

EFFECT OF ANTIBIOTICS ON INTERRUPTION OF INTESTINAL ARTERIAL FLOW

by

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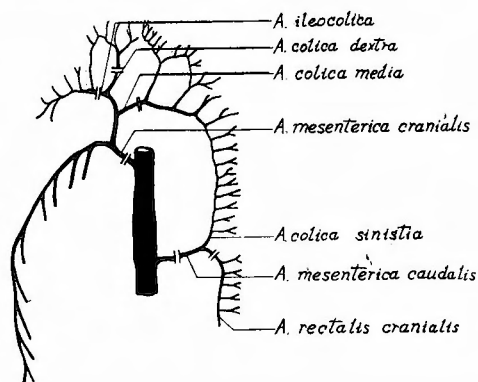
INTRODUCTION

In the present experiments, the intestinal arteries of dogs were interrupted in different positions in order to see if the animals could survive the operation. The result was that some ways of devascularization killed all the dogs that had undergone the operation, while others did not. In order to test their effects on the operation, antibiotics were administered to the dogs whose intestinal arteries had been devascularized in such position as would be fatal to them.

METHOD

Adult dogs were used, as in the previous experiments. Operation were performed under aseptic conditions, with 5% isomytal solution injected intravenously for anesthesia.

The abdomen was opened, and the omentum was cut off. The stomach, large and small bowels, and spleen were then pushed rightward to reach for the root of the A. mesenterica cran., which was doubly clamped, divided, and ligated at its root. The A. ileocolica, A. colica dextra, A. colica media, A. mesenterica caud. and A. rectalis cran. were also doubly clamped, divided, and ligated at their respective branching. Figure 1 shows how the devascularization was performed.



The sign // indicates the position where the artery is interrupted

Fig. 1 Diagram of operative procedure, showing where the principal intestinal arteries are ligated and divided.

During the operation, 1.0 g of crystalline dihydrostreptomycin sulfate "Sankyo" and 200,000 units of crystalline penicillin G "Banyu" (abbreviated to SM and P respectively in the following pages) were given intramuscularly, and after the operation, 0.5 g of SM and 100,000 units of P were injected also intramuscularly every 6 hours for 7 days.

RESULTS OF EXPERIMENTS

(1) Group 1; cases given no antibiotics (Table I)

i) A case in which the A. mesenterica cran. and caud. were ligated and divided

In this case, the A. mesenterica cran. and caud. were both devascularized at the same time. After the operation, the dog had hemorrhagic vomiting, and died at the 13th hour, when an autopsy was performed. There was a lot of dark, foul-smelling, hemorrhagic fluid in the peritoneal cavity. The bowels were dark red from the duodenum to the jejunum, and dark reddish brown from the ileum to the large bowel, becoming edematous and jellied. The whole mucosa was observed to be swollen, hemorrhagic or necrotic, and easy to come off. The mesenteric veins were enlarged and full of blood, and hemorrhagic spots seen here and there. There were a lot of bloody fluid contents in the lumen of the bowel.

Histological examinations revealed that in the bowel wall where great changes were observed, the epithelial cells had come off necrotic, and that a high degree of cell infiltration was observed in the propria mucosae and submucosa, the latter of which had its vessels congested, while the other layers were only slightly degenerated (Figs. 2 and 3).

ii) Cases in which the A. mesenterica cran. was ligated and divided

The 3 cases of this group died between 29 and 87 hours after the operation. At autopsy, there was a great deal of stinking, hemorrhagic fluid in the peritoneal cavity. The bowels had been changed into dark red from the duodenum to the ascending colon, with a lower part of the small bowel having become dark reddish brown, edematous, and jellied. As in case i, the mesentery had hemorrhagic spots, with its vein full of blood.

