SERIAL BIOPSY IN ULCERATIVE COLITIS

BY

S. C. TRUELOVE, M.D., M.R.C.P.
Assistant Physician, Nuffield Department of Clinical Medicine

A. R. HORLER, M.D., M.R.C.P.
Formerly Graduate Assistant, Nuffield Department of Clinical Medicine

AND

W. C. D. RICHARDS, M.B., B.S.
Graduate Assistant, Department of Pathology
(From the Radcliffe Infirmary, Oxford)

[WITH SPECIAL PLATE]

A recent therapeutic trial showed that patients treated with cortisone were nearly three times as likely to go into clinical remission as patients in a control group not receiving cortisone (Truelove and Witts, 1954). However, some workers have considered that corticotrophin (A.C.T.H.) and cortisone may check the bloody diarrhoea of ulcerative colitis without modifying the underlying diseased colon. For this reason we have devised a method which permits us to examine the histological changes in the mucosa of the rectum and sigmoid colon during the course of treatment with corticotrophin and cortisone.

In order to study these changes we decided to use a special instrument which would enable a biopsy to be made under direct vision through a sigmoidoscope and with minimal trauma to the patient. Mr. Richard Salt, chief technician to the Nuffield Professor of Anaesthetics, has made us such an instrument. An essential principle is one employed in the Wood gastric biopsy tube (Wood *et al.*, 1949), in that we rely on sucking a small knuckle

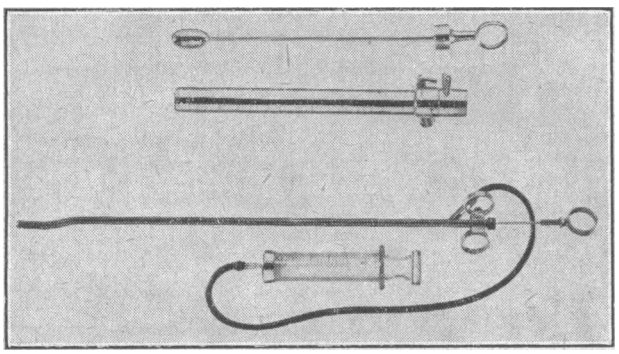

FIG. 1.—The colonic biopsy tube. Note proportions in relation to sigmoidoscope above.

of mucosa into a hole and then cutting it off cleanly with a sharp blade. The size of the hole determines the depth of the biopsy, and we have worked with a size which takes the biopsy down to the muscularis mucosae.

The Colonic Biopsy Tube and its Use

The apparatus used for biopsy (Figs. 1 and 2) is a rigid metal tube with a head which is slightly offset from the body. The head carries the cutting mechanism, which consists of a blade fashioned from a safety-razor blade operating with the edge obliquely set to the line of the instrument so that it has a guillotine action. (A biopsy knife made from a safety-razor blade has already been used by our colleague Dr. John Badenoch in an intestinal biopsy tube which he is developing in association with Mr. Richard Salt; we are grateful to him for permitting us to make use of this method.) The blade is attached to a sliding member in such a way that the edge is held in light pressure against the casing and a clean cut is thus assured. The blade carriage is operated by means of a fine steel tube which runs down inside the main tube and passes out through an airtight rubber gland into a ring for thumb or finger. This inner tube is rigid lengthwise but sufficiently flexible in lateral movement to permit the head to be offset as described. At the tail end of the instrument the main tube is fitted with a side tube to which a 20-ml. syringe for applying suction is attached by a short length of rubber tubing. The instrument is made an appropriate length for the particular sigmoidoscope used. In the present study we have used one suitable for a short (8 in.=20 cm.) sigmoidoscope.

A general sigmoidoscopic examination is made and a site selected for biopsy. In the present study we have taken all the samples at approximately 6 in. (15 cm.) from the anal margin. The lens at the end of the sigmoidoscope is removed, and the biopsy tube is inserted through the sigmoidoscope and the flat face of its head placed against the selected site. An assistant then withdraws the piston of the syringe, and on feeling resistance due to the mucosa plugging the hole in the head of the instrument he signals to the examiner, who operates the blade. The tube is then withdrawn, the end of the head unscrewed, and the biopsy specimen removed by flushing the instrument through with saline solution. The specimen is placed immediately into 10% neutral formol saline for histological examination.

