cancer by carcinogenic agents.

Stewart (1953) has stated that when attempts are made to induce carcinoma in the glandular part of the stomach of rats and mice by the intramural injection of carcinogenic hydrocarbons one of the commonest lesions observed is a curious misplacement of glandular epithelium known as " adenomatous diverticulum," a series of cysts lined by mucus secreting epithelium buried in the wall of the stomach. This is regarded as a pre-cancerous lesion because of the occasional occurrence of carcinoma in association with it.

Predisposition to Cancer

During recent years almost every surgeon who has enquired into the relationship between ulcerative colitis and cancer has reached the conclusion that severe ulcerative colitis predisposes to carcinoma and that the extent of this predisposition has been underestimated in the past because of difficulties in diagnosis, both clinical and pathological. There have been many papers on this subject in American journals and I should like to pay special tribute to the pioneer work of Rankin (1939), Bargen, Dockerty and Shands (1952), Kiefer, Eytinge and Johnson (1951); Weckesser and Chinn (1953); Johnson and Orr (1948); Lyons and Garlock (1951); and Cattell (1953); also to Svartz (1951) in Sweden, and Rice-Oxley and Truelove (1950) in England.

My own observations and those of the authors already quoted have established the fact that the incidence of cancer varies with the severity and duration of the preceding colitis. In a series of cases at St. Mark's Hospital we found that the average duration of symptoms of ulcerative colitis before the onset of secondary intestinal cancer has been 15 years. This latent period before the onset of malignancy corresponds exactly to that observed in another well authenticated pre-cancerous condition, familial intestinal polyposis. A recent statistical analysis of a large series of cases of this disease (Dukes 1952) has shown that 15 years is the average period which elapses between the first symptoms of polyposis and the detection of intestinal cancer.

Frequency of Cancer after Ulcerative Colitis

The question, " How often does cancer follow ulcerative colitis ? " has had many different answers in the past. This is not surprising since some authors have been referring only to severe cases treated by surgeons, others to all cases and others to post-mortem records. A surgical series is likely to show a higher incidence of cancer than a medical because the cases have been more severe and of longer duration.

Our figures at St. Mark's Hospital are as follows :—We have records of 11 cases of cancer following ulcerative colitis. Seven of these were found in total colectomy specimens, two in rectums removed by synchronous combined excision, one by laparotomy and one by post-mortem. The frequency of occurrence of carcinoma can be expressed most accurately by confining the analysis to total colectomy specimens because these constitute a consecutive series, unselected in any way. Seven of the cancers we have met with were found in this consecutive series of 120 colectomy specimens, an incidence of 5·8 per cent. The average age of these 120 patients was 42 years. They were all cases of ulcerative colitis and operated on primarily for this condition. Seven of them were found to be suffering also from cancer of the colon. The point to be considered is this. If 120 other individuals of the same age not suffering from ulcerative colitis were examined in the same way how many cancers would be found ? Certainly much less than seven.

In a former series reported two years ago (Counsell and Dukes 1952) it was said that cancer had been found in 11·1 per cent. of *surgically treated* patients but these were not exclusively colectomy specimens. So the two series are not strictly comparable but apart from this there are other explanations of the discrepancy. There is no doubt that cancer is now being found less frequently in colectomy specimens for the simple reason that surgeons are now operating at an earlier stage of the disease, and before cancer has had time to develop.

Our experience at St. Mark's agrees fairly closely with the figures reported by other observers, due allowance being made for the fact that ours were all severe surgical cases. For instance : Lyons and Garlock (1951) found an incidence of bowel malignancy in 3·9 per cent. of surgically treated ulcerative colitis ; Kiefer, Eytinge and Johnson (1951) recorded carcinoma in 4·4 per cent. of surgically treated cases and in 2 per cent. of medically treated cases and suggest that the true prevalence of cancer in ulcerative colitis patients lies between these extremes. Cattell (1953) has estimated the overall incidence of carcinoma arising from ulcerative colitis as under 3 per cent. but states that in cases sufficiently severe to need surgical treatment it may be between 5 and 12 per cent. Weckesser and Chinn (1953) reported an incidence of 3·4 per cent. and Rice-Oxley and Truelove (1950), 3·1 per cent. ; Rankin (1954) considers that the overall incidence of carcinoma in ulcerative colitis is about 5 per cent.

