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Effects of Jejunoileal Transplantation on Myoelectrical Activity in the Rat Small Intestine

Haruhiko OKAMOTO, Yasuo SAKAI, Kenji SATO, Hitoshi MATSUO, Katsuyoshi HATAKEYAMA and **Terukazu MUTO**

The First Department of Surgery, Niigata University School of Medicine, Niigata, Japan

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Summary. **Background: Clinically, many attempts at small intestinal transplantation in humans have been performed. Although little is known about the long term results on motor function of the transplanted small intestine, small intestinal motility should continue to be one of the most important issues in small intestinal transplantation.**

Study design: We investigated small intestinal motility 10 to 15 months after orthotopic small intestinal transplantation in rats. Six male Lewis rats underwent orthotopic jejunoileal transplantation. Intestinal myoelectric activity was recorded in the rats using Ag-AgCl bipolar electrodes. Six age-matched Lewis rats were also studied as controls.

Results: The cycle length of migrating myoelectric complexes (MMCs) in the transplanted jejunum (T-J), recipient's jejunum (R-J), and jejunum of the control rat (C-J) groups were 16.2±3.8 min, 13.7±1.4 min, and 11.1±0.3 min, respectively. In the C-J and T-J, a respective 98.1% and 96.5% of phase IIIs at the distal site occurred following the phase IIIs at the proximal site within 20% variation of the MMC period. However, between the R-J and T-J, only 31.0% of phase IIIs occurred within 20% variation of the MMC period. Coordination of the MMCs between the recipient and transplanted intestine did not occur at 10 to 15 months after the operation in the rat. During fasting, MMCs were clearly identified in the small intestine of both control and transplanted rats. Feeding interrupted the periodic activity, and irregular spike activity was observed along the entire small intestine, though conversion of the fasting to the fed pattern was delayed by about a minute in the graft intestine. The slow wave frequencies in the T-J, R-J, and C-J were 32.8±2.7 cpm, 36.3±2.7 cpm and 36.3±2.4 cpm, respectively.

Conclusion: These results suggest that the motility of the transplanted small intestine is mostly preserved, however, temporal coordination of the MMCs across the anastomosis did not occur after transplantation.

Key words—transplantation, small intestine, myoelectrical activity.

INTRODUCTION

Recent attempts at intestinal transplantation in humans have been performed under a new regimen of immunosuppression,[1-4] making it possible to expect long survival after intestinal transplantation. In considering the quality of life of these patients, it is important to evaluate the motor function of the transplanted intestine, as impaired motor function may lead to problems such as diarrhea,[5-7] bacterial over growth,[8,9] or malabsorption of both nutrients and immunosuppressants.[10,11]

Little is known about the long term results of the intestinal motor functions after allotransplantation. Until now, many animal experimental studies concerning intestinal motility after transplantation have been performed using bowel isolation or auto-transplantation models in the early postoperative periods. In the present study, we performed an experiment using an orthotopic allotransplantation model in the rat and demonstrated myoelectric activities of the grafted small intestine 10 to 15 months after transplantation. The aim of the present study was to clarify the motor function of the grafted, fully living intestine long after transplantation.

Correspondence: Haruhiko Okamoto, The First Department of Surgery, Niigata University School of Medicine, Asahimachi 1-757, Niigata 951, Japan.

MATERIALS AND METHODS

1. Orthotopic small intestinal transplantation (Fig. 1)

Adult male Lewis rats weighing 180 to 250 g were used (N=6). After an overnight fast, orthotopic small intestinal transplantation was performed under ether anesthesia. Using the technique described by Monchik and Russell,[12] a donor small intestine from 10 cm distal to the pylorus to 10 cm proximal to the ileocecal valve was isolated on a vascular pedicle consisting of the superior mesenteric artery with an aortic cuff and portal vein. Following systemic heparinization, the donor small intestine was removed and the intestinal lumen was immediately flushed with chilled Ringer's solution. The graft was stored in a refrigerator (4℃) while preparing a recipient rat. In the recipient rat, the superior mesenteric artery was anastomosed to the infrarenal aorta and the portal vein was anastomosed to the inferior vena cava using 10-0 nylon suture and microsurgery technique. After the vascular anastomosis was completed, the native intestine from 10 cm distal to the pyloric ring to 10 cm proximal to the ileocecal valve was resected. The graft intestine was then placed in the recipient abdomen and intestinal continuity restored by single layer end-to-end anastomoses using interrupted 6-0 silk sutures. The cross-clamp time averaged 45 min.