The mucous surface was found dark red, and as we came down to the lower part of the small bowel, greater changes appeared in the mucosa. The mucous surface on the antimesenteric upper portion of the small intestine had necrotic spots of irregular shapes, which increased in the anal direction until necrosis spread over all the lower portion of the small bowel. As in case i, the bowel contents were hemorrhagic. If a part of the bowel wall showed a great change to the naked eye, all the layers of that part were, histologically, so necrotic that they were barely distinguishable from one another (Figs. 4 and 5).

iii) Cases in which the four principal colic arteries (A. mesenterica caud., A. colica dex., A. colica med. and A. ileocolica) were ligated and divided

Of the 3 cases belonging to this group, one died from suffocation 12 hours after the operation, and the other two survived. At autopsy, there was no peri-

Table. 1 Cases in which the intestinal arteries were devascularized. No antibiotics were given.

Devascularized arterie	Dog No.	Sex	Weight (kg)	Survival time (Days Hours)	Macroscopic findings						
					Ascites	Color change in bowel	Serosa	Mucosa	Bowel Wall	Mesentery	Bowell contents
A. mesenterica cran. & caud.	72	♂	9.0	13 H dead	# bloody stinking	Duodenum ↓ Colon	dark	dark	soft,	hemorrhagic spots	bloody fluid
A. mesenterica cran.	73	♂	6.0	32 H dead		Duodenum	red or dark	red,			
	75	♀	10.0	87 H dead	↓ Ileum	brown	necrotic				
	77	♀	6.8	29 H dead		# bloody stinking					
A. mesenterica caud.	55	♀	6.8	54 D sacrificed						enlarged	
A. ileocolica	85	♂	3.0	12 H dead							
A. colica dext.											
A. colica med.	86	♂	11.5	15 D sacrificed			Adhesion of small bowel	fresh hemorrhagic spots			small
A. mesenterica caud.	57	♂	6.0	15 H dead	#	Transverse colon ↓ Descending colon	dark reddish brown	dark brown necrotic	soft	vessel	
A. ileocolica	71	♀	9.0	75 H dead	bloody		grayish green	grayish, smooth	thin		
A. colica dext.											
A. colica med.	74	♂	6.5	48 H dead	# purulent		dark reddish brown	dark brown necrotic	soft, perforation (+)		
A. rectalis cran.											

toneal fluid in any of them. The serosa surface showed nothing very unusual, except for #55 in which the loops of small bowel were adherent to the descending colon. The mucous surface did not show any great change, except that in #55, it was slightly atrophic, and that #86 which had new hemorrhage in part of the descending colon. The mesentery had no hemorrhagic spots, either.

Histologically cell infiltration was observed in the propria mucosa; the epithelial cells suffered a slight degree of necrobiosis here and there; a slight degree of edema, congestion, and cell infiltration were recognized in the submucosa; and no ulcers were found (Figs. 6 & 7).

iv) Cases in which the A. mesenterica caud., A. ileocolica, A. colica dext., A. colica med. and A. rectalis cran. were ligated and divided

The 3 cases of this group died 15 to 75 hours after the operation. An autopsy was performed. There was some hemorrhagic or purulent hemorrhagic peritoneal fluid in all of them. Changes were observed covering the area extending from the transverse colon to the descending colon. In #71 the serosa had become thin, with grayish green, dirty, purulent matter on it, while in the others it was dark reddish brown and soft, with large perforation in #74. The mucosa was grayish green and smooth in #71, whereas in the other two it was dark brown and edematous, with its folds disappearing.

Histologically, in all three cases necrosis was observed in the bowel wall to such a high degree that all cells had been destroyed, with their nuclei missing, although the layers were distinguishable from one another (Figs. 8 & 9).

(2) Group 2: cases given antibiotics (Table 2)

The above experiments made it clear what methods of devascularization were fatal to all the dogs that had undergone the operation. In the following, antibiotics (SM and P) were intramuscularly injected into those cases whose bowel arteries were devascularized according to such methods.

i) Cases in which the A. mesenterica cran. was ligated and divided

The 3 cases of this group died 78 to 96 hours after the operation. The autopsy revealed that both had some peritoneal fluid which was hemorrhagic or purulent hemorrhagic and only slightly foul-smelling. As to the bowel wall, the serosa covering the duodenum to ascending colon was dark brown and edematous and the mucosa of these parts was dark brown and necrotic. The cases (#81) had perforations in the ileum. No hemorrhagic spots were observed in the mesentery. The bowel contents were hemorrhagic.