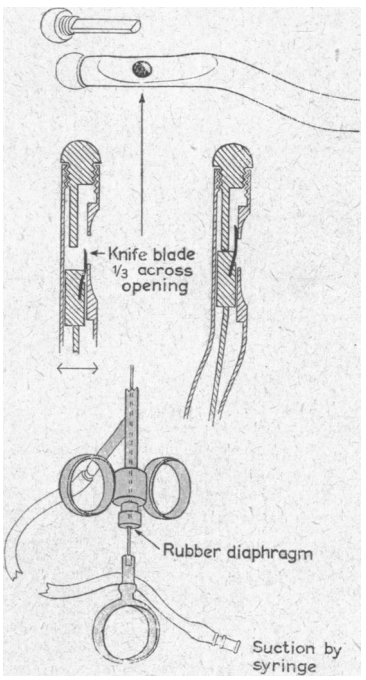

FIG. 2.—Details of colonic biopsy tube.

When using the biopsy tube for patients with severe ulcerative colitis the mucosa may be obscured by a profuse discharge of liquid faeces, blood, pus, and mucus. We have overcome this difficulty by using a suction irrigator (Fig. 3), likewise designed and built by Mr. Salt and based on a suction irrigator for use in dental surgery described by Boston and Macintosh (1939). It consists of two tubes joined along their lengths. One is a fine stainless steel tube fitted with a nozzle and covered with a rubber sheath which projects beyond the nozzle, through which a fine jet of warm saline is driven by means of a Higginson's syringe. The other tube, of much larger bore and made of rubber, is coupled to a suction apparatus with a foot control (Saher and Salt, 1943). The conjoined tubes are passed up the sigmoidoscope and simultaneous irrigation and suction are carried out. A clear view of the mucosa can be obtained by this technique, and we have observed nothing to suggest damage even to an acutely inflamed colon.

Below we report the findings in two patients with ulcerative colitis treated with corticotrophin and cortisone.

Case 1

A farmer aged 29 developed ulcerative colitis in 1951, and suffered from two severe attacks requiring treatment in hospital before he was seen by us. The present episode

began in October, 1954, with severe diarrhoea and much blood and mucus in the stools. Three weeks later (November 1) he was admitted to the Radcliffe Infirmary with fever, tachycardia, and evidence of considerable loss of weight. He was passing about seven stools a day, which were fluid and composed chiefly of blood with an admixture of liquid faeces, pus, and mucus. Hb, 16.3 g. per 100 ml.; E.S.R., 13 mm. in one hour (Westergren). There was some disturbance of blood chemistry, with a low potassium value (14.2 mg. per 100 ml., or 3.6 mEq per litre). Barium enema showed typical changes of ulcerative colitis extending from the rectum up to the middle of the transverse colon. Sigmoidoscopy revealed an intensely hyperaemic mucous membrane with a granular surface. Passage of the instrument and gentle swabbing with gauze caused free bleeding. A biopsy was taken.

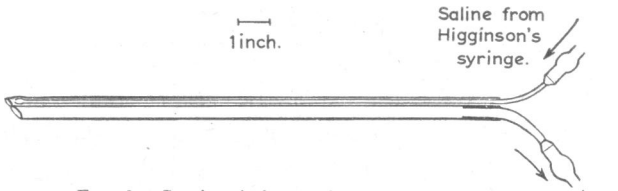

FIG. 3.—Suction irrigator for use through a sigmoidoscope.

Biopsy 1.—The superficial epithelium is rather flattened and darkly staining and there are occasional tiny erosions. One erosion is in relation to a thrombosed subepithelial capillary. The lamina propria is oedematous and infiltrated by lymphocytes, plasma cells, and eosinophil leucocytes. Goblet cells both in the glands and superficial epithelium are reduced in number.