All animals were housed in individual cages and kept in a temperature-controlled room with a 12-hour light-dark cycle. Rats were allowed regular laboratory chow ad libitum until the second operation.

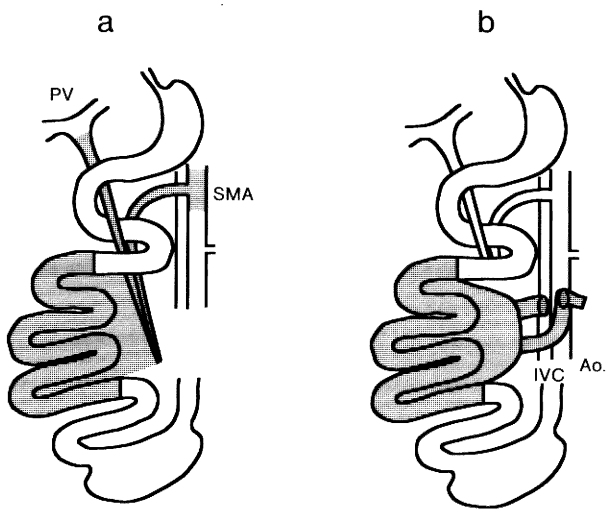

Fig. 1. Method of small bowel transplantation in the rat. **a.** Removal of small bowel on a vascular pedicle of superior mesenteric vessels, **b.** Orthotopic transplantation to restore intestinal continuity.

2. Implantation of the electrodes

Ten to 15 months after the small intestinal transplantation, the rats were reoperated on and 5 to 7 silver/silver chloride bipolar electrodes were sutured onto the serosal surface of the intestine. Two electrodes were placed on the recipient's native jejunum (R-J 1, 2), and 2 or 3 electrodes were placed on the transplanted jejunum (T-J1, 2, 3) near the jejuno-jejunal anastomosis. The remaining electrode was placed on the recipient's native ileum (R-I), if possible. The R-J2 and T-J1 electrodes were implanted 2-3 cm before and beyond the jejunal anastomosis. Lead wires from these electrodes were brought out through the abdominal wall and then tunneled subcutaneously to the back of the neck, where they came together in a polyethylene tube which was sutured to the back of the neck. As a control group, 6 age-matched male Lewis rats were operated on in the same way. Six to 7 electrodes were implanted in approximately the same position as in the transplanted rat's jejunum. On the 3rd postoperative day, the rats resumed a normal laboratory chow diet and were fed ad libitum. All were able to move unrestrained in the cages with the lead wires in the tube apparatus on the back of their neck. In this manner, electrical recordings were successfully performed.

Recording facilities

Myoelectric activity was recorded with an 8-channel electromyogram (EMG) amplifire (EM-101; Fukuda Electronics, Tokyo, Japan) using a cut-off frequency of 30 Hz and a time constant of 0.3 sec to evaluate slow waves (SW) and 0.03 sec to analyze migrating myoelectric complexes (MMCs). The output of each amplifier was connected to the 8-channel thermal pen recorder (WR-3200; Graphtic Corp. Tokyo, Japan) and a tracing was obtained at a chart speed of 2.5 mm/sec for SW analysis or 10 mm/min for analysis of MMCs.

3. Recordings of the myoelectric activity of the small intestine

The experiments were started 6 to 7 days after the operation. Body weights at recording of the transplanted rats and the control rats were 520±80 g and 600±43 g, respectively. Following an overnight fast, intestinal myoelectrical activity was recorded for 3 to 4 h in the fasting state. Then 5 g of ordinary laboratory chow was provided, and the postprandial

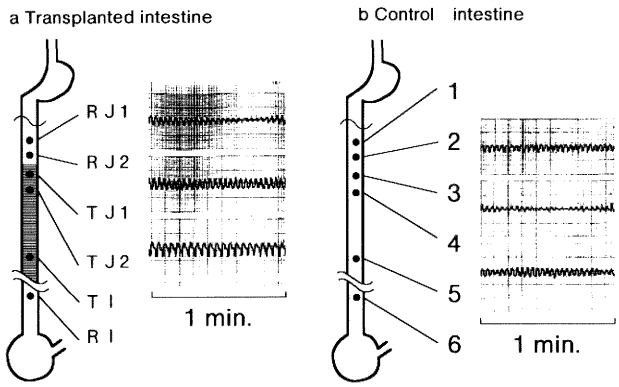

Fig. 2. Slow wave frequencies in recipient's intestine and in a transplanted segment of the transplanted group (**a**) and control group (**b**) are clearly shown.

