

1609

TECHNICAL ASPECTS OF INTESTINAL TRANSPLANTATION

Hiroyuki Furukawa, M.D.

Kareem Abu-Elmagd, M.D.

Jorge Reyes, M.D.

Bakr Nour, M.D.

Andreas Tzakis, M.D.

Satoru Todo, M.D.

Thomas E Starzl, M.D, Ph.D.

From the Pittsburgh Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA 15213

Supported in part by research grants from the Veterans Administration and Project Grant No. DK-29961 from the National Institutes of Health, Bethesda, MD

Address reprint requests to: Thomas E. Starzl, M.D., Ph.D., 5C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA 15213

INTRODUCTION

Since the advent of the potent immunosuppressive agent FK 506, intestinal transplantation has become a feasible therapeutic option for patients with irreversible intestinal failure (1,2). In this chapter, we present our clinical experience with intestinal transplantation, focusing on the technical aspects of both the donor and recipient operations. The logistics of the operative procedure have been described previously (3).

Type of transplantation

From May 1990 to July 1993, a total of 55 patients received intestinal transplantation at our center. The operation was successfully completed in 53 patients. Two adult patients died during dissection of the native organs due to uncontrollable bleeding, complicated by extensive thrombosis in both the splanchnic venous system and inferior vena cava. Of the 53 recipients, 18 patients were given an isolated intestinal graft, 16 received combined intestine and liver, and 9 received multivisceral grafts. Multivisceral grafts consisted of the stomach, liver, pancreas, duodenum, and intestine, except for one patient in which the liver was omitted. The colon was included in the intestinal graft of the last 23 consecutive recipients in an attempt to reduce the incidence of diarrhea and bacterial overgrowth by preserving the ileocecal valve.

Recipients

The recipient population consisted of 24 adults and 29 children. The age of the adult group ranged from 19.1 to 58 years with a mean (\pm SD) of 33.7 ± 10.1 years. The age of the pediatric recipients ranged from 6 months to 15.5 years with a mean (\pm SD) of 3.7 ± 3.8 years. Irreversible intestinal failure was the primary indication for intestinal transplantation. Causes of intestinal failure for the 53 recipients are summarized in Table 1.

Combined intestine and liver transplantation was performed only for patients who had total parenteral nutrition (TPN) related cholestatic liver failure and/or inborn liver disease. Multivisceral transplantation was done for patients who had an uncorrectable disorder of the entire gastrointestinal tract, mostly from extensive thrombosis of the major abdominal vessels.

All recipients received routine gut decontamination preoperatively. The antimicrobial agents used were amphotericin B/mycostatin, aminoglycosides, and polymyxin E. Intravenous antibiotics were also used prophylactically for all patients.

Donors

All donors were cadaveric, ABO identical, of similar size, slightly smaller, or larger than the recipient. The age of the donors ranged from 8 days to 47 years. The lymphocytotoxic crossmatch was strongly positive in four of the 53 patients who were successfully transplanted. No attempts were made to alter the graft lymphoreticular tissue with antilymphocyte preparations

or other modalities. Isolated intestinal recipients who are cytomegalovirus (CMV) seronegative should only receive grafts from CMV seronegative donors. This policy was recently adopted to reduce the incidence of CMV enteritis in this unique population.

Gut decontamination was attempted for all donors. The same antimicrobial agents used for recipients were given to the donors through a nasogastric tube. At the same time, ampicillin and cefotaxime were given intravenously every 6 to 8 hours and at the time of organ procurement.

The University of Wisconsin (UW) solution was used for *in-situ* perfusion and simple cold storage of the entire graft. The total volume of the UW solution used for *in-situ* perfusion was 1 to 2 liters for adult donors and 50 to 100 ml/kg for pediatric donors. Initially, flushing of the intestinal lumen was omitted, but it became a standard procedure later, especially when the colon was procured as a part of the intestinal graft. One to two liters of chilled lactated Ringer's solution containing amphotericin B, aminoglycosides, and polymyxin were used for luminal flushing.

The cold ischemia time ranged from 2.8 to 11.2 hours with a mean of 7.5 ± 2.2 hours. These relatively short cold ischemia times reflect our adopted policy of utilizing local donors, and coordinating the timing for the donor and recipient operations.

Surgical Techniques

I Isolated intestine

A) Donor Operation (Figure 1a,1b)

The retrieval procedure starts with a cruciate abdominal incision. The greater omentum is carefully dissected and separated from the transverse mesocolon. After Kocherizing the duodenum, the cecum, ascending colon, mesenterium and descending colon are mobilized from the retroperitoneum. Attention is then directed to the proximal jejunum, which is transected close to the ligament of Treitz. The third and fourth portion of the duodenum with the attached proximal jejunal segment are further mobilized and dissected from the root of the mesenterium by dividing small numerous branches that communicate between the superior mesenteric vessels, and the duodenum and the pancreas.

