Chapter 20

SPONTANEOUS RECONSTITUTION OF THE INTESTINAL TRACT FOLLOWING COMPLETE TRANSECTION

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Studies in Amphibia

Phylogenetically, the capacity for self-repair reaches its highest development in amphibia. Published information indicates that, in addition to the ability to replace an amputated appendage, larval anurans are capable of replacing a 6-10 cm segment of intestine within forty days of excision.[1] Authoritative reviews of amphibian regeneration assert that this capacity is retained by adult anurans bnt specific information is in fact lacking.[2, 3] Studies to date in adult amphibia have actually been limited to descriptions of changes at the intestinal cut ends following complete transection. These studies disclosed that transection of the intestine with replacement of the open cut ends into the peritoneal cavity is followed by spontaneous reconstitution of the intestinal tract in approximately 30 percent of these animals.[4, 5] This reparative process takes thirty-five to fifty days and is accomplished by a regular pattern of changes, which can be summarized as follows: early adhesion of one cut end to another; aggregation of rapidly proliferating, primitive appearing cells to form a blastema at both cut ends; dedifferentiation of tissues adjacent to the blastema; restoration of luminal and epithelial continuity; and finally, reappearance of normal tissues.

In order to determine whether adult amphibia are capable of replacing an excised segment of intestine, 6-14 cm of the midportion of the intestinal tract was excised in fifteen adult frogs and newts. The proximal and distal cut ends were returned to the peritoneal cavity and the abdominal incision was closed. Although continuity of the gastrointestinal tract was restored within thirty-five to forty days in 40 percent of these animals, replacement of the excised segment was limited to only the few millimeters required for restoration of epithelial continuity (Fig. 20-1). The sequence of histological changes following excision was identical to that described earlier following simple transection (Fig. 20-2).

These results demonstrate that, in contrast to larval amphibians, adult frogs and newts are incapable of replacing more than a few millimeters of