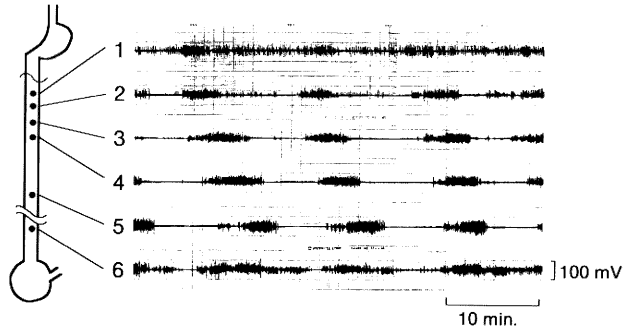

Fig. 3. Normal migrating myoelectric complex in fasting control rat. Numbers 2-5 represent proximal-to-distal electrodes placed at 5-cm intervals on the proximal jejunum. Phase III activity fronts are shown propagating aborally from proximal to distal jejunal electrodes.

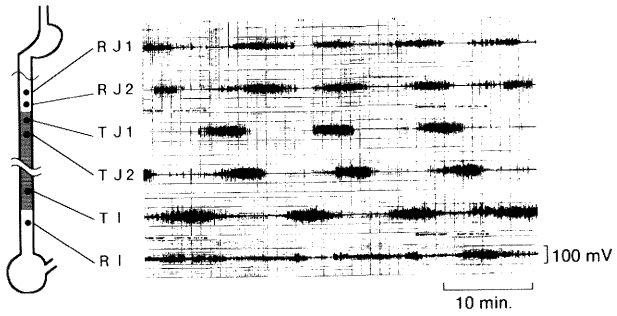

Fig. 4. Interdigestive motility after this model of jejunoileal allotransplantation showing myoelectric activity during fasting. Note the regular occurrence of activity fronts at TJ1 to TI, Which are independent of spike activity at RJ1 to RJ2.

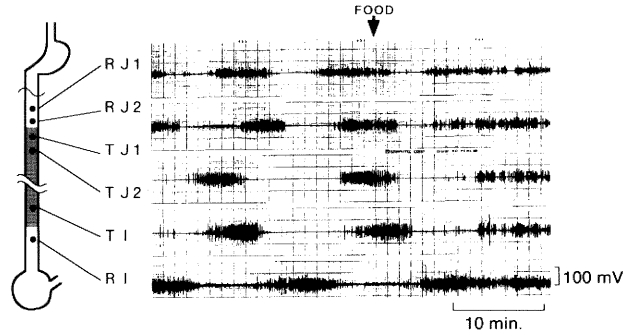

Fig. 5. Postprandial spike patterns in animals with allotransplanted jejunoileum. Early brief spike activity propagates rapidly from the proximal jejunum to distal ileum. Delayed onset of the feeding response in the transplanted segment (TJ1-TI), This segment of the recording commenced 2 min following feeding.

myoelectric activity was recorded continuously for 3 to 4 h. During the experimental period, rats were kept unrestrained and allowed to move freely in the cage. Recording sessions were conducted for at least 8 h, up to a maximum of 24 h. The experiment continued for a period of 3- 4 weeks after the operation.

Analysis of data

The following parameters were determined from the tracing by visual inspection. The slow wave frequency in each segment was determined during phase I of the interdigestive cycle (Fig. 2). The cycle length and the duration of phase III of the MMC at each electrode site was analyzed using the methods described by Sarna.[13] Migration of MMCs was evaluated by measuring the intervals of the phase IIIs between two neighbor sites in the proximal jejunum. The propagation of each (propagating) phase III sequence was estimated, and the MMC was assumed to have migrated between the 2 electrode sites if it occurred within 20% variation of the MMC period.