Just as in the cases of group 1, if a part of the bowel wall was observed with the naked eye to be greatly changed, almost all its layers suffered necrosis histologically. In those portions which were slightly necrotic, however, a higher degree of cell infiltration than in group 1 was observed in the submucosa and muscular coat (Figs. 10, 11, & 12).

ii) Cases in which the A. mesenterica caud., A. ileocolica, A. colica dextra, A. colica media and A. rectalis cran. were ligated and divided

3 cases belonged to this group. They all survived and were then sacrificed for

Table. 2 Cases in which the intestinal arteries were devascularized. Antibiotics were given.

Devascularized arteries	Dog No.	Sex	Weight (kg)	Survival time (Days, Hours)	Macroscopic findings						
					Ascites	Color change in bowel	Serosa	Mucosa	Bowel wall	Mesentery	Bowel contents
A. mesenterica	76	♂	11.0	96 H dead	+ bloody	Duodenum ↓ Ileum	dark	dark	soft	hemorrhagic spots(-)	bloody
cran.	81	♂	10.0	78 H dead	## purulent-bloody		dark	brown,	soft perforation (+)		bloody
	94	♀	10.0	76 H dead	## bloody		red	necrotic	soft		bloody
A. mesenterica caud.	58	♀	7.0	29 D sacrificed			Adhesion of dark red in small bowel stenotic site		stenosis in descending colon	enlarged small vessel	
A. ileocolica	78	♂	6.4	14 D sacrificed							
A. colica dext.											
A. colica med.											
A. rectalis cran.	79	♀	9.0	14 D sacrificed							

an autopsy. There was no peritoneal fluid. Nor did the serosa demonstrate any remarkable changes, except that #58 had the descending colon strictured.

In #58 the mucous surface was dark brown and smooth in the stenotic portion of the bowel. All small mesocolic vessels were seen enlarged.

The histological findings of the large bowel wall were: that the epithelial cells were slightly degenerated; that cell-infiltration was observed in the propria mucosae; and that neither hemorrhage nor cell-infiltration was seen in the submucosa, which was only slightly edematous and congested. In #58 the mucosa and muscularis mucosae of the strictured portion of the colon had become necrotic and ulcerous, while the other portions showed no remarkable changes (Figs. 13 & 14).

(3) Changes checked 3, 6 and 12 hours after the operation in the cases where the A. mesenterica caud., A. ileocolica, A. colica dextra, A. colica media, A. rectalis cran. were ligated and divided (Table 3).

Table. 3 3, 6 and 12 hour follow-up of the cases in which the four principal colic arteries and A. rectalis cran. were devascularized.

	Reoperation	Dog No.	Sex	Weight (kg)	Macroscopic findings		
					Peritoneal fluid	Serosa	Mucosa
Cases	at 3rd hour	89	♀	8.5	+ slightly bloody	slightly dark reddish in part of descending colon	red hemorrhagic portion (+)
given no antibiotics	at 6th hour	82	♀	9.0	+ slightly bloody	slightly dark reddish from transverse colon to descending colon	edematous, dark red
	at 12th hour	92	♂	5.0	++ slightly bloody turbid, stinking	dark reddish from transverse colon to descending colon	dark red
Cases	at 3rd hour	90	♂	9.0			fresh red, hemorrhagic
given	at 6th hour	83	♀	7.0			fresh red, hemorrhagic
antibiotics	at 12th hour	91	♀	6.5		slightly dark reddish in a part of descending colon	hemorrhagic, partly dark red

Six dogs were chosen and their A. mesenterica caud., A. ileocolica, a. colica dextra, A. colica media and A. rectalis cran. were all ligated and divided. Three of them were given antibiotics, but the others were not. They were sacrificed at the 3rd, 6th and 12th hour after the operation—one from each group at a time.