In nonpancreatic donors, the portal and superior mesenteric veins are exposed by transecting the pylorus and the neck of the pancreas. After exposing the anterior surface of the portal and superior mesenteric veins, the lateral and posterior walls are dissected from the pancreas and duodenum by interrupting the pancreatic and duodenal tributaries. Meanwhile, a short segment of the splenic vein at the confluence is dissected and encircled for future cannulation. After dissecting the infrarenal aorta and exposing the iliac arteries, the origin of the inferior mesenteric artery is carefully identified. The sigmoid colon is then transected after being mobilized by dissecting the mesocolon down to the rectosigmoid junction. The distal abdominal aorta and the splenic vein are cannulated after systemic heparinization

of the donor. The supraceliac or thoracic aorta is cross-clamped, and the graft is perfused via the abdominal aorta and portal vein with an adjusted volume of UW solution. To separate the liver from the intestine, the portal vein is transected above the confluence of the superior mesenteric and splenic veins. The liver graft is then retrieved using standard techniques (4,5). For the intestinal graft, the origins of the superior mesenteric artery and the inferior mesenteric artery are cut individually using the Carrel patch technique. The intestine is removed and immersed in UW solution.

In pancreatic donors, both the superior mesenteric artery and vein are completely dissected and isolated below the intrapancreatic border or just above the origin of the middle colic vessels. After perfusion, the superior mesenteric vessels and inferior mesenteric artery are divided and the intestinal graft is removed. The iliac artery and vein obtained from the same donor are fashioned to the superior mesenteric artery and vein of the graft on the back table.

B) Recipient Operation

In all patients, the abdomen is opened through a midline incision, with a unilateral or bilateral transverse extension if indicated. All adhesions from multiple previous surgical procedures are carefully dissected. The remaining portions of the native intestine are resected in recipients with primary intestinal disease. The duodenum is carefully identified and preserved in most patients. Dissection of the main stump of

either the superior mesenteric vein, splenic vein, or the side of the portal vein is performed in all recipients. Exposure of the infrarenal aorta proximal to the origin of the inferior mesenteric artery is also performed before bringing the graft to the operative field.

a) Vascular Anastomoses (Figure 2)

In isolated intestinal transplantation, the superior mesenteric artery of the graft is anastomosed to the anterior wall of the recipient infrarenal aorta. Interposition grafts are used when technically indicated.

The venous outflow of the intestinal graft is drained into the recipient portal venous system by anastomosing the donor superior mesenteric vein to either the stump of the recipient superior mesenteric vein, its confluence with the splenic vein, or the side of the portal vein. The recipient inferior vena cava can also be chosen for the route of graft venous outflow.

b) Intestinal Reconstruction (Figure 3)

Continuity of the alimentary canal is established at the time of transplantation. The proximal jejunum of the graft is anastomosed to either the jejunum, duodenum, or stomach of the recipient. The distal end of the graft is anastomosed to either the native ileum, transverse colon, descending colon, or rectum. The Bishop-Koop ileostomy, with or without "chimney" colostomy, is our current method of enterostomy. Construction of the temporary enterostomy facilitates clinical, endoscopic, and

histologic monitoring of the graft. Terminal ileostomy or colostomy is performed for most patients who lost their native rectosigmoid colon. Gastrostomy is added in most of the recipients to ameliorate the symptoms of delayed gastric emptying.

Exteriorization of both the proximal and distal ends of the graft using the chimney method was performed for the first 6 patients. In the remaining recipients, the proximal enterostomy is substituted by insertion of a jejunostomy tube, which is used for early gut decompression and temporary enteral feeding.

Initially, most of the proximal and distal gastrointestinal anastomoses were performed in an end-to-side or side-to-side fashion. Recently, the technique was modified to an end-to-end anastomosis as often as possible, to improve graft motility based upon experimental observations in dogs.

II Intestine combined with liver

A) Donor Operation (Figure 4a,b, 5)

After entering the abdominal cavity, the liver is mobilized by dividing its ligaments. The gallbladder is incised following transection of the common bile duct, and the biliary system is washed out. The portal vein is exposed after dividing the right gastric and gastroduodenal arteries. The left gastric and splenic arteries are then identified and divided. The remaining steps of mobilizing and dissecting the intestinal part of the graft are the same as those used to retrieve the isolated intestinal graft in a nonpancreatic donor. It is important to

emphasize that the pancreas has to be sacrificed in order to procure the liver and intestinal grafts *en bloc*. Complete dissection and separation of the superior mesenteric vessels from the duodenum and pancreas is carried out primarily on the back table.