Measures to correct the electrolyte disturbances were successfully adopted, but without effect on the patient's general condition or the bloody diarrhoea. Six days after his admission treatment with cortisone by mouth in a dose of 50 mg. four times a day was begun. Three days later the haemoglobin level having fallen to 10.8 g. per 100 ml., 2 pints (1.1 litres) of whole blood was transfused. Cortisone therapy was continued for two weeks without any appreciable improvement in the patient's condition. At the end of this time he was passing ten stools a day containing much blood and he had lost 10 lb. (4.5 kg.) in weight. Sigmoidoscopy with biopsy was performed after one week and also after two weeks. There was no sigmoidoscopic improvement on the first of these examinations, and there was deterioration on the second in so far as passing the instrument caused the mucosa to bleed even more freely than on earlier examinations.

Biopsy 2.—Inflammatory changes are more intense than in Biopsy 1. In particular, there are larger superficial erosions, and neutrophil granulocytes are more frequent in the cellular exudate. There are small plugs of fibrinous exudate containing polymorphonuclear leucocytes on the surface of some erosions. Congestion of the capillaries and interstitial oedema are marked. In places small pseudo-villous projections of the superficial mucosa can be seen.

Biopsy 3.—The appearances are similar to those in the previous biopsy, but no erosions are seen.

At this stage (November 20) we decided to discontinue cortisone therapy and to give corticotrophin instead in the form of daily intramuscular injections of 100 units of the gel. The response was good. Within four days the daily number of stools had fallen to four and his general condition was improving. Thereafter he made an uninterrupted recovery, and ten days after the introduction of corticotrophin therapy he was passing only one stool a day with a small amount of blood. During this period the only additional therapy was a transfusion of 3 pints (1.7 litres) of blood. He continued to pass one or two normally formed stools a day gradually becoming completely free from blood.

During the phase of clinical improvement on corticotrophin therapy the sigmoidoscopic picture showed undoubted improvement with less vascularity, and there was no bleeding on passing the instrument. A biopsy specimen taken early in this phase still showed gross inflammatory changes.

Biopsy 4 (November 30).—Mucosal inflammatory changes, including capillary congestion, interstitial oedema, and infiltration by plasma cells, lymphocytes, and eosinophil granulocytes, are still present. One glandular tubule shows infiltration with polymorphonuclear leucocytes. There are small patches of subepithelial oedema and occasional tiny superficial erosions.

Two subsequent biopsy specimens during this phase of improvement showed a remarkable change towards normal appearances.

Biopsies 5 and 6 (December 13).—As compared with the previous four biopsies there is a striking change. The superficial and glandular epithelium is essentially normal. Occasional patches of oedema and haemorrhage are present in the interstitial tissue, but the cellular content is not abnormal.

When the patient left hospital on December 23, 1954, he was symptom-free and gaining weight. He continued in clinical remission and the sigmoidoscopic and histological appearances were essentially normal. The corticotrophin was gradually reduced, and finally discontinued on March 12, 1955. He then weighed 12 st. 11 lb. (81.2 kg.) and was in robust health. Three weeks later he was normal in all respects.

A summary of the findings in this case is given in Table I. Biopsies illustrating the three phases of severe symptoms, clinical improvement, and remission are reproduced in the Special Plate.

Case 2

A housewife aged 29 was first admitted to hospital under our care in May, 1954, with a three-year history of passing blood and mucus with her motions and with intermittent diarrhoea in addition. The sigmoidoscopic appearances were

