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Spontaneous Reconstitution of the Mammalian Intestinal Tract following Complete Transection (40914)[1]

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Abstract. To determine whether the mammalian intestinal tract is capable of reconstituting itself following complete transection, a 1-cm segment of the small or large bowel was excised in 44 rats. In an additional group of 52 rats the colon was transected distal to a diverting colostomy. In each case the open-cut ends of the intestine were simply dropped back into the peritoneal cavity and the abdominal incision was closed with sutures. Eight animals survived simple transection (18%) regaining functional intestinal continuity in 2 weeks and a morphologically normal appearing intestine in 1 month. When the colon was transected distal to a diverting colostomy the survival rate increased almost four-fold with complete reconstitution of the transected segment in 80% of the survivors.

The term "regeneration" was applied to the transected mammalian intestine in 1920 when Florence Sabin (1) described various aspects of the histological response to tissue damage in a surgical anastomosis. Recognizing that the intensity of the initial inflammatory response regulated the nature of the reparative process which followed, she wrote: "the most striking point about end-to-end anastomosis, as it has been developed by Dr. Halsted and Dr. Holman, is the very slight damage to all of the tissues and therefore the slight amount of regeneration called for." Since a proper surgical anastomosis minimizes regenerative activity, it seemed likely that replacement of the open-cut ends into the peritoneal cavity would have exactly the opposite effect. Based on studies in amphibia by Goodchild (2) and by O'Steen (3), it also seemed possible that regenerative activity induced by this maneuver might be intense enough to affect spontaneous reconstitution of the transected intestine. When they transected the intestine in adult frogs and newts and replaced the open-cut ends into the peritoneal cavity, Goodchild and O'Steen found that spontaneous reconstitution occurred in about 30% of these animals. An attempt to determine whether the intestinal tract of adult rats retains any trace of this capacity for spontaneous reattachment and reconstitution formed the basis for this study.

Materials and methods. Ninety-seven male Wistar rats (300–400 g) were weighed and then fasted preoperatively for 24 hr but had access to a solution of 5% dextrose in saline. Under ether anesthesia and using a clean but not sterile technic, the abdomen was opened through a 4-cm midline incision and the intestine was transected in four groups of rats as follows: Group 1: In 28 rats the ileum was transected in two places, 1 cm apart, at a point approximately midway between the end of the duodenum and the caecum. The 1-cm segment of intestine intervening between the two sites of transection together with a few millimeters of adjacent mesentery were removed. Group 2: In 5 rats the caecum and adjacent mesentery were removed. Group 3: In 9 rats a 3-cm segment of colon midway between the caecum and the rectum together with adjacent mesentery were removed. Group 4: In 53 rats the left colon was divided and the two ends exteriorized as an end colostomy and mucus fistula. After irrigating the distal colon through the mucus fistula, the distal segment was transected 2 cm beyond the mucus fistula. In all 97 rats the open-cut ends of the intestine were simply dropped back into the peritoneal cavity

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and the abdominal incision was then closed with a continuous silk suture. Food was withheld during the next 24–36 hr although animals continued to have access to a solution of glucose in saline. Thereafter animals were fed Purine Laboratory Chow and water *ad libitum*. Surviving animals were reexamined at fortnightly intervals for 1–2 months (the longest period studied to date) by opening the abdomen under ether anesthesia. All other animals were autopsied within 24 hr of death. After gross examination of the site of transection, this segment of the intestine was removed, opened, fixed in 10% buffered formalin, sectioned and stained with hematoxylin and eosin, and examined microscopically.

Results. Twenty-one rats in groups 1–3 died within 48 hr of operation and in each case examination disclosed complete separation of the cut ends of the intestine as well as peritonitis. An additional three animals died in from 49 to 96 hr but evidence of peritonitis was found in only one. The cut ends of the intestine were still separated in this animal as well as in a second that apparently died of obstruction of the proximal segment. In contrast, the cut ends were firmly attached to one another in the third animal which also appeared to die of obstruction. Seven more animals in groups 1–3 died between 96 and 168 hr and an additional 5 died in from 1–2 weeks following operation. No evidence of peritonitis was found in any of these 12 animals and in each case, with two exceptions, the intestinal ends were firmly attached to one another. In one of the two exceptions, the intestinal ends were still separate but sealed and in the other the distal-cut end had attached to the side of the proximal segment, the end of which was also sealed. All 12 of these animals appeared to have died from intestinal obstruction due to an adhesive band, an inflammatory mass or a blind cul-de-sac.