After cross-clamping, both the infrarenal aorta and the portal vein are individually perfused with the adjusted volume of UW solution. A Carrel patch is fashioned containing the origins of both the celiac axis and superior mesenteric artery on the aorta. The infrahepatic vena cava is transected above the renal veins. The inferior mesenteric artery is preserved and procured using the Carrel patch technique. The organs are removed *en bloc* and placed in the standard plastic bag containing cold UW solution, and packed in an ice container for transport.

On the back table, the suprahepatic and infrahepatic vena cava are prepared in the same way as for liver transplantation. When the pancreas and duodenum are attached to the combined grafts, both are carefully dissected and separated from the graft. After dissecting both the celiac axis and the superior mesenteric artery down to the origin of the middle colic artery, the Carrel patch is anastomosed to an aortic graft for common vascular conduit (Figure 5).

B) Recipient Operation

For most patients, hepatectomy is performed with preservation of the retrohepatic cava. This method can eliminate the use of a veno-venous bypass at the anhepatic phase. Most of

the recipients have thrombosed major vessels from total parenteral nutrition (TPN), or the major vessels need to be preserved for postoperative maintenance of TPN. After hilar dissection, transient or permanent portocaval shunt is routinely created to facilitate venous decompression and drainage of the recipient's remaining upper abdominal organs (Figure 7a,7b left). The remaining native intestine is then dissected with identification of the duodenojejunal segment and the distal colon, if present. After exposure of the infrarenal aorta, the graft is brought to the operative field.

a) Vascular Anastomoses

The hepatic venous flow is reconstructed by the piggy back technique (7). The common arterial conduit of the entire graft is anastomosed to the recipient infrarenal aorta (Figure 6). After reperfusion, the previously performed portocaval shunt is converted to a portoportal shunt by reanastomosing the recipient portal vein to the side of the graft portal vein (8) (Figure 7b right). In patients whose portal vein is too short, or when the graft portal vein is too small, the recipient portocaval shunt is left in place permanently.

b) Intestinal and biliary reconstruction (Figure 8)

The biliary reconstruction of the new liver is performed by a simple loop choledochojejeunal anastomosis. Continuity of the gastrointestinal tract is restored in a similar fashion to that described for the isolated intestinal graft. Tube gastrostomy and/or tube jejunostomy are routinely performed for these patients.

III Intestine as part of a multivisceral graft

A) Donor Operation (Figure 9)

En bloc retrieval of the multivisceral grafts that include the stomach, duodenum, pancreas, intestine, and liver is a unique technical procedure (3) that requires the following modifications.

1. Devascularization of the greater gastric curvature with preservation of the gastroepiploic arch. The short gastric vessels in the greater omentum are ligated and divided.
2. Splenectomy is done either in-situ or on the back table. In-situ splenectomy is performed after complete mobilization of both the spleen and pancreas from the retroperitoneal structures. Meticulous dissection of the splenic hilus and individual ligation of the splenic vessels are mandatory to avoid injury to the pancreas.
3. The esophagogastric junction is transected using the stapler technique.
4. The multivisceral graft is perfused only through the distal abdominal aorta with one to two liters of UW solution.
5. Pyloroplasty or pyloromyotomy is performed either on the back table or after implantation of the graft.

B) Recipient Operation (Figure 10)

Exenteration of whole abdominal organs in most of the recipients is a surgically challenging procedure. This is extremely difficult in patients who have Budd-Chiari syndrome and have extensive thromboses in the portal system, hepatic veins,

and vena cava. To control intraoperative blood loss, balloon occlusion of the celiac and superior mesenteric arteries was successfully attempted preoperatively in two such patients.

a) Vascular Anastomoses

As with the combined (liver-intestine) graft, the vascular reconstruction of the multivisceral graft includes both hepatic venous and graft arterial anastomoses. The graft suprahepatic vava is anastomosed to the recipient hepatic veins using a piggy back method. The arterial conduit is anastomosed to the recipient infrarenal aorta.

b) Gastrointestinal Reconstruction

Proximal reconstruction of the alimentary tract is established by anastomosing the distal esophagus or the remaining small portion of recipient stomach to the anterior gastric wall of the graft. Distal continuity of the intestinal tract is established as with the other grafts.

c) Biliary Drainage

Temporary diversion of the bile flow is always added in all multivisceral recipients to minimize the risk of postoperative pancreatitis. This is achieved through cannulation and external drainage of the common bile duct via the cystic duct.

Variation of the surgical techniques

The cumulative surgical experience with intestinal transplantation necessitated subsequent modifications in both donor and recipient operations.

With the possible need for additional organ replacement at the time of dissection and transplantation, multivisceral retrieval has been recently adopted as our standard procurement technique. The graft is then tailored on the back table based upon the organs needed.

The evolution of the vascular and enteric anastomoses with preservation of the ileocecal valve by transplanting part of the donor colon has been previously described. Recently, a pull-through operation was performed in two pediatric recipients who had multiple juvenile polyposis and Hirschsprung's disease. Both patients are doing well with functional anorectal sphincters. The entire colon down to the rectosigmoid was required at harvesting with preservation of its marginal blood supply including the inferior mesenteric arcade.