TABLE I.—*Summary of Findings in Case 1*

Biopsy No.	Date	Hormone Therapy	Clinical Picture	Sigmoidoscopy	Histology
1	Nov. 5, 1954	—	Ill with severe bloody diarrhoea	Intensely hyperaemic mucosa, which bled freely	Marked inflammation. Erosion
2	Nov. 13, 1954	Cortisone, 50 mg. q.d.s.	Unchanged	Unchanged	Marked inflammation. Several erosions
3	Nov. 20, 1954	,, ,,	Unchanged. Ten motions a day, chiefly blood	Worse	Marked inflammation
4	Nov. 30, 1954	A.C.T.H. gel, 100 units daily	Greatly improved. One motion a day with small amount of blood	Much improved. Slight hyperaemia and granularity	Inflammation. Erosion
5	Dec. 13, 1954	,, ,,	Still improving. Bowels normal. General condition better	Approaching normal	No inflammation
6	Dec. 23, 1954	,, ,,	General condition greatly improved. Bowels normal	Almost normal	,, ,,
7	Jan. 7, 1955	A.C.T.H., 80 units daily	Well	Normal	,, ,,
8	Feb. 28, 1955	A.C.T.H., 40 units on alternate days	,,	,,	,, ,,
9	Mar. 28, 1955	—	,,	,,	,, ,,

TABLE II.—*Summary of Findings in Case 2*

Biopsy No.	Date	Hormone Therapy	Clinical Picture	Sigmoidoscopy	Histology
1	Nov. 22, 1954	—	General condition good. Passing blood per rectum with each motion	Hyperaemia and granularity of rectal mucosa	Severe inflammation
2	Nov. 29, 1954	Cortisone, 25 mg. q.d.s.	Unchanged	Unchanged	Severe inflammation. Erosions
3	Dec. 16, 1954	,, ,,	Improving. Almost normal	Almost normal	Inflammatory changes less severe. No erosions
4	Jan. 7, 1955	,, ,,	Occasional trace of blood in stools	,, ,,	Slight residual inflammation
5	Feb. 28, 1955	,, ,,	,, ,, ,,	,, ,,	Almost normal
6	Mar. 31, 1955	—	Occasional trace of blood in stools; otherwise normal	,, ,,	Normal

those of mild ulcerative colitis extending up to 20 cm. from the anal margin. She responded rapidly and completely to intramuscular corticotrophin. Thereafter she remained symptom-free until September, 1954, when she again passed blood per rectum. Sigmoidoscopy on October 4 and November 22 showed gross hyperaemia of the mucosa of the rectum and lower sigmoid colon, with bleeding on gentle swabbing.

Biopsy 1 (November 22).—There are marked mucosal inflammatory changes. The superficial epithelium is composed of darkly staining flattened and cuboidal cells and shows occasional foci of degenerate cells and small erosions. The interglandular connective tissue is heavily infiltrated with lymphocytes and plasma cells and contains fairly numerous eosinophil granulocytes and polymorphonuclear leucocytes. Polymorphs are also seen transmigrating the surface epithelium and gland tubules.

At this stage treatment with cortisone in a dose of 25 mg. four times a day by mouth was started. Two weeks later there was no change in her clinical state or in the sigmoidoscopic appearances. A second biopsy showed no improvement.

After a further 18 days of treatment she was almost symptom-free, a small amount of blood being passed only occasionally. Sigmoidoscopy showed only patchy hyperaemia and granularity in the rectum.

Biopsy 3 (December 18).—As compared with the previous biopsies inflammatory changes are much less marked, although increased numbers of lymphocytes, plasma cells, and eosinophil granulocytes are still present.

Treatment was continued and she was kept under observation. She remained feeling well, the only symptom being an occasional trace of blood at the end of defaecation. Sigmoidoscopy on January 7, 1955, showed very slight granularity of the rectal mucosa but no other abnormality, and Biopsy 4 showed further improvement in the histological picture. She continued well apart from the occasional passage of a trace of blood with the motions. The dosage of cortisone was then reduced, and treatment was finally stopped on March 5. On March 31 she remained well.

Biopsy 5 (February 28).—Slight generalized interstitial oedema and increase in lymphocytes.

Biopsy 6 (March 31).—Normal colonic mucosa, with slight interstitial haemorrhage of traumatic origin.

The findings in this case are summarized in Table II, and the histological appearances are illustrated in the Special Plate.

Discussion

Most authors seem to be agreed that the histological changes in ulcerative colitis are those of a non-specific inflammation. The changes found in specimens of the bowel obtained surgically or *post mortem* have been well described by Warren and Sommers (1949); and biopsy studies have been made by Levine and others (1951), including some on patients who were responding favourably to corticotrophin therapy.

