tropical sprue and the second had coeliac disease. The latter patient, however, had treatment with a gluten-free diet for two years before the jejunal biopsy was done. Whether or not a gluten-free diet will cause an abnormal mucosal pattern to revert to normal is a matter of doubt (Rubin *et al.*, 1960b). The third patient had laboratory evidence of primary malabsorptive disease, and it is unlikely that the normal mucosal pattern was due to folic-acid therapy. Her response to this treatment was entirely satisfactory and there was no evidence of any other cause for megaloblastic anaemia. Indeed, if a non-pregnant patient who is not suffering from primary malnutrition or taking anticonvulsant drugs develops megaloblastic anaemia and has hydrochloric acid in the gastric juice, the cause of the anaemia is almost certain to be in the alimentary tract, and primary malabsorptive disease or tropical sprue are the most likely causes.

The other two patients are less satisfactory, and raise the problem of the number of tests that have to be positive before a diagnosis of primary malabsorptive disease can be made. Steatorrhoea may be due to various causes; a flat glucose curve does not necessarily mean malabsorption, and vitamin-B_{12} absorption may be impaired because of a blind loop or disease of the ileum. The folic-acid-absorption test, though very useful, particularly in untreated patients, may suggest malabsorption merely because a urine collection has been incomplete. We have not found serum-folic-acid curves to be particularly helpful (Girdwood and Delamore, 1961). Moreover, barium examination of the small intestine may not reveal even gross disease (Doig and Girdwood, 1960).

Laparotomy in Malabsorptive Conditions

Laparatomy was not performed in our five patients with a normal mucosal pattern, and the diagnosis seemed to be satisfactorily established without this in Cases 1 and 2. Subject to tests of pancreatic function and other obvious investigations being first completed, it is difficult, however, to be certain that malabsorptive disease is primary rather than due to organic disease of the small intestine when the jejunal mucosa is normal and there is no history of tropical sprue or coeliac disease. Under these circumstances laparotomy is justifiable.

The two patients with carcinoma of the small intestine had been fully investigated and the results of all the tests were compatible with a diagnosis of primary malabsorptive disease. This seemed to be confirmed by jejunal biopsy, and, unless it be argued that everybody with small-intestinal malabsorption should have a laparatomy, there were no features prior to the development of intestinal obstruction that called for surgical intervention. It would be difficult to justify surgical exploration of the abdomen in all patients with intestinal malabsorption, but it must be accepted that the presence of a jejunal mucosal pattern compatible with primary malabsorptive disease does not exclude the possibility of another lesion developing or being present in the small intestine.

Summary

Jejunal biopsies were carried out by the oral route in 24 patients with malabsorptive disease of the idiopathic steatorrhoea type (primary malabsorptive disease) and in 18 other patients, six of whom had steatorrhoea from other causes. In these 18 patients the mucosa was normal.

Of the patients with primary malabsorptive disease, 9 had absent villa, 10 had abnormal villi, and 5 had a normal mucosa. There was no obvious correlation between the type of mucosal appearance and either the symptoms or the results of laboratory tests of absorption. There was nothing in these results to justify the view that primary malabsorptive disease with absent villi has a different aetiology and symptomatology from primary malabsorptive disease with abnormal villi.

Reference is made to the difficulty of diagnosing primary malabsorptive disease when the jejunal mucosal pattern is normal, and to three patients with the jejunal pattern of primary malabsorptive disease who developed surgical complications because of malignant disease of the small intestine.

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EXTRAMURAL AND INTRAMURAL BLOOD-SUPPLY OF COLON*

BY

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[WITH SPECIAL PLATE]

Drummond in 1914 was one of the first to describe the importance of the marginal artery of the colon, and later the vasa recti and their relationship of the possible causation of diverticula in the colon. We have in recent years repeated this work using newer techniques, which have given us fuller details of the anatomy of the extramural and intramural vessels of the colon. These investigations have been carried out on necropsy bodies and on specimens removed at operation. The findings on the gross topographical anatomy of the main vessels of the colon have previously been described (Griffiths, 1956), and in this paper it is intended to deal with the abnormalities and variations of the marginal artery and the intramural vessels of the colon and their importance in surgery of the colon.