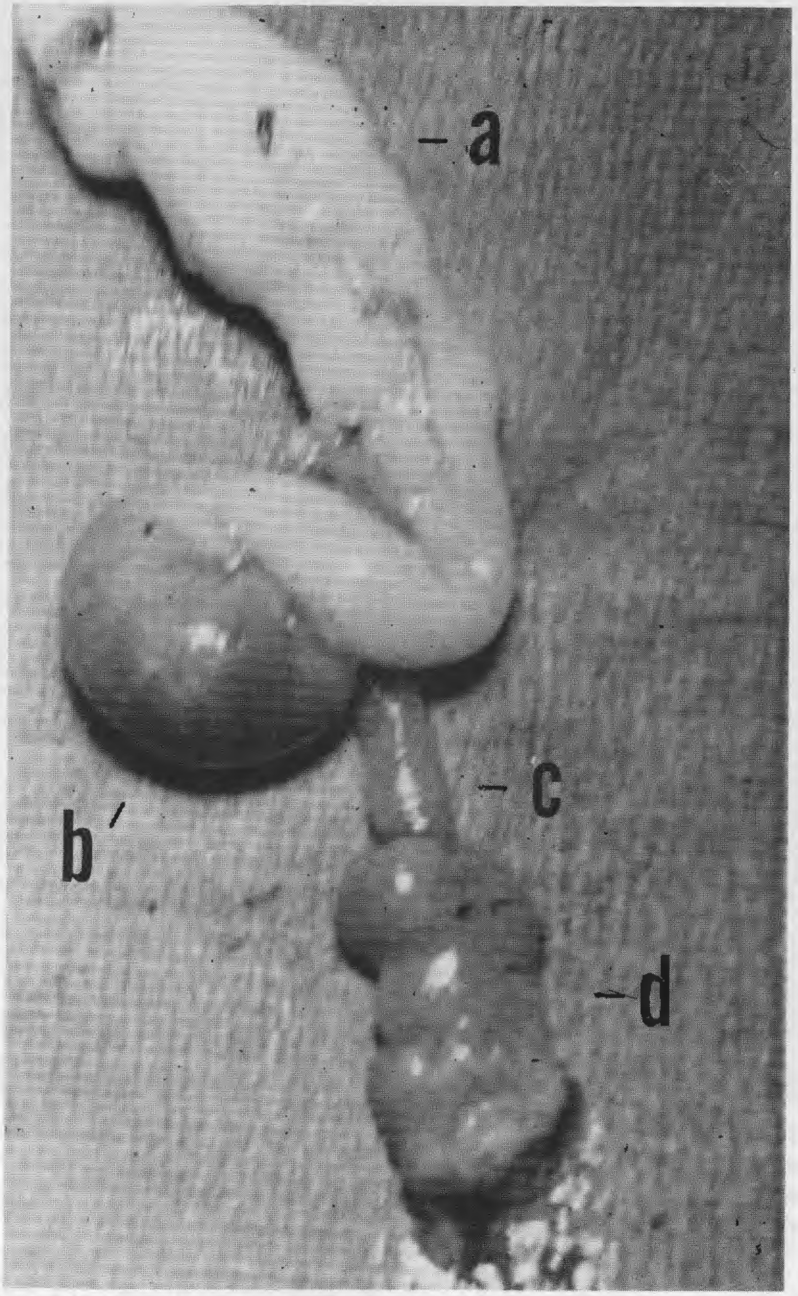

Figure 20-1. The reconstituted intestinal tract of an adult frog forty days after excision of a 9 cm segment of the intestine. The lighter structure in the upper portion is stomach (a); the darker loop just below the stomach is the duodenum (b); and the short narrow segment distal to the duodenum is the remaining distal small intestine (c) which is continuous with the rectum (d). The cut end of the duodenal loop has joined the cut end of the small intestine. The excised 9 cm segment has not been replaced.

Figure 20-2. Longitudinal section of the junction of cut ends of ileum forty-eight hours after transection. The two cut ends were found adherent to one another but became slightly separated during histological processing. This view shows the early appearance of a mass of undifferentiated cells forming at both cut ends. (×40)

intestine within forty days of excision. A possibility that adult amphibians might require more than forty days to restore full intestinal length seems unlikely in view of the fact that by this time the intestine has acquired a nearly normal histological appearance with almost complete disappearance of the blastema and mitotic activity. Thus, in adult frogs and newts, the reparative process terminates with restoration of epithelial and luminal continuity.

Reconstitution of the Mammalian Intestine

Available information, reviewed recently by Williamson[6, 7] indicates that the mammalian intestine undergoes extensive structural alterations following excision or bypass of a long segment. Regarded as compensatory adjustments to the loss of functioning tissue, these alterations also reflect a considerable capacity for regenerative repair.

Florence Sabin applied the term "regeneration" to describe certain aspects of the response to tissue damage in a surgical anastomosis of the mammalian intestine. Recognizing that the intensity of the initial inflammatory response regulated the nature of the reparative process that 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."[8] Since a proper surgical anastomosis minimizes regenerative activity, replacement of the open cut ends into the peritoneal cavity would be expected to have the opposite effect. Based on the earlier studies in amphibia by Goodchild[4] and by O'Steen,[5] it also seemed possible that regenerative activity induced by this maneuver might be intense enough to effect spontaneous reconstitution of the transected intestine even in mammals. An attempt to determine whether the mammalian intestinal tract retains any trace of the amphibian's capacity for spontaneous reattachment and reconstitution formed the basis for additional studies in rats.

Materials and Results

Under ether anesthesia the intestine was transected in four groups of rats as follows: Group 1: In twenty-eight animals 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 five the caecum and adjacent mesentery were removed. Group 3: In nine a 3 cm segment of colon midway between the caecum and the rectum together with adjacent mesentery were removed. Group 4: In fifty-three 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 ninety-seven rats the open cut ends of the intestine were simply dropped back into the peritoneal cavity and the abdominal incision was then closed with a continuous silk suture.

Figure 20-3A. Longitudinal section of ileum (bottom) to colon (top) junction six days after excision of the caecum. A mass of proliferating cells extends through all layers of the intestine and fills part of the lumen (right) (×40). (Reproduced with permission of the Society for Experimental Biology and Medicine.)

Details concerning pre- and postoperative care and gross and microscopic findings are discussed in an earlier report.[9] The sequence of histological changes can be summarized as follows: mucosal eversion occurred at both cut ends and the submucosa filled with exuded mononuclear cells; primitive appearing and rapidly proliferating mesenchymal cells then accumulated in serosal and muscular layers to form a mass that