In the present paper we describe a method of studying the histology of the mucosa of the bowel in relation to the changes observed in the clinical picture and on sigmoidoscopy throughout the course of treatment with corticotrophin or cortisone. In the two patients studied, biopsy specimens taken when the disease was clinically active showed marked inflammatory changes in the mucosa. Clinical remission was accompanied by sigmoidoscopic improvement and reversion of the mucosa to normal. It would be manifestly unwise to read too much into so small a study, but we consider that further use of the method may improve our knowledge of ulcerative colitis. In particular, the possibility exists that we may find that administration of corticotrophin and cortisone needs to be continued until the mucosa is histologically normal if rapid relapse is not to follow cessation of treatment. Another possibility is that the method will find some application when new treatments require evaluation.

We must emphasize that the method is at present purely a research procedure which is not intended to supplant the conventional methods of colonic biopsy. Colonic biopsy is widely used in the diagnosis of carcinoma and other discrete lesions of the rectum and lower bowel, and an excellent account of the methods available has been given by Gabriel and others (1951). However, these conventional methods involve the removal of a considerably larger fragment of mucosa than we have chosen to work with, and we do not consider that they would be safe methods to use for repeated biopsy studies such as we have made.

From the point of view of the information it can yield, the gravest objection to the present method is that it deals with only a tiny sample of a large stretch of mucous membrane. A similar objection applies to all biopsy methods, such as needle biopsy of the liver, sternal puncture, and gastric biopsy, and accounts for their occasional errors without seriously weakening their great value. In the case of ulcerative colitis the mucosa is diffusely inflamed and the biopsy is carried out under direct vision, so this objection has less weight. Moreover, by taking successive biopsies on a larger group of patients it will soon become clear whether random sampling errors are large enough to nullify the possible uses of the method.

No research method should be used without due attention to its possible risks to the patient. We believe that the risk with our method is slight, although theoretically any break in the rectal or colonic mucosa may predispose to ischiorectal abscess or perforation of the bowel. So far as we have gone, the small erosions created by the biopsy have healed by the next examination, without visible scarring or other evidence of damage. It should also, perhaps, be mentioned that the repeated sigmoidoscopic examinations with biopsy were made with the understanding and willing co-operation of the patients concerned.

Summary

A method of colonic biopsy which is suitable for studying the mucosal changes in ulcerative colitis during the course of the illness is described.

Several biopsy specimens have been taken from each of two patients who responded well to treatment with corticotrophin or cortisone.

The mucosa initially showed marked inflammatory changes. As clinical remission occurred there was

corresponding sigmoidoscopic improvement and the mucosa reverted to normal.

Some possible uses of this method of study are discussed.

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GIANT-CELL ARTERITIS WITH ANEURYSMS

EFFECTS OF HORMONE THERAPY

BY

R. J. HARRISON, M.R.C.P.
Physician, St. James' Hospital, London

C. V. HARRISON, M.D.
Professor of Morbid Anatomy, University of London, Postgraduate Medical School of London

AND

H. KOPELMAN, M.D., M.R.C.P.
Physician, St. Margaret's Hospital, Epping

[WITH SPECIAL PLATE]

Giant-cell or temporal arteritis is now a well-recognized entity with which most physicians and pathologists are familiar. The morphological changes were surveyed by one of us a few years ago (Harrison, 1948), and the clinical picture has recently been reviewed by Roux (1954), who traced over 200 cases in the literature. Our reasons for recording another two cases are: (1) to draw attention to some of the less common manifestations of the disease; and (2) to describe the effects of hormone therapy on the histology of the arterial lesions, our findings in this respect being different from those of previous workers.

Case 1

A 56-year-old housewife was well until December, 1953, when she complained of lassitude, gradual loss of weight, and night sweats. She also had a non-productive cough, for which her practitioner prescribed a linctus and phenobarbitone. In July, 1954, she noticed a painless swelling in the right side of her neck, and a week later a similar swelling appeared in the right infraclavicular region.