Experimental injections carried out on necropsy cadavers or post-operative specimens have no value in defining the feasibility or otherwise of surgical procedures, but they can be helpful in demonstrating the basis on which clinical experiments should be conducted.

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Braithwaite (1955), experimenting on rats, demonstrated the effect of ligation of various colic vessels on the viability of the colon. These conclusions are valueless when applied to human subjects, as there is a basic difference between the morphology of the colon in the two species.

Okinczyc (1907), performing survival experiments on dogs, ligated the marginal artery at two points on the transverse colon, and demonstrated that the intestine between the sites of ligation remained viable. This finding does not agree with the results of injections performed on human beings and is contrary to experience obtained at operation. Litten (1875) was the first to ligate the inferior mesenteric artery in a dog, and he stated that gangrene of the distal colon ensued. Rothschild (1929) demonstrated that the marginal artery in dogs was able to maintain the blood-supply to the colon after ligation of the colic vessels.

Care must be taken in interpreting the findings of injection experiments. Sudeck (1907) and Manasse (1907), though performing excellent experiments, drew false conclusions from their findings. Radiographs published by Sudeck in his original article in 1907 illustrated the adequacy of the anastomosis between the last sigmoid artery and the superior rectal artery, his hypothesis of a "critical point" being based on injection experiments which did not allow for post-mortem spasm or the viscosity of his injection material.

Necropsy spasm occurs in all arteries within two to three hours of death (Bayliss, 1902; McWilliam and Mackie, 1908), but can be overcome by infusing the arteries with a weak solution of ammonia before the injection experiments are performed. Post-mortem clotting interferes with filling of the smaller vessels in necropsy cadavers, but this can be eliminated in post-operative specimens by infusion with normal saline solution immediately after removal. The viscosity of the injection mass can be controlled by using varying dilutions; in the injection experiments described below a barium and gelatin mixture was used, the viscosity of which was much greater than that of blood, and no filling of the mural vessels occurred in experiments 1, 2, and 3. In experiment 4 the post-operative specimens were injected with a "micro-opaque" solution and the mural vessels filled.

Method of Investigation

The marginal artery was investigated in necropsy bodies by injecting through the aorta a barium suspension containing gelatin. The colon was then removed, and a radiograph was taken which outlined the colon and showed the vessels filled with barium. The intramural blood-vessels of the colon were investigated in operative specimens by injection through a large vessel as soon after removal as was possible, thus preventing both post-mortem spasm of the larger vessels and also blockage of the smaller vessels by post-mortem thrombosis. As soon as the operative specimens could be obtained they were washed through with normal saline containing heparin, and then injected with a "micro-opaque" solution mixed with methyl cellulose diluted with water to the required consistency. The methyl cellulose was used as a dispersing medium to avoid clumping of the barium particles in the small vessels, thus giving a more uniform result during microradiography. Immediate fixation of the colon in formalin prevented leakage of the injected suspension from the smaller vessels, the larger arteries and veins having been tied off. By using "kodaline" film and long exposure with a standard *x*-ray unit it is possible to obtain a negative which can be enlarged up to 60 times without the grain of the film interfering with the details of the anatomy of the vessels.

The injected specimens were also embedded in low-viscosity celloidin as described by Parks (1958), modified after Chesterman and Leach (1949). Transverse sections of the colon were then cut at 100μ, stained with anthracene blue, and mounted. These were then used as negatives in a photographic enlarger and prints made of enlargements, showing the barium-filled vessels in the transverse section of the wall of the intestine.

Anastomosis Between Inferior and Superior Mesenteric Arteries

The anastomosis which occurs between the inferior and superior mesenteric arteries was first demonstrated by injection techniques by Archibald (1908) and Rubesch (1910), who injected radio-opaque material into the superior mesenteric artery and demonstrated a rich anastomosis between the middle and left colic arteries. These experiments have been personally repeated and others performed to prove the effectiveness of this anastomotic channel.

Experiment 1

The inferior mesenteric artery was ligated at its origin in 12 necropsy bodies, and radio-opaque solution was injected as described previously, but with the cannula in the aorta above the origin of the superior mesenteric artery. There was filling of all the branches of the inferior mesenteric artery down to the rectum, including the smaller vessels of the colon and rectum.