In the cases which did not receive any antibiotics hemorrhagic peritoneal fluid was observed to be increasing in quantity as time passed, until it turned turbid at the 12th hour. In the others which received antibiotics, however, it was not until 12 hours after the operation that slightly hemorrhagic fluid was recognized. The serosal surface of the untreated cases dark reddish brown and edematous 12 hours after the operation, while that of the treated cases showed a very slight degree of color change only in part of the descending colon at the 12th hour. The mucous surface of the large bowel had hemorrhage at the 3rd hour in the treated as well as in the untreated cases. In the untreated cases a reddish brown necrotic area

spread over the transverse and descending colons 6 hours after the operation, whereas in the treated cases the change appeared only in part of the descending colon at the 12th hour.

Histological examinations revealed the following facts. In the untreated cases, at the 3rd hour, there were hemorrhage and enlarged capillaries in the mucosa, slight degeneration in the epithelial cells and a slight degree of edema and congestion in the submucosa. At the 6th hour, all layers but a outer part of the longitudinal muscular layer had already become necrotic, and the veins of the submucosa were greatly enlarged. Thrombosis was also observed. In the treated cases the finding at the 3rd hour were much the same as those of the untreated ones. At the 6th hour, however, a high degree of cell infiltration was observed in the propria mucosae, and the epithelial cells were greatly degenerated, although there was nothing wrong with the other layers. At the 12th hour, the mucosa was highly necrotic in some parts or other, with a high degree of cell infiltration, which was also observed here and there in the muscularis mucosae and submucosa, where congestion and perivascular infiltration were seen (Figs. 15, 16, 17, 18, 19 & 20).

SUMMARY AND DISCUSSION

NIEDERSTEIN, ICHIKAWA and others reported that if the interruption of the A. mesenterica cran. was performed on a dog, the animal immediately died of hemorrhage, with "hämorrhagische Gangrän" in the lower part of its small bowel. My experiments came to the same conclusion.

Antibiotics did not save those dogs whose A. mesenterica cran. was ligated and divided. Nor were they able to prevent the necrotic area from spreading in the small bowel. It is believed, however, that antibiotics have a certain degree of effectiveness, seeing that the mesentery had no hemorrhagic spots, that the peritoneal fluid was not foul-smelling, and that the period of survival was likely to be prolonged.

The effectiveness of antibiotic protection against bowel wall necrosis can also be proved by the following histological findings. In those cases which received antibiotics, the area where slight changes were observed showed a higher degree of cell infiltration than in those which received no antibiotics.

According to HASEGAWA, the devascularization of the four principal colic arteries causes the animal to die of necrosis in the bowel wall 12 to 15 hours after the operation. In my present experiments, however, the 3 cases which underwent such devascularization survived, with only slight local changes in the large bowel.

The A. rectalis cran. as well as the four principal colic arteries had to be devascularized to make the animals die. In this case, however, necrosis was prevented by the administration of antibiotics, so that all the dogs survived, although one of them had stenosis and ulcers in the descending colon. Less than 6 hours after the A. rectalis cran., as well as the four principal colic arteries, were devascularized, the cases which received no antibiotics showed a considerably high degree of necrotic change in the bowel wall. On the contrary, the cases which received antibiotics did not suffer

necrosis, but had a high degree of cell infiltration which showed the viability of the tissues of the bowel wall. From these facts it may be concluded that antibiotics should be given clinically as early as possible after the operation in order to protect the bowel wall from developing necrosis.

CONCLUSION

The intestinal arteries of dog were ligated and divided in different ways, and crystalline dihydrostreptomycin sulfate and crystalline penicillin G were given to them. The results are as follows:

- 1) The cases belonging to the below three groups died :
 - (1) cases in which the A. mesenterica cran. was devascularized ;
 - (2) cases in which the A. mesenterica cran. and caud. were devascularized ;
 - (3) cases in which the A. mesenterica caud., A. ileocolica, A. colica dextra, A. colica media, i. e., the four principal colic arteries and A. rectalis cran. were devascularized. On the other hand, the cases whose four principal colic arteries were devascularized survived.
- 2) Administration of antibiotics was not able to save those cases in which A. mesenterica cran. was devascularized. The spans of their lives, however, were somewhat prolonged by SM and P, and both macroscopic and microscopic findings showed the effectiveness of the antibiotics.
- 3) Administration of dihydrostreptomycin and penicillin saved the animals whose A. rectalis cran. as well as the four principal colic arteries, was devascularized.