The Risk of Cancer

In view of this evidence we are now justified in saying that any patient in whom severe ulcerative colitis has lasted more than 10 to 15 years has entered a phase of life when intestinal cancer has become a definite risk. The danger of cancer will increase still further as the years pass by and will become in the end a veritable sword of Damocles suspended overhead. Of course the risk of cancer is not in itself sufficient to justify colectomy

if there is no other indication for such radical treatment but it may sometimes be considered as an additional argument in favour of colectomy in a long-standing case of ulcerative colitis. However, usually when severe ulcerative colitis has lasted for 10 years or more there are sufficient indications for surgical treatment on other grounds.

The Seed and the Soil

The pre-cancerous nature of ulcerative colitis cannot be fully explained, but it is obvious that two influences are operative which we know to predispose to cancer in other organs of the body. One of these is continual regeneration of epithelium in excess of normal requirements and the other is the presence of abundant vaso-formative tissue ready to support and nourish the growing epithelium. The epithelium may be likened to the seed and the vaso-formative tissue to the soil.

In using the familiar analogy of the seed and the soil I am not forgetful of the warning expressed by Professor R. A. Willis in a very apt quotation at the beginning of the eleventh chapter of his monumental text book, " The Pathology of Tumours," which expresses astonishment at human proneness " to explain any phenomenon which appears remarkable by means of infinitely greater and more incomprehensible wonders." In speaking of seed and soil I may appear to be doing this but my excuse is that if we think in these terms we can at once focus our attention on what I believe to be very important factors in the situation which develops in long-standing ulcerative colitis, namely the constant excessive regeneration of epithelium with liability to misplacement and the fertile soil provided by the granulation tissue in which clumps of growing epithelium may be embedded. The importance of this environmental factor becomes apparent when we recall the ease with which cancer cells may be implanted in the granulation tissue of raw surfaces, wounds or surgical sutures.

SUMMARY

Microscopic examination of a colectomy specimen from a case of severe ulcerative colitis generally shows that the damage to the mucosa is even greater than had been apparent to the naked eye, but a closer study of sections often reveals also unanticipated indications of attempts at healing or repair.

Restoration of mucosa is seldom complete if ulceration has extended deep into the submucosa. Reparative processes may be accompanied by misplacement of epithelium, an accident which may be of importance in relation to the subsequent development of cancer.

The incidence of intestinal cancer secondary to ulcerative colitis varies with the severity and duration of the colitis. The average duration of symptoms of ulcerative colitis before the onset of secondary cancer is about 15 years.

In a consecutive series of 120 patients with ulcerative colitis treated by colectomy intestinal cancer was found in seven cases, an incidence of 5·8 per cent. The average age of these 120 patients was 42 years.

A patient in whom severe ulcerative colitis has lasted more than 10 to 15 years should be regarded as having entered a period of life when intestinal cancer has become a definite risk.

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PARLIAMENTARY AND SCIENTIFIC COMMITTEE

MEMBERS OF THE Parliamentary and Scientific Committee, to the number of about thirty, paid a visit to the College on 5th May, and were taken on a conducted tour of the departments of Anatomy, Pathology and Physiology, and the clinico-pathological laboratories of the Imperial Cancer Research Fund. Afterwards they had luncheon with members of the Museum and Research Committee.

Among those present were Viscount Hinchingbrooke, Lord Calverley, the Rt. Hon. A. Bottomley, Sir Hugh Linstead and Sir Harold Roper, and the medical representatives were Lord Webb-Johnson, Dr. R. F. B. Bennett and Dr. Somerville Hastings.

The Committee consists of members of both Houses of Parliament and of representatives of various scientific bodies which are affiliated to it, and is designed to provide a permanent liaison between scientific bodies and Parliament. It provides members of Parliament with authoritative information for use in debates and informs them of results of scientific research which bear upon questions of public interest. It provides its members with a summary of scientific matters dealt with in Parliament.

Members of the Committee expressed keen interest in what they saw at the College and were most appreciative of the hospitality given to them.