Experiment 2

On three necropsy bodies experiments were carried out which simulated the effect of high ligation of the inferior mesenteric artery during operative procedures on the distal colon and rectum. Silver clips were placed on each branch of the inferior mesenteric artery ½ in. (12.7 mm.) distal to its junction with the marginal artery, and radio-opaque material was injected, as described in experiment 1. It was demonstrated conclusively that the marginal artery along the descending colon was capable of supplying the gut down to the sigmoid colon and rectum, though the inferior mesenteric and its branches had been ligated. These experiments have been confirmed clinically at operation, when the inferior mesenteric artery has been ligated on the aorta, and an adequate blood-supply to the distal colon, dependent on the marginal artery, has been observed.

Experiment 3

During injection of necropsy bodies a cannula was inserted into the aorta below the origin of the superior mesenteric artery, a ligature being placed around the aorta at this site, and the extent to which the inferior mesenteric artery could supply the colon was demonstrated. In 16 bodies filling of the superior mesenteric artery and its branches occurred, with, in some of them, retrograde filling of the aorta above the site of the ligature through the orifice of the superior mesenteric artery. In other cases, though the colic vessels were filled, there was no filling of the mesenteric branches of the superior mesenteric artery. This was due to the ostial stenosis which occurs at the origin of the inferior mesenteric artery, diminishing the pressure under which the injection material enters the artery. In six bodies the cannula was inserted directly into the inferior mesenteric artery; in these the injection material filled all the branches of the superior mesenteric artery.

Anastomosis Between Superior Rectal and Middle Rectal Arteries

Experiment 4

In three necropsy bodies radio-opaque material was injected into the aorta following ligation of the inferior mesenteric

FIG. 1.—Radiograph of an injected post-operative specimen following restorative resection of the rectum. The arrow indicates the arterial anastomosis which exists between the last sigmoid artery and the superior rectal artery.

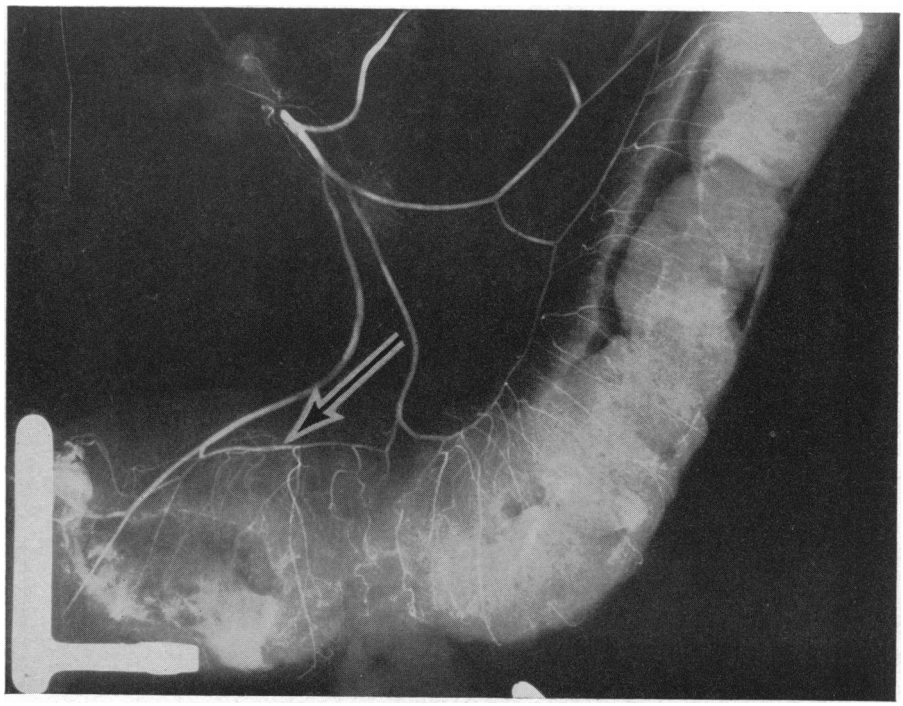

FIG. 1

FIG. 2.—Radiograph of a post-operative specimen of the sigmoid colon laid open, demonstrating the long colic arteries, or vasa recti (V.R.), and the short colic arteries, or vasa brevia (V.B.), arising from the marginal artery (M.). Note the arcade formation between the vasa recti, forming a second arcade (S.A.).