At this time there was a pulsating aneurysmal dilatation of the right external carotid artery 1½ in. (3.75 cm.) long and 1 in. (2.5 cm.) across. Similar aneurysmal swellings were also present in the left and right infraclavicular regions and in the right axilla. The fingers of the right hand showed early clubbing, and this hand was warmer than the left. She was afebrile, and weighed 9 st. 12 lb. (62.6 kg.). There was no skin rash or muscle tenderness and no arthritis. Her blood pressure was 130/90 mm. Hg and her pulse 84. No other abnormality was found on clinical examination.

Blood culture was sterile on three occasions. Examination of the blood showed: Hb 75% (Haldane); W.B.C. 11,000 per c.mm. (differential count normal); albumin 3.2 g. and globulin 3.7 g. per 100 ml. (A./G. ratio 0.9); blood urea 19 mg. per 100 ml.; Wassermann reaction negative. Urine: no albumin; centrifuged deposit—no R.B.C. E.S.R. 80 mm. in one hour (Westergren).

Giant-cell arteritis was suspected, and 15 mm. of the affected left suprascapular artery was removed for examination. The specimen contained one small segment of artery that was healthy, the rest being enlarged to twice the normal diameter. Microscopically the lumen in the thickened part of the artery was reduced to a slit by massive thickening of the intima by loose mucoid connective tissue infiltrated with inflammatory cells (Special Plate, Fig. 1). The media was virtually destroyed for about half its circumference, the elastica being broken into fragments. There was a heavy cellular infiltration consisting of polymorphonuclear leucocytes, macrophages, and lymphocytes. Giant cells were seen in relation to fragmented elastic tissue. The picture was typical of giant-cell arteritis in an active stage.

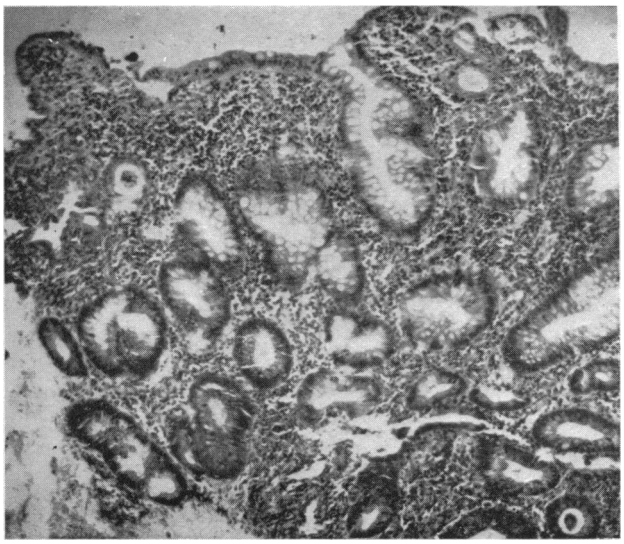
As soon as the diagnosis was confirmed oral administration of cortisone was started, 200 mg. being given daily during the first week. Thereafter the daily dosage was 150 mg. during the second, 100 mg. during the third, 50 mg. during the fourth, and 25 mg. during the fifth week. After the first week the erythrocyte sedimentation rate (E.S.R.) fell to normal and remained so; during and after the course of treatment the patient experienced a general feeling of well-being. No significant change in her weight or blood pressure occurred during treatment.

There was still some doubt whether the inflammatory processes were still active or not, and a second biopsy was performed five weeks after the first, the right acromio-thoracic axis being exposed by a transverse incision below the clavicle. The axis itself was dilated; a large fusiform aneurysm of the axillary artery at least 4 cm. in diameter was defined and palpated. The acromio-thoracic axis with its four branches was removed for section. On microscopical examination the main artery showed signs of healed arteritis (Plate, Fig. 2), but its branches were normal. The intima was thickened by loose mucoid connective tissue exactly like that of the earlier biopsy. For about half the circumference the elastica was fragmented and the media thinned (owing to loss of most of its muscle) and vascularized. In spite of these changes there was no inflammatory cellular infiltration.