In one of our multivisceral recipients, the normal native liver was preserved and the retrieved liver was separated and given to another recipient. Technically, the liver was separated from the grafts by dissecting and transecting the common hepatic artery below the origin of the gastroduodenal artery and the portal vein above the confluence of the splenic and superior mesenteric veins.

Postoperative management

FK 506 is the primary immunosuppressive agent. The drug is given initially as a continuous infusion at a dose of 0.15mg/kg/day. It is then switched to an oral dose of 0.3 mg/kg/day, in two divided doses, one to two weeks after transplantation when the patient becomes tolerant to enteral feeding. Gradual withdrawal of intravenous FK506 doses is adopted in all cases with several days of overlap with oral therapy. The trough plasma levels of FK 506 are monitored daily with a target therapeutic level between 1 and 3 ng/ml. Methylprednisolone is started intraoperatively with 1 gram bolus followed by a steroid taper for 5 days and maintained with a dose of 20 mg/day thereafter. The dose is scaled down for children. Prostaglandin E1 is started intraoperatively at a dose of 0.2 to 0.6 mg/kg/hr and continued for 7 to 14 days. A low dose of azathioprine (1 to 2 mg/kg/day) is added in selected cases.

Recovery of intestinal graft function is assessed primarily by serial GI radiographs, FK 506 oral pharmacokinetics, and D-xylose absorption test. Frequent anthropometric measures, serial serum albumin measurements, trace element and fatty acid analyses are assessed to monitor and direct the nutritional management of these patients.

Intestinal allograft rejection is monitored using clinical, endoscopic, and histopathologic parameters. Surveillance endoscopy with multiple mucosal biopsies is performed once or twice per week for the first three months, and whenever it is clinically indicated thereafter. Acute graft rejection is

treated either by augmenting FK506 therapy, steroid bolus, steroid recycle, or OKT3 based upon the severity of the rejection episode (9).

Results

Forty of the 53 recipients (75.5%), 18 adults (75.0%) and 22 children (75.9%), are currently alive 4 weeks to 37 months after intestinal transplantation. Of the 40 current survivors, 33 (82.5%) patients are free of TPN and enjoying an unrestricted oral diet (Table 2).

In one of the multivisceral grafts, severe hemorrhagic pancreatitis developed after transplantation which dictated removal of the pancreas 7 days after surgery.

The recipient operation was associated with variable technical complications. These included enteric anastomotic leak (n=3), biliary leak (n=1), hepatic artery thrombosis (n=1), colon perforation (n=1), and gastrostomy leak (n=1).

Retransplantation was successfully performed in two recipients with one isolated graft and one combined grafts, respectively. In another patient with composite (liver - intestine) graft, retransplantation of the liver alone was done due to thrombosis of the hepatic artery.

REFERENCES

1. Todo S, Tzakis AG, Abu-Elmagd K, et al: Cadaveric small bowel and small bowel-liver transplantation in humans. Transplantation 1992; 53:369-376.
2. Todo S, Tzakis AG, Abu-Elmagd K, et al: Intestinal transplantation in composite visceral grafts or alone. Ann Surg 1992; 216:223-234.
3. Starzl THE, Todo S, Tzakis A, et al: The many faces of multivisceral transplantation. Surg Gynecol Obstet 1991; 172:335-344.
4. Starzl TE, Hakara TR, Shaw BW Jr, Hardesty RL, Rothenthal TJ, Griffith BP, Iwatsuki S, Bahnson HT: A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158: 223-230: 1984.
5. Starzl TE, Miller C, Bronznic B, Makowka L. An improved technique for multiple organ harvesting. Surg Gynecol Obstet 1987; 1987;165:343-248.
6. Casavilla A, Selby R, Abu-Elmagd K, et al: Logistics and technique for combined hepatic-intestinal retrieval. Ann Surg 1992; 216:85-89
7. Tzakis A. Todo S, Starzl TE: Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 1989; 210:649-652.
8. Tzakis A. Todo S, Reyes J, et al: Piggyback orthotopic intestinal transplantation. Surg Gynecol Obstet 1993; 176:297-298.
9. Abu-Elmagd k, Tzakis A, Todo S, Reyes J, Fung J, Nakamura K,

Wright H, Furukawa H, Demetris J, Van Thiel DH, and Starzl
TE. Monitoring and treatment of intestinal allograft
rejection humans;Transplant Proc 1993: 25: 1202.