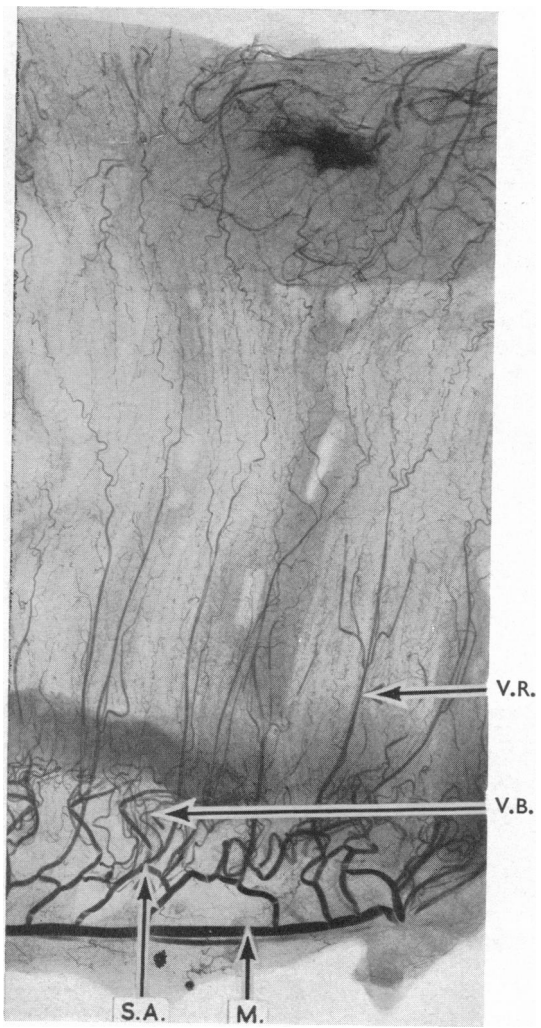

FIG. 2

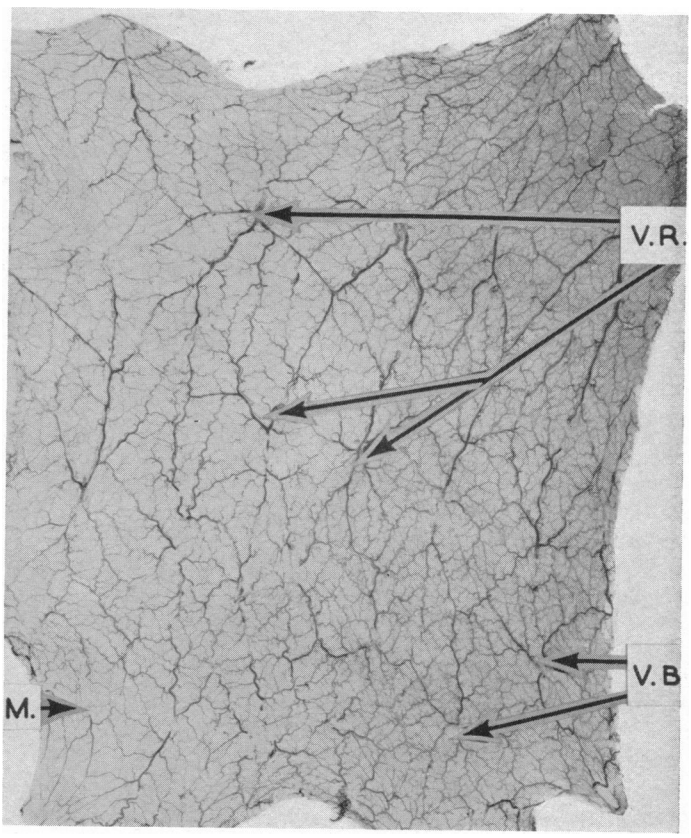

FIG. 3.—Radiograph of the mucosa of the colon which has been dissected off the muscle wall, showing the submucosal plexus. M. is the mesenteric border; V.R. indicates the division of the vasa recti, and V.B. the division of the vasa brevia.