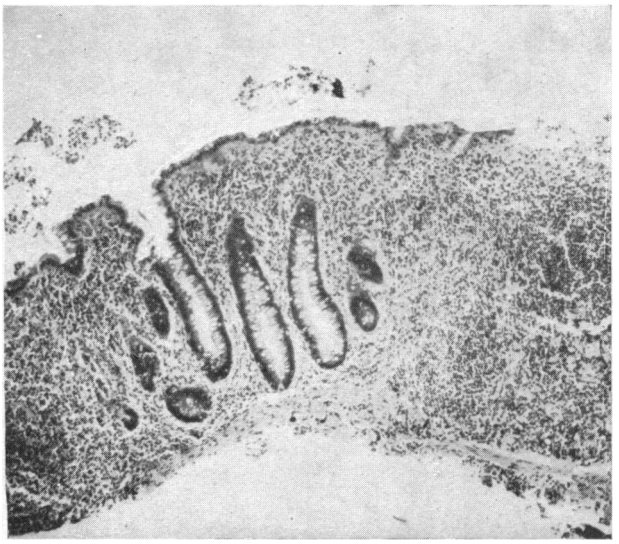
For fear of recrudescence an oral maintenance dose of 25 mg. cortisone daily was continued. By December the aneurysmal swelling of the right external carotid artery had disappeared. In early January there was severe pain in the right arm with increased swelling in the right axillary region. This persisted, and after several days the right hand and fingers were numb and cold. On January 17 there was sudden onset of right wrist-drop with loss of sensation over the upper limb and especially marked in the right hand. The swelling in the axilla was no longer pulsatile and was very firm; no bruit was heard over it. The E.S.R. at this time was 11 mm. in one hour (Westergren). It was considered that there was a large thrombosed aneurysm in the axilla, and this was confirmed by arteriography. An operation to relieve nerve pressure was performed on January 25, cortisone treatment being discontinued.

At operation (Mr. Andrew M. Desmond) the main mass of the aneurysm was found to be false and occupying the lower part of the axilla. The smaller upper part of the aneurysm was a fusiform dilatation apparently of the subclavian artery just beyond the acromio-thoracic axis. There was no demonstrable communication between the two parts of the aneurysm. The false aneurysm was opened, the clot evacuated, and the bleeding controlled. A piece of the end of the aneurysm and the adjoining vessel was taken for histological examination.

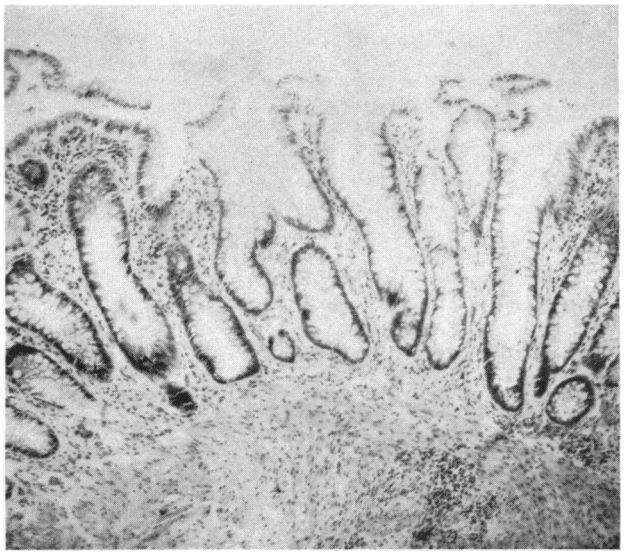
Sections from the normal part of the vessel disclosed that it was a vein and not an artery as supposed. At this level the intima showed some thickening and there were a few minute foci of cellular infiltration in the intima and media; in other respects the part was healthy. A longitudinal section through the end of the aneurysm (Plate, Fig. 3) showed thinning-out of the vein wall without (in the tissue taken) any sign of medial destruction. An organizing thrombus was attached to one wall close to a venous valve; there was no sign of inflammatory activity. Fragments from the wall of the false aneurysm showed only fibrous tissue with no vascular residue.