Table 1. Causes of Intestinal Failure

Children	Adults
Volvulus	Crohn's Disease
Gastroschisis	Thrombotic Disorder
Necrotizing Enterocolitis	Intestinal Trauma
Intestinal Atresia	Desmoid Tumor
Pseudo-obstruction	Intestinal Adhesions
Microvillus Inclusion Disease	Intestinal Polyposis
Intestinal Polyposis	
Hirschsprung's Disease	

Table 2. Current Status of Intestinal Transplantation

Type of Graft	Median Follow-up (months)	Patient Survival	Graft Survival	Patients at home	Patients TPN Free
Isolated Intestine	10 (0.2-26)	13/18 (72%)	12/19 (63%)	10/13	10/13
Liver Intestine	11 (1.5-36)	19/26 (73%)	19/27 (70%)	13/19	17/19
Multivisceral	4 (0.4-22)	8/9 (89%)	8/9 (89%)	5/8	6/8

FIGURE LEGENDS

Figure 1a, 1b. Isolated intestinal graft.

1a: full-length vascular pedicle of the superior mesenteric artery (with Carrel patch) and vein.

1b: Note iliac arterial graft was used as an extension of the superior mesenteric artery.

Figure 2. Vascular anastomosis of the isolated intestinal transplantation.

Four type of venous anastomosis shown with numbers performed. anastomosis of the donor superior mesenteric vein (SMV) to (A) the distal end of the superior mesenteric vein (SMV), (B) the confluence of superior mesenteric vein with the splenic vein, (C) the main trunk of the portal vein, and (D) the inferior vena cava (IVC) of the recipient.

Figure 3. Gastrointestinal reconstruction of the isolated intestinal transplantation.

Note the direct colonocolostomy and Bishop-Koop method to exteriorize distal ileum for biopsy monitoring.

Figure 4a, 4b. Combined liver and intestinal graft.

Carrel patch including celiac axis and superior mesenteric artery. Note the continuity of donor portal vein.

Figure 5. Aortic conduit anastomosed to the Carrel patch containing celiac artery and superior mesenteric artery.

Figure 6. Arterial anastomosis of the combined liver and intestinal and multivisceral transplantation.

Aortic conduit (left) in most of the recipient. Aortic bifurcation conduit (middle) and whole abdominal aorta (right) are variations.

Figure 7a,7b. Vascular anastomoses of the combined liver and intestinal transplantation.

Note that the venous outflow of the retained recipient viscera was directed into the recipient vena cava (IVC) by portacaval shunt after hepatectomy (7a, arrow) and after implantation (7b, left), which is switched into the recipient portal vein (7b, right).

Figure 8. Gastrointestinal reconstruction of the combined liver and intestinal transplantation.

Choledochojejunostomy, end-to-side proximal enterostomy, Bishop-Koop ileostomy, and colonocolostomy in order.

Figure 9. Multivisceral graft.

Barrel patch including celiac axis and superior mesenteric artery. Splenectomy was performed during donor operation or on the back table.

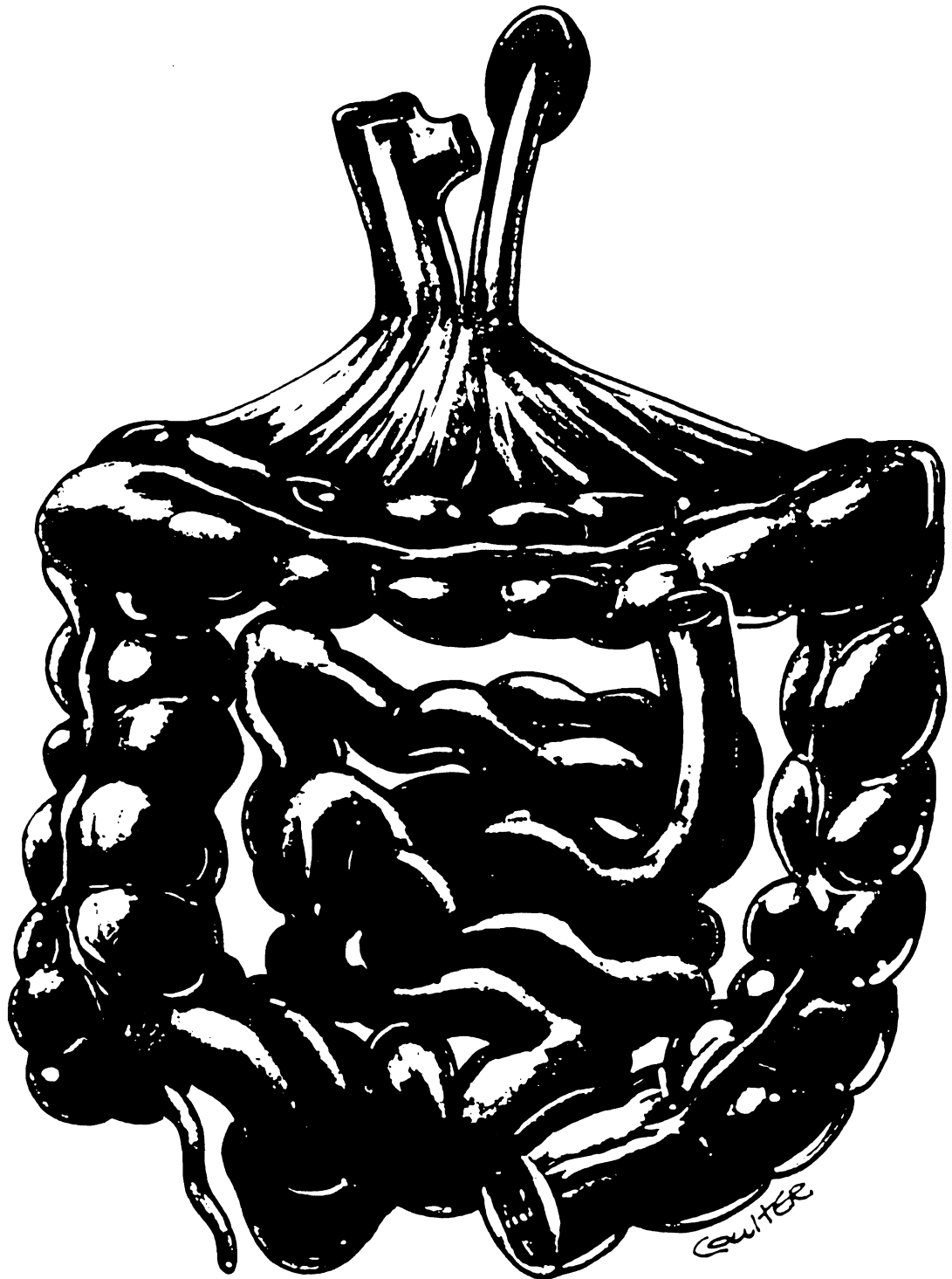
Figure 10. Vascular and gastrointestinal reconstruction of multivisceral transplantation.