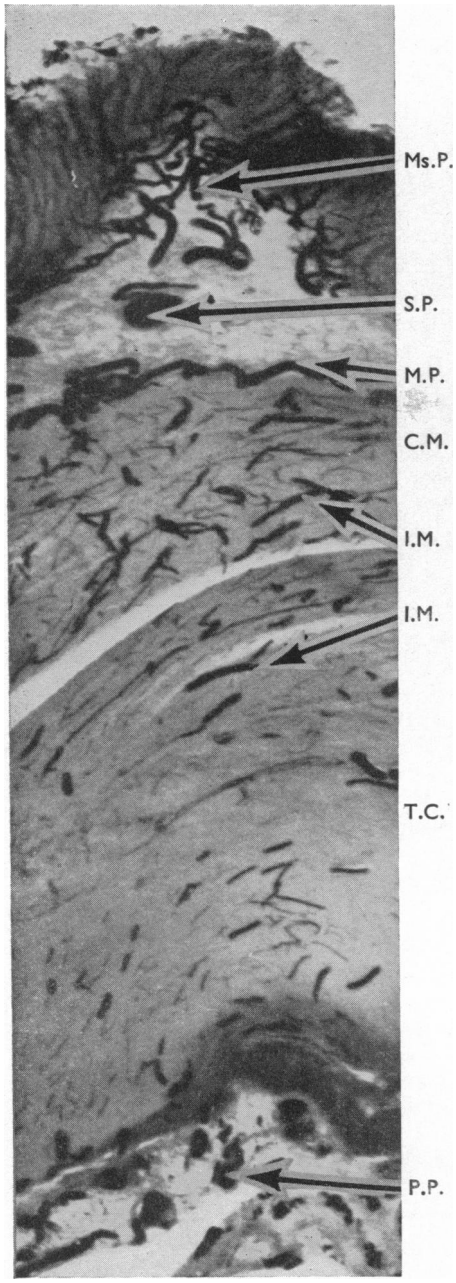

FIG. 4.—Photographic enlargement (×40) of a celloidin section, demonstrating the intramural plexuses of the colon. P.P. is the peritoneal plexus; T.C. the taenia coli; I.M. the intramuscular plexuses; C.M. the circular muscle; M.P. the muscular plexus; S.P. the submucosal plexus; and Ms.P. the mucosal plexus.