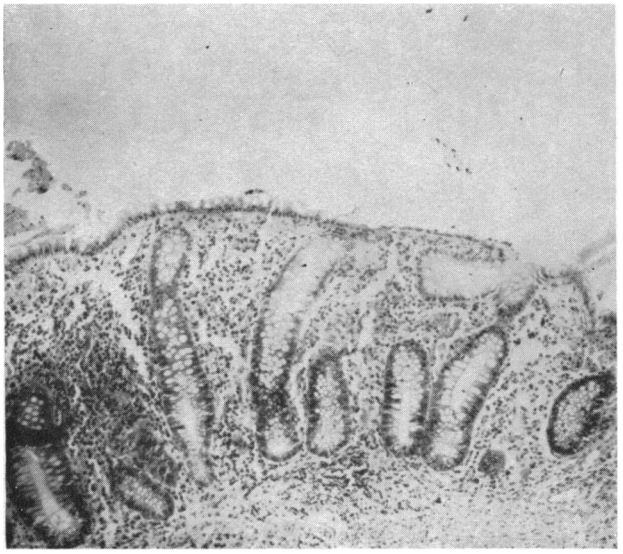
Case 1, Biopsy 2: Stage of severe symptoms.



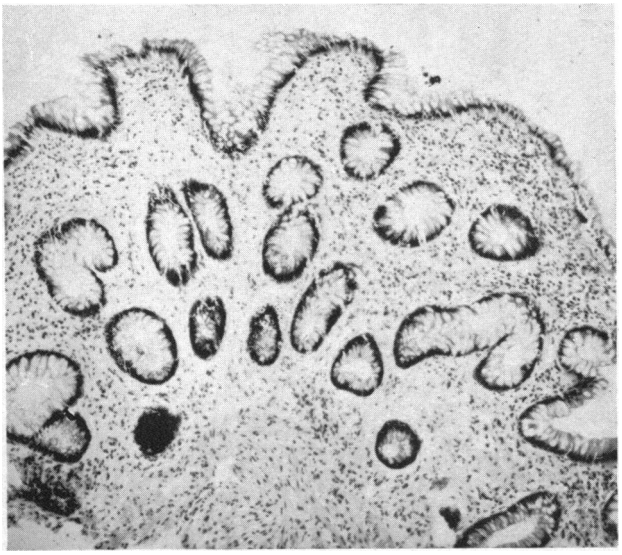
Case 2, Biopsy 1: Stage of symptoms.



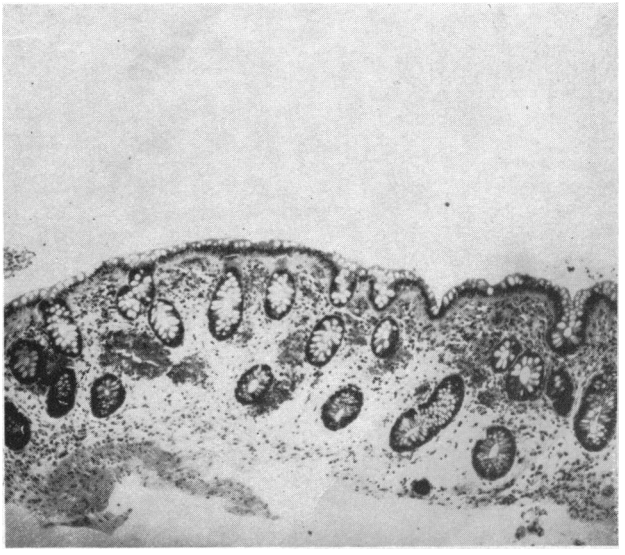
Case 1, Biopsy 6: Stage of clinical improvement.



Case 2, Biopsy 3: Stage of clinical improvement.



Case 1, Biopsy 7: Stage of clinical remission.



Case 2, Biopsy 6: Stage of clinical remission.