Barrel patch containing the celiac axis and the superior

mesenteric artery with extension with aortic conduit was
- anastomosed to the infrarenal aorta in end-to-side fashion.

Note anastomosis of the recipient remnant stomach to the anterior
wall of the graft stomach. Pyloroplasty was made on the back
table.

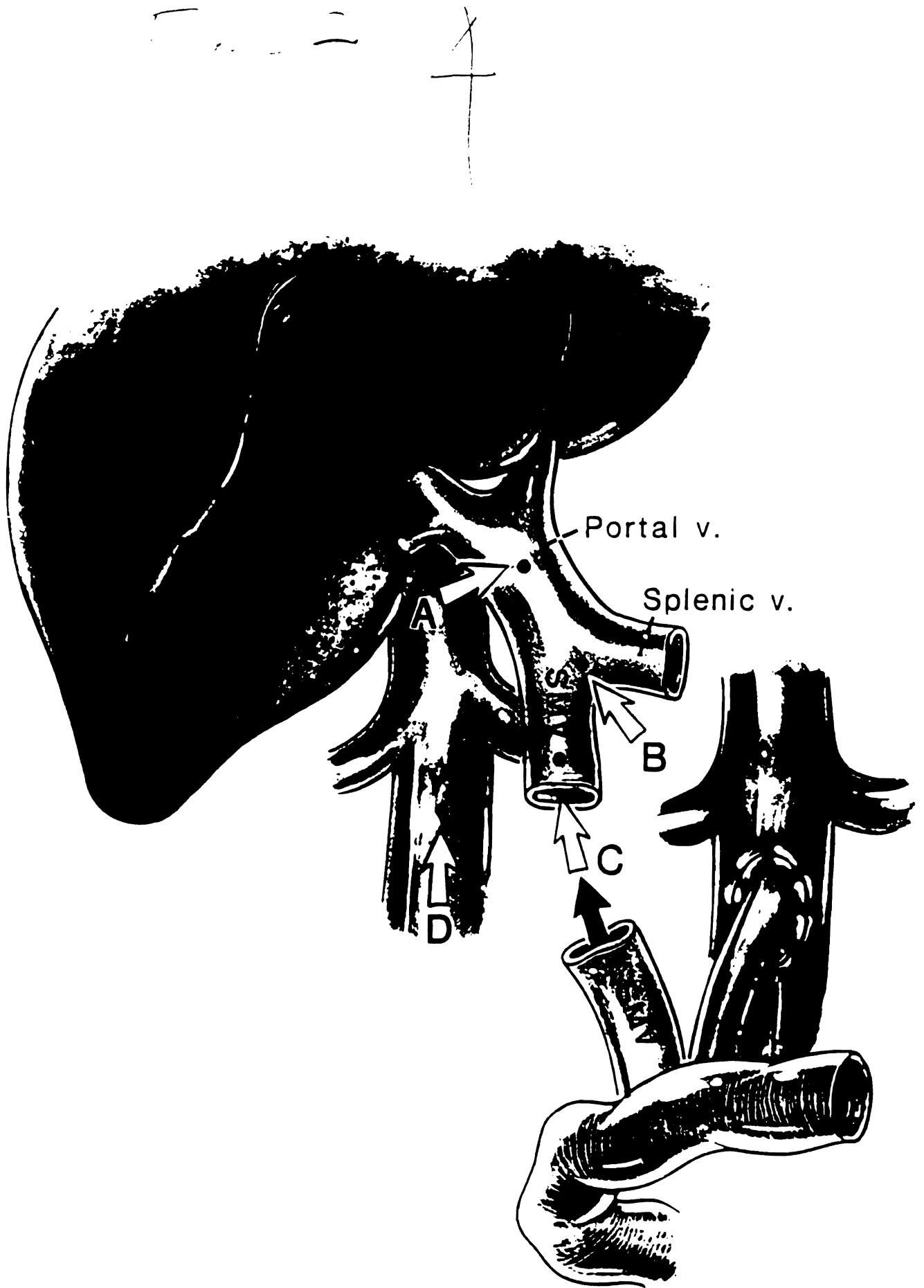