All values are expressd as the mean ± SD. Statistical analysis was performed by a one way of variance. Paired and unpaired t-tests or the x^2 test was employed to test any difference between two groups. Any p value of <0.05 was considered significant.

RESULTS

General condition

The transplanted animals lost weight only in the

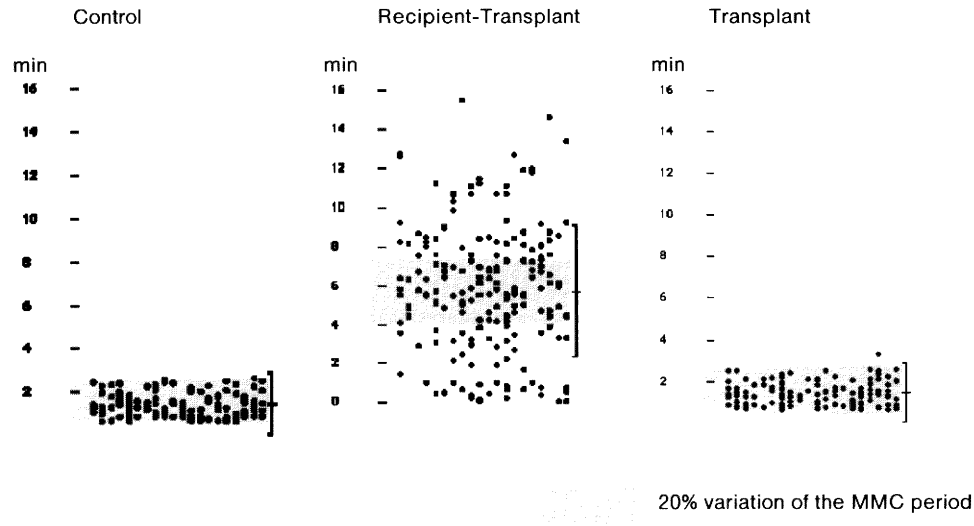

Fig. 6. The intervals of the phase IIIs between two neighboring sites in each segment.

Table 1. Characteristics of the migrating motor complex after jejunoileal allotransplantation

	Slow wave frequency (cycles/min)	Duration of phase III (min)	Period of MMC (min)
T-J	32.8±2.7 (n=42)	4.3±0.1 (n=208)	16.2±3.8 (n=168)
R-J	36.3±2.7 (n=42)	3.8±0.3 (n=240)	13.7±1.4 (n=174)
C-J	36.3±2.4 (n=42)	3.8±0.4 (n=157)	11.1±0.3 (n=126)

T-J, transplanted jejunum
R-J, recipient's jejunum
C-J, control's jejunum

early postoperative period. All of the animals with transplanted small intestines demonstrated slight diarrhea in the first 2 or 3 weeks. Stools became progressively more solid 2 to 3 months after the first operation, and at the time of the second operation, stools were almost normal in gross appearance.

Fasting myoelectric activity

During fasting, MMCs were clearly identified in every record (Figs. 3 and 4); phase III of the MMC occurred regularly and migrated to the distal intestine. The duration of phase III and cycle length of the MMC at each of the sites were as shown in Table 1. In the transplanted jejunum, the duration of phase III and the cycle length of MMC were longer, but only to an insignificant degree jejunum.

Postprandial myoelectric activity

Ingestion of a meal disrupted the fasting periodic activity by inducing a postprandial pattern of recurrent but irregular spike activities. The response in the transplanted intestine was delayed by about a minute compared with the recipient's jejunum (Fig. 5). The pattern of electrical activity in the postprandial period was similar and lasted about 220 min in both segments. Thereafter, fasting cyclic activity gradually returned and phase III of the MMC reappeared in both the native intestine and the transplanted intestine. Recovery from the postprandial pattern, including its duration of about 220 min, was also similar.

Migration of MMCs

In the control rat jejunum and the transplanted jejunum, respectively, 98.1% and 96.5% of phase IIIs at the distal site occurred following the phase IIIs at the proximal site within 20% variation of the MMC period, respectively. The phase IIIs intervals between the recipient jejunum and the transplanted jejunum varied. Only 31.0% of phase IIIs of the transplanted jejunum occurred within 20% variation of the MMC period. Fig. 6 shows the intervals of the phase III between two neighboring sites in each segment.