I wish to thank Prof. Dr. CHISATO ARAKI and Assist. Prof. Dr. ICHIO HONJO for their guidance throughout the period of this work.

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和 文 抄 録

腸管動脈遮断に於ける抗生剤の効果

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犬の腸管動脈に於て、上腸間膜動脈、下腸間膜動脈、廻結腸動脈、右結腸動脈、中結腸動脈、上直腸動脈等を単独に或は組合せて種々に結紮切断し、それらの遮断型式による実験犬の生死を確めた後、実験犬に死を来す遮断方式を採用し、これらに抗生剤を投与して其の効果を檢した。抗生剤として動脈遮断時硫酸ザヒドロストレプトマイシン1.0g及結晶ペニシリンGナトリウム20万単位を筋注し、術後毎6時に夫々其の0.5g及10万単位を筋注し7日間連続した。

1) 上腸間膜動脈遮断、上及下腸間膜動脈遮断、或は廻腸動脈、右結腸動脈、中結腸動脈、下腸間膜動脈及上直腸動脈同時遮断では実験犬は何れも死亡し、廻結腸動脈、右結腸動脈、中結腸動脈及び下腸間膜動脈同時遮断では生存した。

2) 腸間膜動脈遮断群に抗生剤を投与しても生存例は得られなかつたが、生存時間の多少の延長を認め、且剖検時腹水は血性ではあるが悪臭は殆どなく、腸間膜の出血斑も殆ど認められなかつた。組織学的にも壊死性変化の軽度な部分の腸壁には抗生剤非投与群に比して粘膜下層、筋層の細胞浸潤が著しく認められた。

3) 廻結腸動脈、左結腸動脈、中結腸動脈、下腸間膜動脈及上直腸動脈同時遮断群に於て抗生剤を投与して全例生存せしめ得た。

4) 同上遮断群に於て抗生剤使用及非使用の場合を継時的に觀察するに、非使用例に於ては腸管壊死性変化は6時間で既に全層に進行しているが、抗生剤投与例に於ては粘膜層に止つて居り腸管壊死に対する抗生剤の防禦効果が認められた。

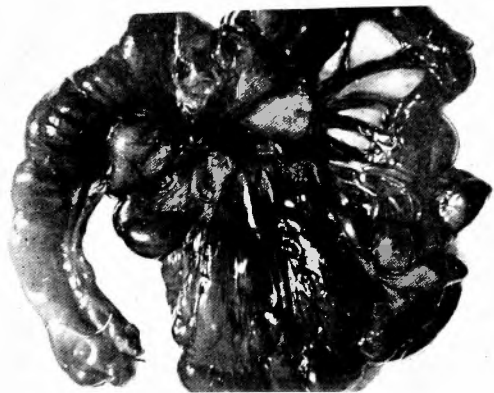


Fig. 2 Specimen of devascularized intestine of #72.

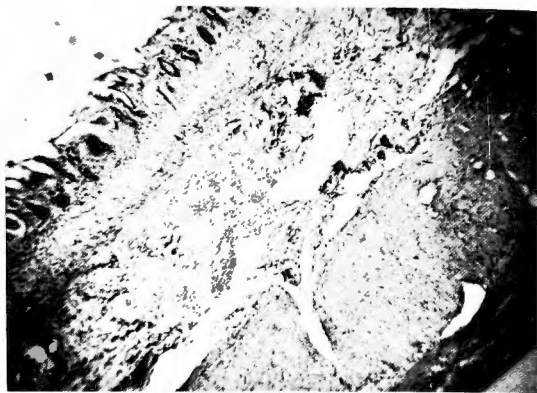


Fig. 3 Microscopic appearance of ileum of #72. (H-E stain $\times 50$)

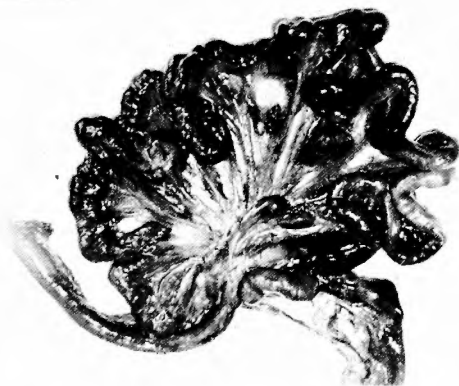


Fig. 4 Specimen of devascularized intestine of #73.