Histological examination of the site of transection in these animals disclosed a sequence of changes closely resembling those described earlier in amphibia by Goodchild and by O'Steen. Initially, a mass of blood clot and fibrin formed over the cut ends and the submucosa became congested, edematous, and filled with exuded mononuclear cells. Mucosal eversion was noted at both cut ends. Cells in the serosal and muscular layers gradually lost their characteristic appearance and were replaced by primitive appearing mesenchymal cells. The numbers of these cells increased rapidly to form a mass which filled both cut ends and then became continuous (Fig. 1). Islands of mucosal epithelial cells extended into and then surrounded this mass (Fig. 2). An epithelial-lined lumen from both the proximal and distal segments gradually replaced the mass of proliferating cells and luminal and epithelial continuity were gradually restored.

Eight of the original 44 animals in groups 1–3 were alive and well at 2 weeks (18%) (Fig. 4). Of this group, 6 had undergone transection of the ileum, one of the caecum, and one of the colon. All of these rats were passing fecal pellets. Examination of the peritoneal cavity at 2 weeks in these animals disclosed that the peritoneal surfaces were completely normal and that the two ends of the intestine were firmly attached to one another. Luminal continuity was confirmed in each case by milking air and fluid from the proximal to the distal segment. Proximal to the site of this spontaneous anastomosis, the intestine was markedly distended and had a thickened wall. By the end of 2 more weeks (1 month postoperatively) each of these animals had regained its preoperative weight. The dilatation and thickening of the intestine had diminished markedly and all tissues had acquired a normal appearance (Fig. 3). Histological studies at 4–8 weeks confirmed that luminal and mucosal continuity were complete. An incomplete muscularis was usually the only histological sign of the site of previous transection.

Thrirteen of the 53 animals in group 4 died within 48 hr of operation due to retraction of the proximal colostomy and peritonitis or intraperitoneal bleeding. Of the remaining animals with an intact colostomy, 16 subsequently died of either peritonitis or intestinal obstruction, a mortality rate of 40%. Examination of the 24 survivors at 4–6 weeks disclosed end-to-end reconstitution of the colon in 19. A narrow lumen at the junction of the two cut ends