Slow wave frequency (SWF)

In the control rat, the mean slow wave frequency was 36.3±2.4 cycles/min in the proximal jejunum. In the transplanted rat, the mean slow wave frequency was 36.3±2.7 cycles/min in the recipient's native jejunum and 32.8±2.7 cycles/min in the transplanted jejunum, respectively (Table 1). There was no significant difference between the two groups.

DISCUSSION

In the present study, we demonstrated the continued and regularly occurring periodic activity of the rat small intestine in a chronic allotransplantation model. The slow wave frequencies and cycle length of MMCs in the transplanted intestine were similar to those of the untreated rat intestine. Further, feeding also disrupted MMCs by inducing a postprandial pattern of irregular spike activities. However, temporal coordination between native intestine and transplanted intestine did not occur or was not reestablished even long after the transplantation.

Although several studies of the electrical activity of small intestinal grafts have been performed, there is no conclusive answer as to whether a small intestinal graft has sufficient myoelectrical activity to have an impact on intestinal function after transplantation. Intestinal motility is controlled by a complex interplay of hormonal, extrinsic and intrinsic neural, and intraluminal influences. The procedure of small intestinal transplantation assures complete extrinsic denervation and interruption of myoneural continuity. There are numerous reports on the effect of denervation or transection on *in vivo* small intestinal myoelectrical activity using autotransplantation or other denervated intestine models.[5-7,13-23]

Slow wave frequencies were decreased by ablation of the myenteric neurons using simple transection of the intestine[13,24] or serosal application of a chemical agent.[17] Quigley demonstrated that slow wave frequency was reduced in canine autotransplanted intestine.[5] In the rat, Yamazato[22] also showed reduced slow wave frequency by complete extrinsic and enteric denervation in the Iowa model II. In the transplanted rat intestine, Vane[21] demonstrated that slow wave frequency was significantly impaired soon after intestinal transplantation. Early recovery of slow wave frequency was not observed until at least 40 h post-transplant, and myoelectrical complex potentials were not observed until post-operative day 11 in the grafted intestine. In using a chronic rat allotransplantation model, our results differ from others. The present study showed no significant difference in slow wave frequencies between the transplanted intestine and the native intestine. el-Murr[16] also reported no significant change in slow wave frequencies using the Iowa model III. It should be remembered, however, that responses might vary among animal species[24] or at different points of observation. Slow wave frequencies in the rat fully recovered 10 to 15 months after transplantation.

The present study also demonstrated the regular occurrence and migration of MMCs in the transplanted intestine, though the duration of phase III and MMCs cycle length were longer—though insignificantly—than in the control rat's native intestine. It has been already shown that the autotransplanted small intestine is capable of generating its own MMC in several studies in dogs.[5-7]

In canine studies, MMC periods were shown to be shorter in the transplanted intestine[6,7,19] or in the distal intestine of the transection model than in the intact intestine.[13] Quigley[5] reported that the duration of phase III was consistently longer within the autotransplanted segment, while the MMC periods were similar in controls and all animals with autotransplanted jejunoileum. Some studies demonstrated MMC periods as being longer in the transplanted intestine in rat.[8,14,16] The present study also demonstrated that the duration of phase III and the MMC cycle of transplanted intestine were longer than those of control or recipient intestine, though this difference was not statistically significant.

Ingesting small meals did not abolish the MMC in the autotransplanted canine intestine,[5,7,19] while large meals inhibited postprandial motility with a delayed onset and shortened duration. Extrinsic nerves and anoxic or cooling damage to enteric nerves and muscle are thought to play a major role in the conversion of a fasting to a postprandial pattern, while hormones have a lesser role. Yamazato[22] showed that postprandial inhibition of the MMC was not affected by intramural discontinuity or elimination of extrinsic and enteric innervation in the rat complete denervation model, suggesting that an unidentified hormonal agent must be responsible for mediating postprandial motility. Others[19,14] also suggested that hormones participate in the conversion of a fasting to a fed motor pattern. In the present study, the major component of the myoelectrical response to feeding in the transplanted intestine was not impaired except for a slight delay in onset. Further, the duration of the postprandial period was almost same in the recipient intestine, which also suggests a hormonal effect on postprandial motility.