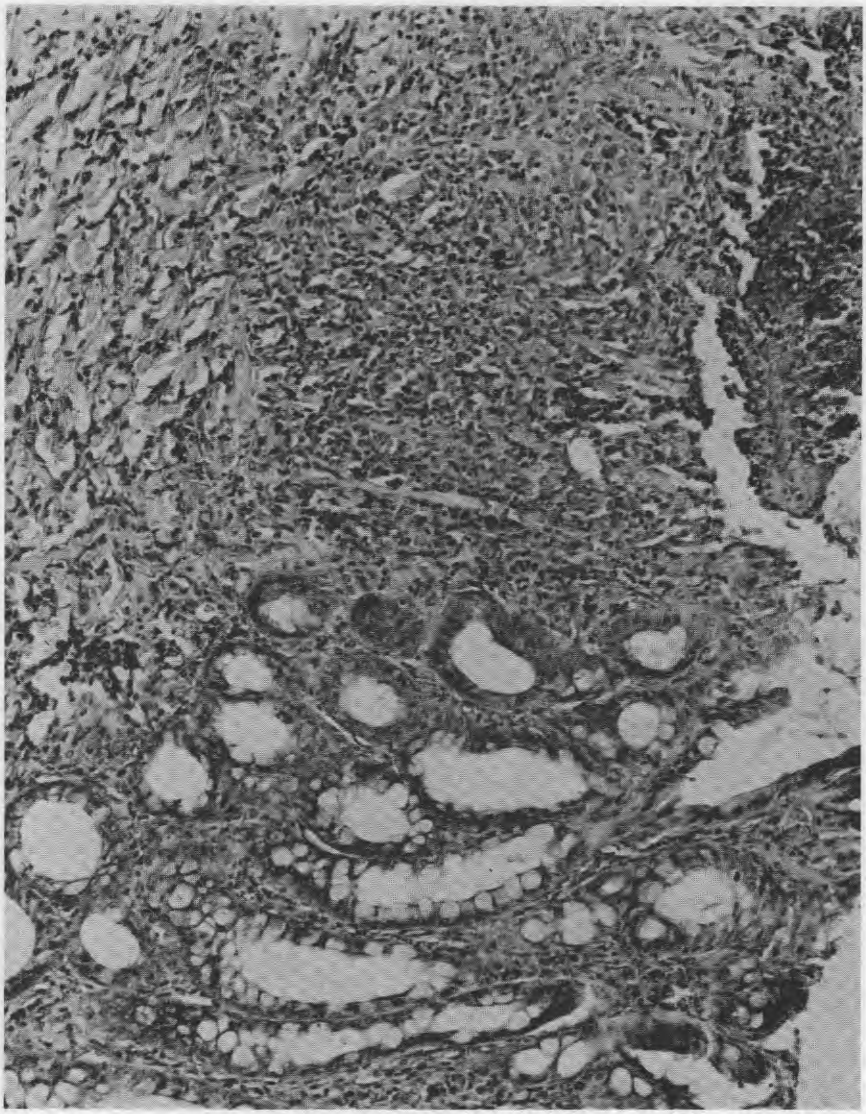

Figure 20-3B. Higher power view of an area of Figure 20-3A showing the advance of epithelial structures into the mass of proliferating cells (×200). (Reproduced with permission of the Society for Experimental Biology and Medicine.)

gradually became continuous from one segment to the other. This mass was gradually infiltrated and replaced by advancing epithelial cells and formation of a lumen. The entire sequence of changes closely resembled that described earlier in amphibia (Fig. 20-3).

Eight of the original forty-four animals in groups 1-3 were alive and well at two weeks (18%). Of this group, six had undergone transection of the ileum, one of the caecum, and one of the colon. All of these rats were

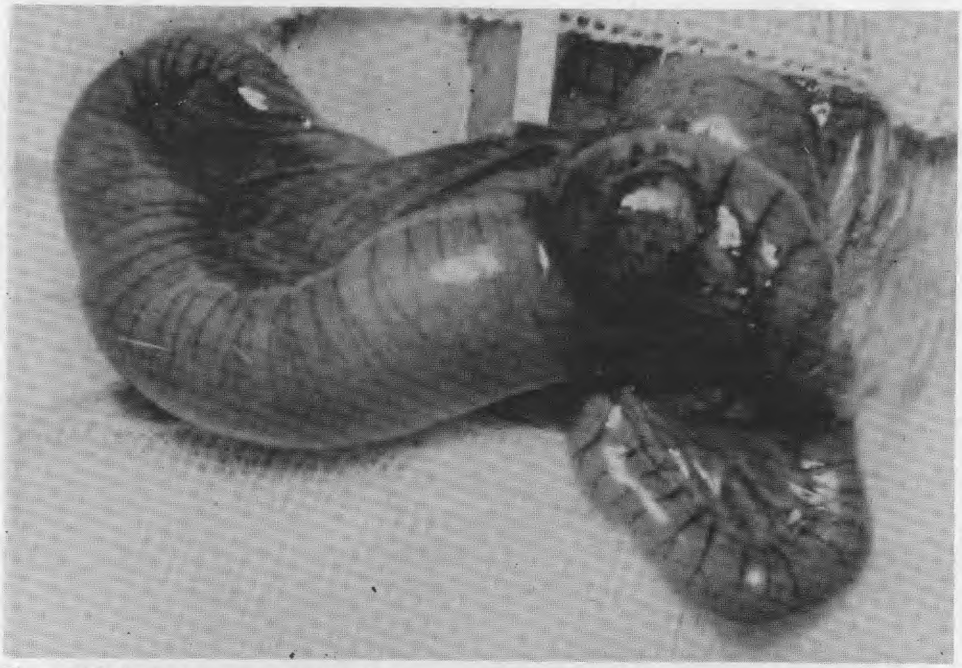

Figure 20-4. Appearance of a spontaneous anastomosis between cut ends of ileum, one month after transection. The mesenteric edge of one cut end has become attached to the antimesenteric edge of the other. (Reproduced with permission of the Society for Experimental Biology and Medicine.)

passing fecal pellets. Examination of the peritoneal cavity at two 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 two 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 (Figs. 20-4, 20-5, 20-6). Histological studies at four through eight weeks confirmed that luminal and mucosal continuity were complete (Fig. 20-7). An incomplete muscularis was usually the only histological means of identifying the site of previous transection.