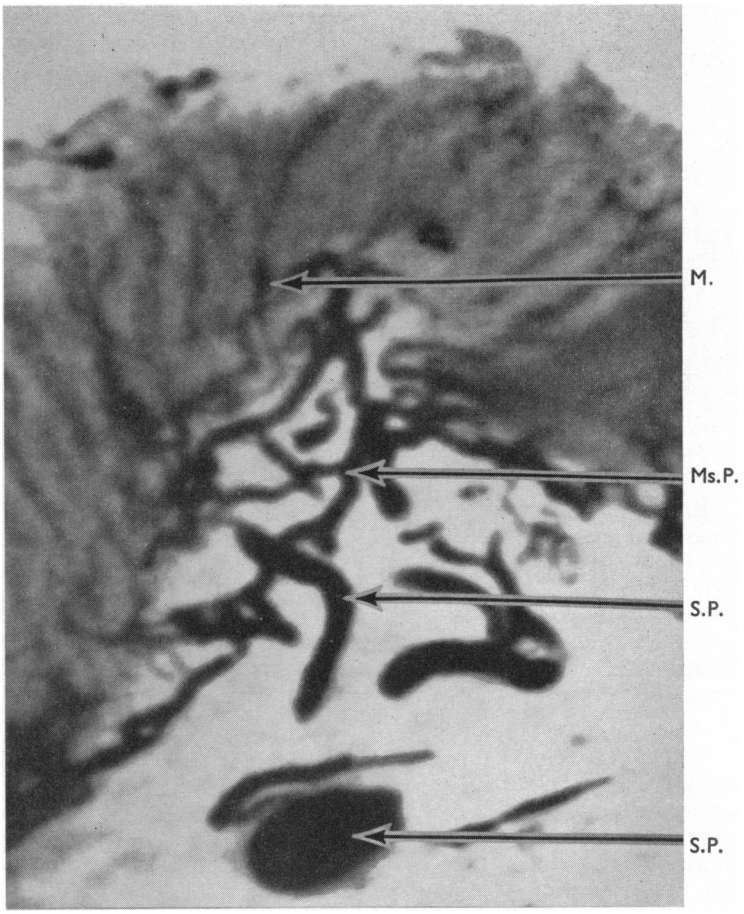

FIG. 5.—Photographic enlargement (×76) of a celloidin section, showing the mucosal plexus. Note the fine arterioles (M.) passing upwards to the mucous membrane from the plexus Ms.P. Branches from the submucosal plexus (S.P.) feed the mucosal plexus.

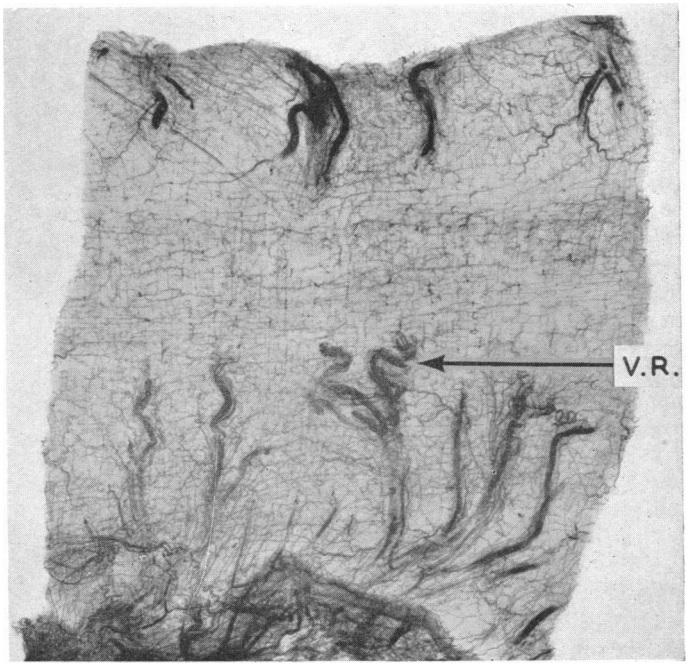

FIG. 6.—Radiograph of the muscle wall of the colon, the mucosa having been dissected free. Note the fine intramuscular plexus only supplied by small arteries from the submucosal plexus, and the point at which the vasa recti (V.R.) pierce the muscle coat.

FIG. 6

and superior mesenteric arteries at their origin. The injection material passed around the marginal artery to the descending colon, demonstrating the effective anastomosis which exists between the middle rectal branch of the internal iliac artery and the superior rectal artery. Injection of the inferior mesenteric artery in six post-operative specimens following synchronous combined excision of the rectum for carcinoma showed filling of the middle rectal arteries through a rich anastomosis with the superior rectal artery.

These findings confirm, contrary to what has been stated by many investigators, that there is a constant and abundant anastomosis between the superior rectal branch of the inferior mesenteric artery and the middle rectal branch of the internal iliac artery. This observation was substantiated on many occasions at operation during restorative resection of the rectum and sigmoid colon, where high ligation of the inferior mesenteric artery had been performed, the distal colon or rectum invariably providing evidence of an adequate residual blood-supply.

These experiments demonstrate (1) the functional anastomosis which exists between the inferior and superior mesenteric arteries; (2) that ligation of the inferior mesenteric artery is a feasible operation; (3) the adequacy of the marginal artery to form a collateral channel; and (4) the presence of an adequate anastomosis between the middle rectal and superior rectal arteries.