It is not known whether coordination occures with

the native intestineal rhythm after small intestine allotransplantation. It has been shown that MMC occur not only in the innervated intestine, but also in the autotransplanted segments.[5,6,7,19] This observation may indicate that the transplanted intestine has its own pacing mechanism for the MMC which is totally independent of extrinsic innervation and also independent of the continuity of enteric nerves. Temporal coordination of motor patterns becomes reestablished 6 to 12 weeks after simple intestinal transection without extrinsic denervation.[13] Such recovery reflects the regeneration of enteric nerves across the anastomosis. Sarr[6] has shown that complete extrinsic denervation of the small intestine with the preservation of enteric myoneural continuity has no effect on the presence of fasting motor patterns in the denervated intestine or in their temporal coordination with the proximal intact intestine. These results suggest that intraluminal factors or the regrowth of enteric neural connections may control the migration of MMC.

In canine autotransplantation studies, Sarr[7] described a temporal reassociation of the MMC between the duodenum and jejunoileum, late after autotransplantation. Quigley[5] found that coordination of either slow wave or phase III activity with the proximal innervated intestine did not recover with time. The damage to enteric neurons during autotransplantation impairs regeneration across an anastomosis. In studies in the rat, Yamazato[22] represented incoordination in propagation of the MMC across an intestinal anastomosis in the Iowa model II which provided complete extrinsic and enteric neural denervation. el-Murr[16], however, described an opposite result in the Iowa model III. These models are closely related to the transplantation model except that the two intestinal segments are of the same origin. This most likely suggests reestablishment of enteric neural continuity across the anastomosis.

In a rat transplantation model, Telford[14] showed that 59% of duodenal MMCs migrate to the isograft, while 80% of duodenal MMCs migrate to the jejunoileum in controls. The MMCs are assumed to have migrated from the duodenum to the jejunum if they are detected in the jejunum less than 5 min after being initiated in the duodenum. We considered 5 min to be a little too long to decide whether or not MMCs had migrated in the small intestine. In our study, 98.1% and 96.5% of phase IIIs at the distal site occurred following the phase IIIs at the proximal site within 20% variation of the MMC period in control and transplanted intestine, respectively. However, only 31.0% of phase IIIs occurred within 20% variation of the MMC period between the recipient's jejunum and the transplanted jejunum. In our complete allotransplantation model, coordination did not occur even late after transplantation. This suggests that enteric neural continuity across the anastomosis is not reestablished between organs of different origins.

We performed a myoelectrographic evaluation of the transplanted small intestine in rats after a period of one year, corresponding to approximately one third of human life expectancy, (25 years). Though all of the rats demonstrated slight diarrhea during the first 2 or 3 weeks after transplantation, stools became progressively more solid in the following 2 to 3 months. Their eating habits returned to normal 1 or 2 weeks after transplantation and they gradually gained weight. In the present study, we demonstrated that the transplanted intestine has qualitatively normal myoelectric activity late after transplantation.

Based on the results of the present study and previous studies of the long term effects on nutrition, absorption, or motility in the transplantation model, we conclude that a small intestinal graft has sufficient intestinal function late after intestinal transplantation.

REFERENCES

1) Grant D, Wall W, Mimeault R, Zhong R, Ghent C, Garcia B, Stiller C, Duff J: Successful small-bowel/liver transplantation. *Lancet* **335:**181-184, 1990.
2) Deltz E, Schroeder P, Gundlach ML, Hansmann M, Leimenstoll G: Successful clinical small-bowel transplantation. *Transplant Proc* **22:** 2501, 1990.
3) Abu-Elmagd K, Todo S, Tzakis A, Reyes J, Nour B, Furukawa H, Fung JJ, Demetris A, Starzl TE: Three years clinical experience with intestinal transplantation. *J Am Coll Surg* **179:** 385-400, 1994.
4) Todo S, Tzakis A, Reyes J, Abu-Elmagd K, Furukawa H, Fung J, Starzl TE: Intestinal transplantation: 4-year experience. *Transplant Proc* **27:** 1355-1356, 1995.
5) Quigley EMM, Spanta A, Rose SG, John Lof M, Thompson JS: Long-term effects of jejunoileal autotransplantation on myoelectrical activity in canine small intestine. *Dig Dis Sci* **35:** 1505-1517, 1990.
6) Sarr MG, Kelly KA: Myoelectric activity of the autotransplanted canine jejunoileum. *Gastroenterology* **81:** 303-310, 1981.
7) Sarr MG, Duenes JA: Early and long term effects of a model of intestinal autotransplantation on intestinal motor patterns. *Surg Gynecol Obstet* **170:** 338-346, 1990.
8) Pernthaler H, Eigentler A, Pfurtscheller G, Plattner R, Ofner D, Klima G, Kreczy A, Saltuari L, Margreiter R: The impact of jejunal transplant peristalsis on enteric flora. *J Pediatr Surg* **30:** 573-576, 1995.