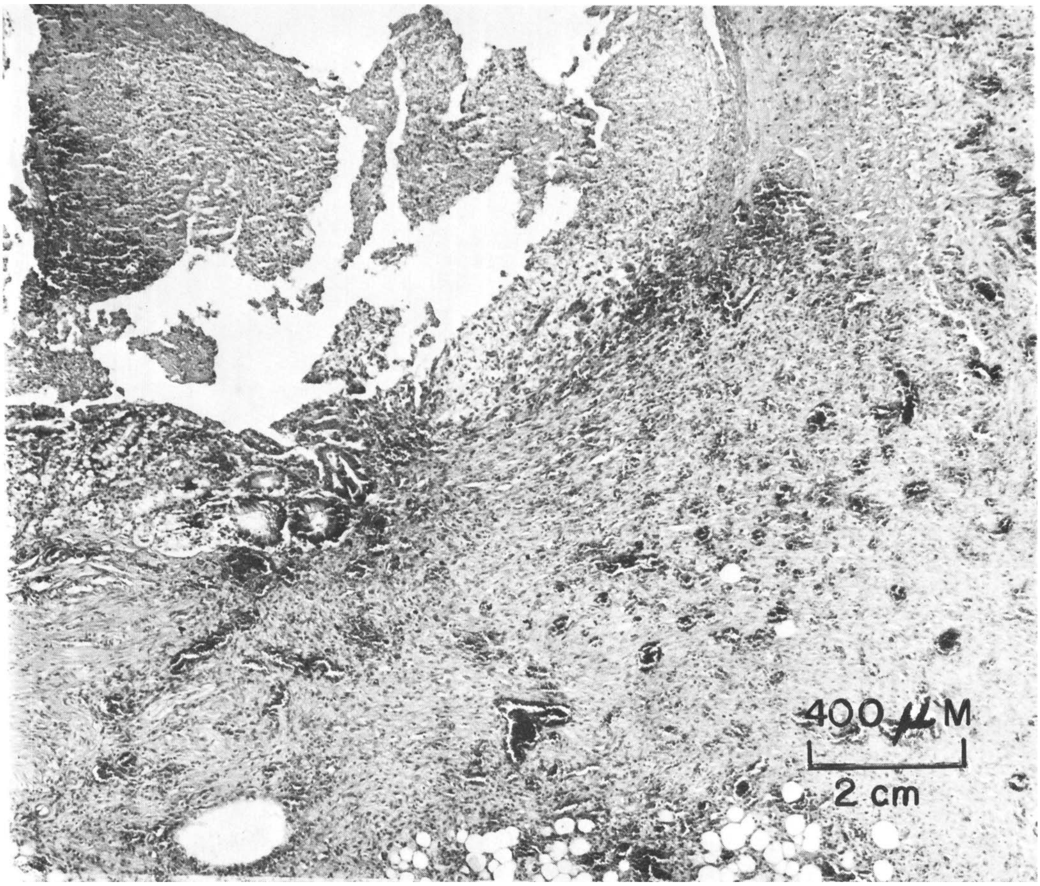

FIG. 1. Longitudinal section of ileum (right) to colon (left) junction 6 days after excision of the caecum. A mass of undifferentiated cells extends through all layers of the intestine and fills part of the lumen (above) (40×).

was a common finding in these animals. The cut ends were widely separated but sealed in the remaining 5 animals.

Discussion. The results indicate that the mammalian intestinal tract is capable of reconstituting itself following complete transection. This process takes about 2 weeks and is accomplished by a regular pattern of histological alterations which can be summarized as follows: early adhesion of one cut end to the other; aggregation of rapidly proliferating, primitive appearing cells at both cut ends; dedifferentiation of adjacent tissues; and finally, restoration of luminal and epithelial continuity. This complex process can be viewed as an exaggerated form of "regenerative" changes which accompany a faulty surgical anastomosis and is comparable in all respects to that observed earlier in amphibia.

The mechanism responsible for bringing the two cut ends of the intestine together is unknown. Additional studies are required to determine whether the underlying mechanisms are predominantly chemical or bioelectrical. In some respects this attachment resembles the convergence of a regenerating nerve on a distal nerve stump, a process Weiss believed to be guided by formation of a fibrin clot (4). More recent studies in this regard implicate nerve growth factor as a specific chemotatic agent (5) and recall Ramon Y Cajal's belief that the cut end of a regenerating nerve is guided by a chemical attractant (chemotaxis) (6). On the other hand, Schauble *et al.* showed that local