Thirteen of the fifty-three animals in group 4 died within forty-eight hours of operation due to retraction of the proximal colostomy and peritonitis or to intraperitoneal bleeding. Of the remaining animals with an intact colostomy, sixteen subsequently died of either peritonitis or intestinal obstruction, a mortality rate of 40 percent. Examination of the twentyfour survivors at four to six weeks disclosed end-to-end reconstitution of the colon in nineteen. A narrow lumen at the injunction of the two cut ends was a common finding in these animals. The cut ends were widely separated but sealed in the remaining five animals.

Discussion

These results indicate that the mammalian intestinal tract is capable of reconstituting itself following complete transection. Accomplished by a regular pattern of histological alterations resembling those observed in amphibia, spontaneous reconstitution can be viewed as an exaggerated form of the "regenerative" changes that accompany a faulty surgical anastomosis. It can hardly be regarded as a mere evolutionary vestige.

Reparative mechanisms are generally much less efficient in higher vertebrates than in amphibia. According to Becker and Spadaro,[10] true regenerative healing in mammals is believed to occur only in fractures. Considered in these terms the ability of the mammalian intestine to reconstitute itself following complete transection represents a curious exception to the evolutionary trend. While the term "regeneration" is often applied to restoration of the mammalian liver following partial hepatectomy, this process, as Prehn has emphasized,[11] is actually accomplished by prolifera-

Figure 20-5. Appearance of a spontaneous anastomosis between cut ends of ileum one month after transection. Some hypertrophy of the wall of the proximal segment persists.

Figure 20-6. Appearance of a spontaneous anastomosis between cut ends of the colon six weeks after transection. The relatively avascular area in the center of the exposed segment marks the site of junction.

tion of remaining liver cells rather than by dedifferentiation and aggregation of primitive appearing cells.

The mechanism responsible for bringing the two cut ends of the intestine together is unknown. In some respects this phenomenon resembles the convergence of a regenerating nerve on a distal nerve stump, a process Weiss believed to be guided by formation of a fribrin clot.[12] More recent studies in this regard implicate nerve growth factor as a specific chemotactic agent [13] and recall Ramon y Cajal's belief that the cut end of a regenerating nerve is guided by a chemical attractant (chemotaxis).[14] Schauble et al. showed that local alterations in direct current electric potential develop on injured peritoneal surfaces,[15] a phenomenon that could also account for reattachment of the cut ends of the intestine. An earlier observation 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 supports such a possibility.[16]

Since a prolonged leak of intestinal contents into the peritoneal cavity would be incompatible with survival, the ends of the transected intestine must have remained open for only a short time in the twenty-three animals in groups 1-3 that survived for more than forty-eight hours. By preventing the leak of intestinal contents into the peritoneal cavity, the proximal colostomy in animals undergoing distal transection of the colon (group 4) increased the survival rate almost fourfold.

The findings described here have no direct clinical application at present. Additional studies may disclose better methods for insuring spontaneous reconstitution with a lower mortality and morbidity, particularly when the colon is transected distal to a diverting colostomy. In this event,

Figure 20-7. Longitudinal section of the junction between ileum (right) and colon (left) four weeks after excision of the caecum. The mass of cells has disappeared and epithelial continuity is complete. The muscularis mucosa is still thinned out at the site of anastomosis. (×40)

surgeons might have an alternative to either construction of a Hartmann pouch or to a difficult anastomosis deep in the pelvis.

Studies of intestinal reconstitution in experimental animals may also contribute to the investigation of atresia and other intestinal malformations. Based on close similarities between ontogenic development of the intestine and the sequence of histologic alterations responsible for reconstitution, it might be possible to combine transection with administration of known intestinal tetratogens to produce intestinal malformations in small mammals. This approach could also be employed to test the teratogenicity of new drugs on the intestinal tract. Current techniques rely on fetal surgery for the experimental induction of intestinal malformations and on the administrations of drugs to pregnant animals for teratogenicity testing. The unpredictability of these methods, their cost, and the technical difficulties render the likelihood of rapid progress in this field remote. Reports by Bazzoli et al.[17] indicating that administration of thalidomide to adult newts with regenerating forelimbs results in malformations of these limbs and by Speirs[18] showing that the teratogenic effects of thalidomide in man include intestinal malformations support the feasibility of using spontaneous intestinal reconstitution to study these problems.

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