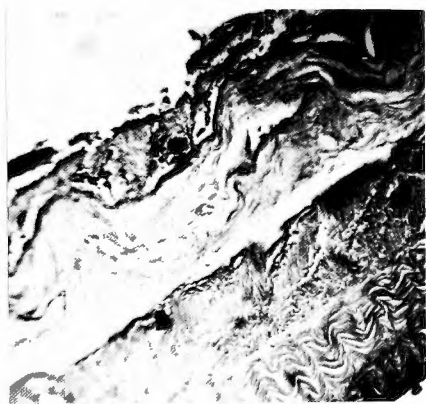


Fig. 5 Microscopic appearance of ileum of #73.

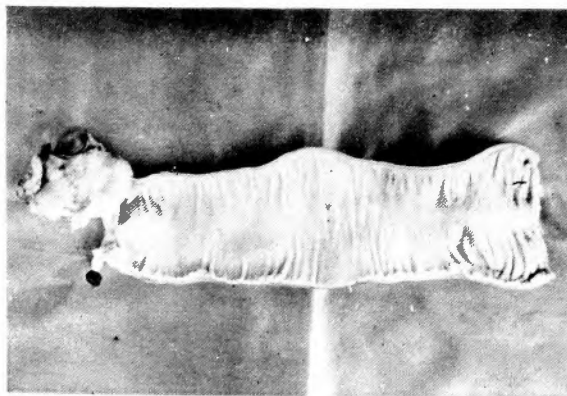


Fig. 6 Appearance of mucous surface of colon in #55.

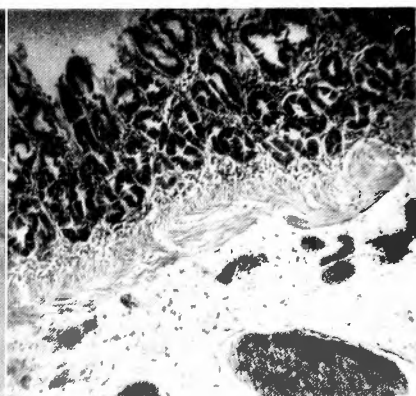


Fig. 7 Microscopic appearance of large bowels of #55 (H-E stain $\times 50$)

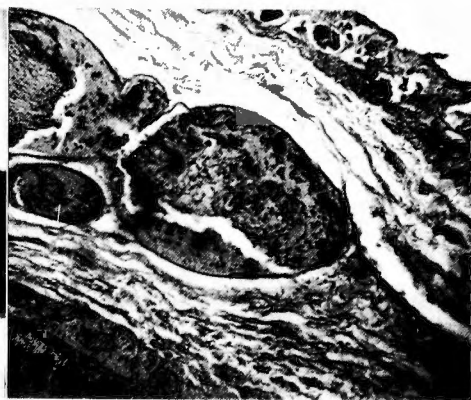
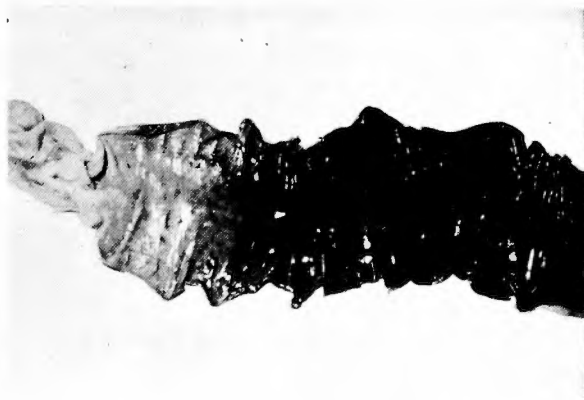


Fig. 8 Appearance of mucous surface of colon in #57.

Fig. 9 Microscopic appearance of colon of #57. (H-E stain $\times 50$)



Fig. 10 Specimen of intestine of #76.