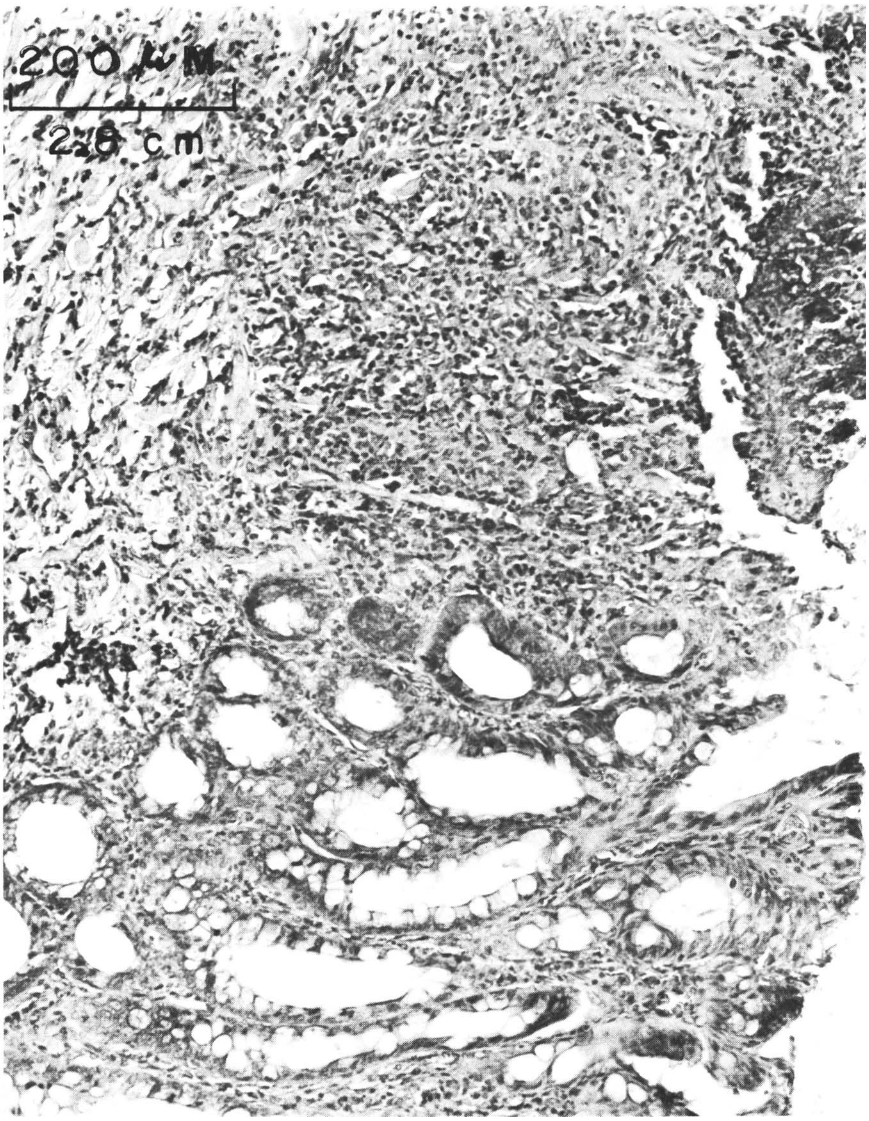

FIG. 2. Higher power view of an area of Fig. 1 showing the advance of epithelial structures into the mass of undifferentiated cells (200×).

alterations in direct current electric potential develop on injured peritoneal surfaces (7) and this could also account for reattachment of the cut ends of the intestine. The observation by Dumont *et al.* that exceedingly small alterations in bioelectric activity, experimentally induced on an uninjured peritoneal surface, attract the omentum and cause it to become fixed to the site, provides support for such a possibility (8).

Based on the knowledge that a prolonged leak of intestinal contents into the peritoneal cavity is incompatible with survival, it is likely that the ends of the transected intestine remained open for only a short time in the 23 animals in groups 1–3 that survived for more than 48 hr. The overriding importance of limiting the leak of intestinal contents into the peritoneal cavity is evident from a comparison of the mortality in group 4 with that in groups 1–3. Thus

FIG. 3. Appearance of a spontaneous anastomosis between cut ends of ileum, 1 month after transection. The mesenteric edge of one cut end has become attached to the antimesenteric edge of the other.

60% of animals undergoing transection of the colon distal to an intact colostomy survived compared to only 18% in groups 1–3. By preventing peritonitis from the leak of intestinal contents into the peritoneal cavity, the proximal colostomy increased the survival rate almost fourfold in animals undergoing transection of the distal colon.

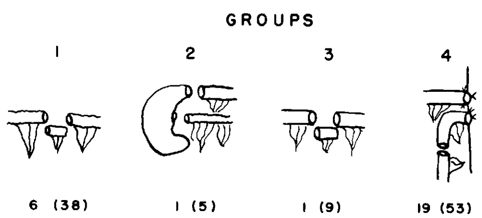

FIG. 4. Schematic representation of experimental design in four groups of rats. The numbers at the bottom give the number of survivors with reconstitution of the gut and the numbers in parentheses, the total number of animals in each group.

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