9) Scott LD, Cahall DL: Influence of the interdigestive myoelectric complex on enteric flora in the rat. *Gastroenterology* **82:** 737-745, 1982.
10) Kirsch AJ, Kirsch SS, Kimura K, LaRosa CA, Jaffe BM: The adaptive ability of transplanted rat small intesine. *Surgery* **109:** 779-787, 1991.
11) Tompson JS, Rose SG, Spanta AD, Quigley EMM: The long-term effect of jejunoileal autotransplantation on intestinal function. *Surgery* **111:** 62-68, 1992.
12) Monchik GJ, Russell PS: Transplantation of the small bowel in the rat. *Surgery* **70:** 693-702, 1971.
13) Sarna S, Condon RE, Cowles V: Enteric mechanisms of initiation of migrating myoelectric complexes in dogs. *Gastroenterology* **84:** 814-822, 1983.
14) Telford GL, Nemeth MA, Sarna SK, Harris MS, Ramaswamy K, Schraut WH, Lee KK, Johnson CP, Walgenbach-Telford S: Myoelectric activity and absorptive capacity of rat small intestinal isografts. *Dig Dis Sci* **41:** 1082-1087, 1996.
15) Bueno L, Praddaude F, Ruckebusch Y: Propagation of electrical spiking activity along the small intestine: intrinsic versus extrinsic neural influences. *J Physiol* **292:** 15-26, 1979.
16) el-Murr M, Kimura K, Ellsberg D, Yamazato M, Yoshino H, Soper RT: Motility of isolated bowel segment Iowa model III. *Dig Dis Sci* **39:** 2619-2623, 1994.
17) Fox DA, Bass P: Selective myenteric neural denervation of the rat jejunum, differential control of the propagation of migrating myoelectric complex and basic electric rhythm. *Gastroenterology* **87:** 572-577, 1984.
18) Johnson CP, Sarna SK, Cowles VE, Osborn JL, Zhu YR, Bonham L, Buchmann E, Baytiyeh R, Telford GL, Roza AM, Adams MB: Motor activity and transit in the autonomically denervated jejunum. *Am J Surg* **167:** 80-88, 1994.
19) Sarr MG, Duenes JA, Tanaka M: A model of jejunoileal *in vivo* neural isolation of the entire jejunoileum: Transplantation and the effects on intestinal motility. *J Surg Res* **47:** 266-272, 1989.
20) Spada M, De Ponti F, Alessiani M, Costa A, Girani M, Dionigi P, Vischi S, Peloni G, Reyes J, Todo S, Crema A: Monitoring of intestinal myoelectrical activity after isolated small bowel transplantation in FK 506 immunosuppressed pigs. *Transplant Proc* **26:** 1537-1539, 1994.
21) Vane DW, Grosfeld JL, Moore W, Abu-Dalu K, Hurwitz A: Impaired bowel motility following small intestinal transplantation. *J Surg Res* **47:** 288-291, 1989.
22) Yamazato M, Kimura K, Yoshino H, Murr M, Ellsbury D, Soper RT: The isolated bowel segment (Iowa model II): motility across the anastomosis with or without mesenteric division. *J Ped Surg* **27:** 691-695, 1992.
24) Kato H: Rat small intestinal motility after massive bowel resection. *Arch Jpn Chir* **52:** 690-703, 1983.
24) Diamant NE, Bortoff A: Effect of transection on the intestinal slow-wave frequency gradient. *Am J Physiol* **216:** 734-743, 1969.