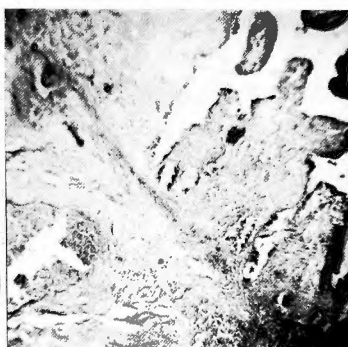


Fig. 11 Histological findings of ileum of #76. (H-E stain $\times 50$)



Fig. 12 Microscopic appearance of jejunum of #76 (H-E stain $\times 50$)

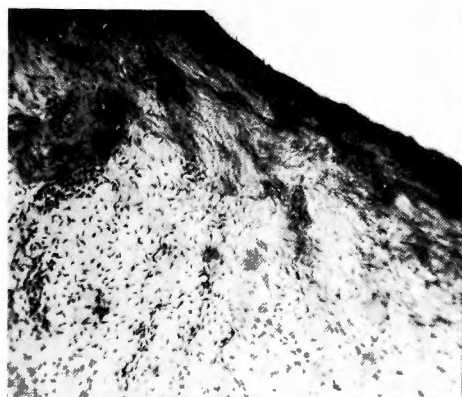


Fig. 13 Microscopic appearance of stenosed portion of descending colon of #58. (H-E stain $\times 50$)

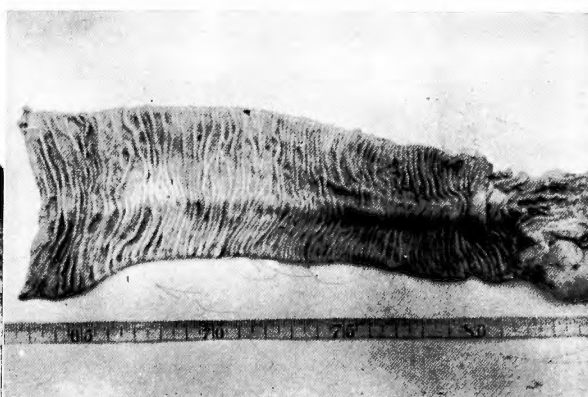


Fig. 14 Appearance of mucous surface of colon of #78. (H-E stain $\times 50$)

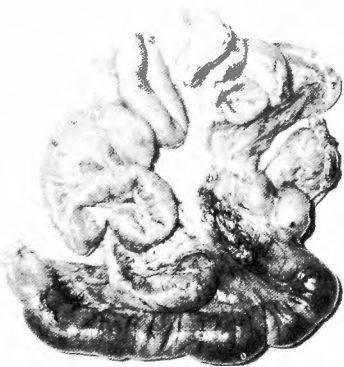


Fig. 15 Specimen of intestine of #82.



Fig. 16 Appearance of mucous surface of colon of #82.

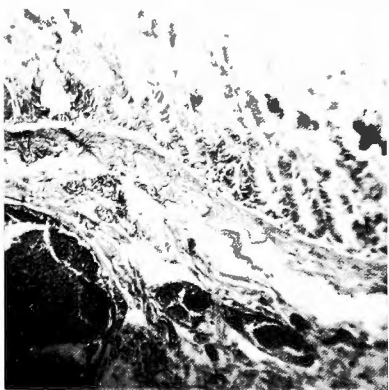


Fig. 17 Microscopic findings of colon of #82. (H-E stain $\times 50$)



Fig 18 Specimen of intestine of #83



Fig. 19 Appearance of mucous surface of colon of #83.

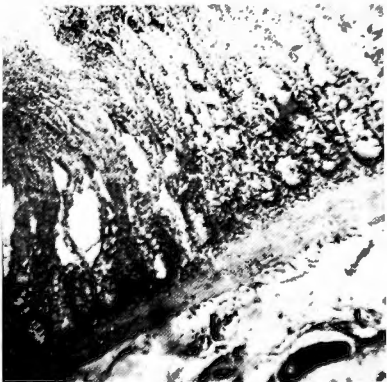


Fig. 20 Microscopic appearance of colon of #83. (H-E stain $\times 50$)