Marginal Artery

The marginal artery is the functional vessel of the colon, and the branches of the superior and inferior mesenteric arteries feed the arterial channel running along the mesenteric border of the whole colon. Injection experiments as described above demonstrate the free anastomosis between the superior and inferior mesenteric arteries afforded by the marginal artery, thus enabling any colic branch to be ligated without danger of ischaemia occurring in the colon of a fit patient. Ligation of the inferior mesenteric artery in patients with carcinoma of the distal colon and rectum (Morgan and Griffiths, 1959) has been shown to be a feasible and relatively safe procedure. Sudeck, and later Drummond, described a critical point between the last sigmoid artery and the superior rectal artery, but this is a misnomer, as has been shown by many recent investigations. There is an anastomosis between these two vessels, as demonstrated in Special Plate, Fig. 1. The marginal artery may continue and anastomose directly with the superior rectal artery, or, as is more common, there is an arcade formation supplemented by the recto-sigmoid branches of the superior rectal artery, as shown by Pope and Buie (1929).

During the present investigation into the topographical distribution of the inferior mesenteric artery it was shown by injection experiments and dissections that the marginal artery at the splenic flexure is often poorly developed in a large number of patients. This is of no significance except after ligation of the inferior mesenteric artery during operative procedures on the distal colon and rectum, when the main blood-supply to the distal colon will be via the marginal artery from the middle colic branch of the superior mesenteric artery. In these cases it is imperative to see that the bifurcation of the left colic artery is left intact, to ensure a secondary arcade for the marginal artery in this area.

Vasa Recti and Brevia

The colon is supplied by vasa recti and brevia which arise from the marginal vessels. There is very little anastomosis between these vessels outside the wall of the large intestine, in marked contradistinction to the many arcades which form in the mesentery of the small intestine. The vasa recti, however, do form a few small arcades in the mesentery of the sigmoid colon, as seen in Special Plate, Fig. 2, but they are of no functional value as collateral channels.

The vasa recti, as soon as they arise from the marginal artery, divide into anterior and posterior branches, except in the sigmoid colon, where they may form these secondary arcades. They then pass around on the serosal circumference of the gut before dividing into two or three branches to within a few millimetres of the antero-lateral or postero-lateral taenia of the large intestine and, piercing the circular muscle of the colon, become submucosal. The length of the vasa recti varies with the distance of the marginal artery from the "mesenteric" border of the colon. They tend to be longer in the ascending and transverse colon, as the marginal artery forms loops between the colic vessels in this region; consequently they are farther away from the medial border of the colon. Along the descending colon, however, the marginal artery runs close to the intestine, and therefore the vasa recti are shorter.

The vasa brevia are smaller arteries arising from the vasa recti and not from the marginal artery. They pass directly to the "mesenteric" border of the colon and pierce the muscle coat on either side of the mesenteric taenia to join the submucosal plexus. These smaller vessels are more numerous than the long vessels, and always form a fine anastomotic network between one another on the "mesenteric" border of the colon.

Intramural Plexuses

There are three plexuses in the wall of the colon. The largest and most important is the rich submucosal plexus, which extends as an unbroken "chain mail" throughout the colon. A smaller mucosal plexus is formed under the mucosa, from which the arterioles supplying the mucosa are derived. The muscular plexus, which is not very well developed, lies on the mucosal surface of the circular muscles. The branches of the long and short arteries of the colon pierce the circular muscle coat at four main sites. The larger branches of the long vessels, as they pass into the submucosa, divide into two or three branches which pass directly around to the "anti-mesenteric" border of the colon to anastomose with the corresponding arteries of the other side, thus forming a rich "anti-mesenteric" submucosal anastomosis. Smaller branches pass towards the "mesenteric" border to join with the more numerous, but smaller, branches of the short colic arteries on the "mesenteric" border. The short colic arteries in their turn anastomose with one another on the "mesenteric" border of the intestine (Special Plate, Fig. 3). The main branches of the short and long arteries also anastomose freely with the branches from subsequent arteries on either side, so forming a rich submucosal plexus along the circumference and length of the colon. This arterial plexus resembles that shown by Barclay (1951) to exist in the stomach. Saunders *et al.* (1957), describing their finding of the arterial supply in skeletal muscle, showed a similar meshwork of vessels, which they termed a "macromesh," inside which there exists a further network of smaller vessels termed "micromesh," from which the arterioles supplying the capillaries arise. Inside the "macromesh" of the submucosal plexuses of the colon there are further plexuses which join to form

a fine network of arteries situated immediately under the mucous membrane between it and the muscularis mucosae (Special Plate, Fig. 4). From this plexus very fine arteries pass up into the mucosa vertically from the horizontal mucosal plexus, and in Fig. 5, on the Special Plate, the mucosal plexus can be seen giving off numerous mucosal arteries. The mucosa has a very rich blood-supply, and it is true to say that the mucous membrane rests on a carpet of blood-vessels, as has been well shown by Brockis and Moffat (1958) in their "neoprene" latex injections of these plexuses.

An injection of the venous system shows that the veins follow an identical pathway and pattern to the arteries, forming similar plexuses. The veins drain from the capillary plexus which is in the mucosa itself as small mucosal veins to join the submucosal plexus.

No muscular branches are given off by either the long or short arteries, the circular muscle and the taeniae coli receiving their blood-supply from the submucosal plexus. A muscular plexus is formed from arteries arising from the submucosal "macromesh" on the mucosal surface of the circular muscle, and from this plexus smaller arteries are given off which pierce the muscle to form the intramuscular plexus. Special Plate, Fig. 6 shows the muscle coats of the colon after dissection of the mucous membrane and the submucosal plexus, from which it can be seen that the muscle has a poor vascular pattern made up of small arteries.

Marginal Artery in Operations

Injection experiments have been performed on operative specimens which demonstrate the importance of preserving the marginal artery up to the point at which the colon is divided in operative resection. If a ligature is placed around the marginal artery at the midpoint of an operative specimen of colon, and one end of the artery is injected with a radio-opaque material of comparable viscosity to blood and under pressure equal to that of the patient's blood-pressure, the vessels in the wall of the colon will fill up to the ligature, but there is very little filling beyond this point. From this it can be concluded that there is a poor collateral circulation between the vasa recti and brevia, and, despite the richness of the submucosal plexus, it is too narrow in calibre to allow the development of any extensive intramural collateral. This is in contrast to the intramural collateral that develops in the stomach and to a lesser extent in the small intestine. Care must, therefore, be taken not to ligate the marginal artery proximal to the proposed site of an anastomosis, and it is inadvisable to "clean" the "mesenteric" border of its vasa recti at the site of anastomosis or possibly to damage these vessels by removing the appendices epiploicae, as this would produce ischaemia at the ends of the gut which is being anastomosed.

Many post-operative fistulae occurring after anastomosis in the colon are in part due to the inadvertent devascularization of the ends of bowel following misplaced ligature of the marginal artery. It has been emphasized by Naunton Morgan (personal communication) that the marginal artery should be ligated 1 in. (2.5 cm.) beyond the site of section of the colon, thus obviating the danger of the marginal artery being distorted after mobilization of the colon. It is often difficult to verify the viability of the colon during resection procedures, in particular where high ligation of the inferior mesenteric artery has been performed in operations on the distal colon and rectum. Pulsations of the larger vessels may be markedly diminished because of spasm from handling, and the colour of the large intestine is not always a safe guide; but the adequacy of the blood-supply is really proved by the division of the marginal artery below the selected site of resection, before the application of artery forceps.

Summary

The extramural and intramural vessels of the colon have been reinvestigated, using necropsy and operative specimens injected with "micro-opaque" solution, and a technique of microradiography has been developed to demonstrate the intramural plexuses. The importance of the marginal artery during operative procedures on the colon is emphasized.

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INCIDENCE OF SOME AETIOLOGICAL FACTORS IN HUMAN LEUKAEMIA

BY

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Radiations, chemical agents, and heredity are among the factors suspected of being concerned in the cause of some cases of leukaemia. An investigation designed to estimate the incidence of these and other factors in an unselected population has been in progress for some time, and the preliminary results of the first two years are now reported. With the aid of a detailed questionary, interviews were conducted by doctors with as nearly as possible all new patients having leukaemia (including myelomatosis) throughout New Zealand, and with control patients matched for age and sex. The results were centrally coded and analysed. The controls were chosen from hospital patients. Since this might be thought to introduce bias, especially in measuring exposure to drugs and *x* rays, two further control groups were formed to test this possibility. These consisted