Amia 2a



1

470011b





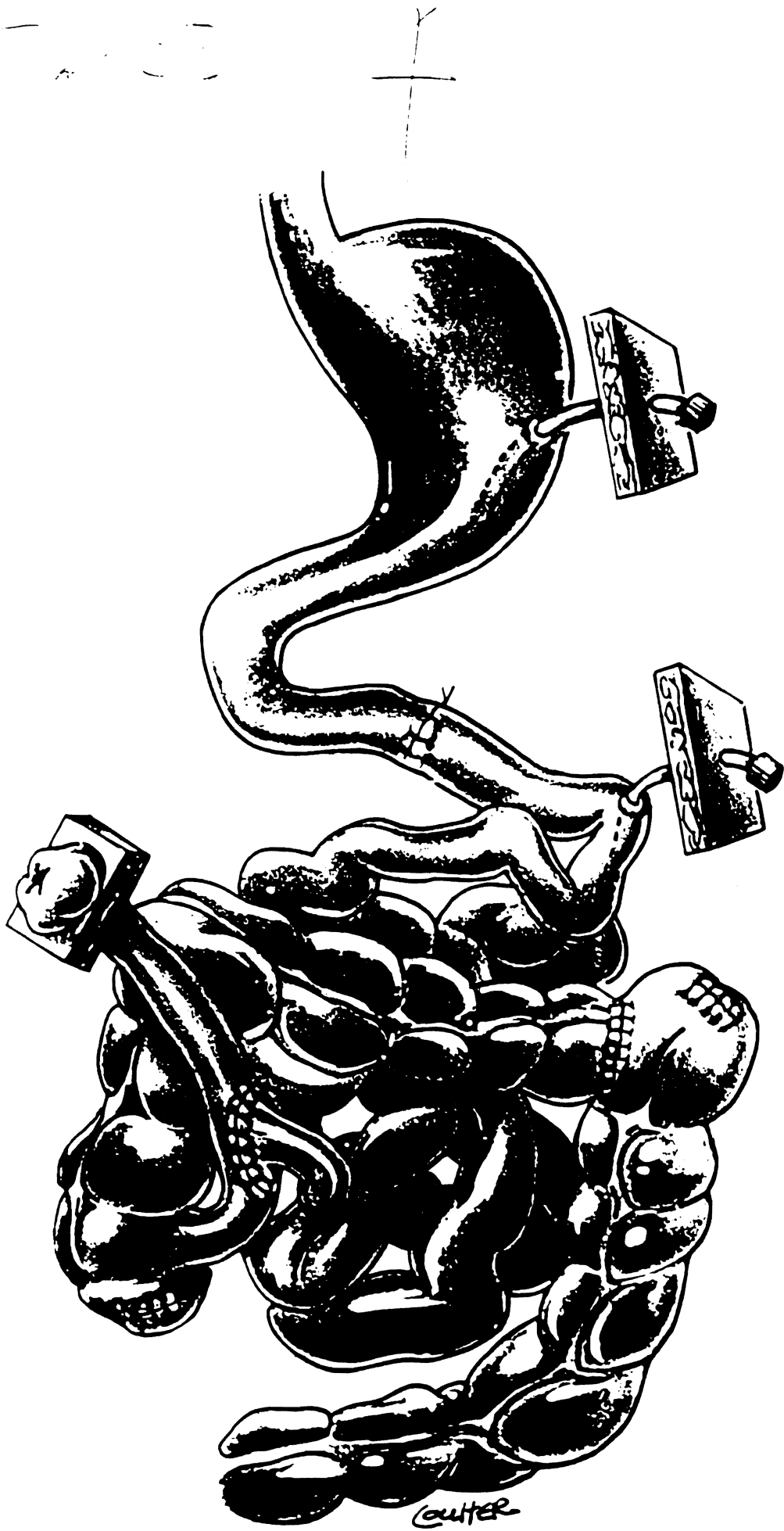
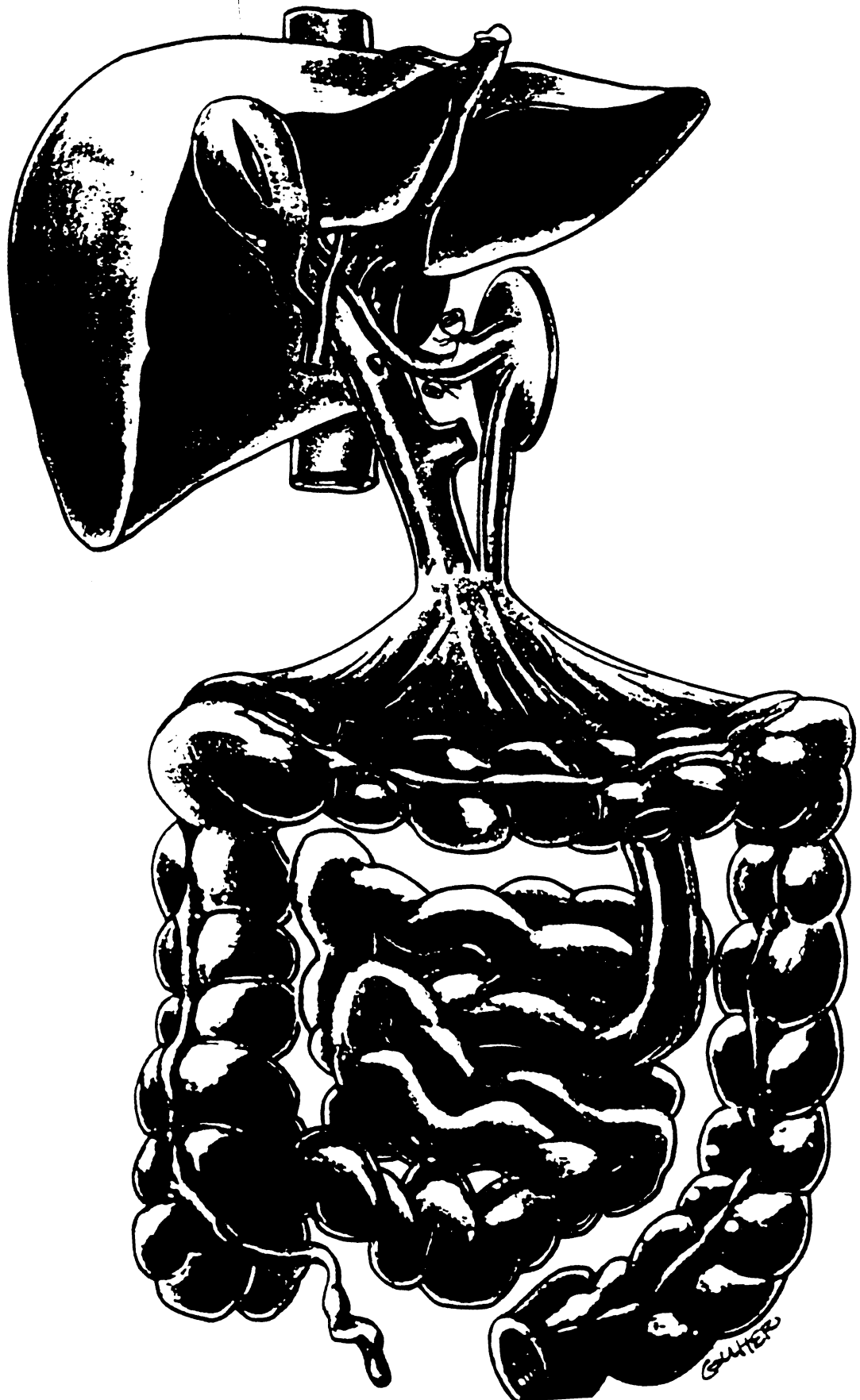


Figure 4a 4





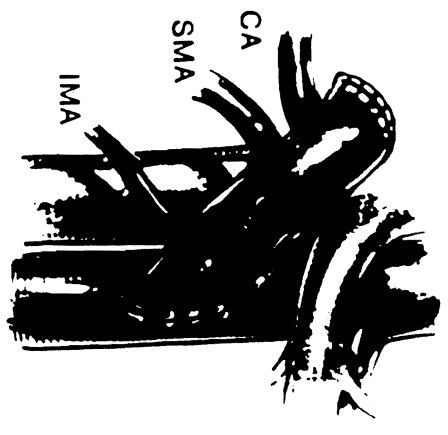
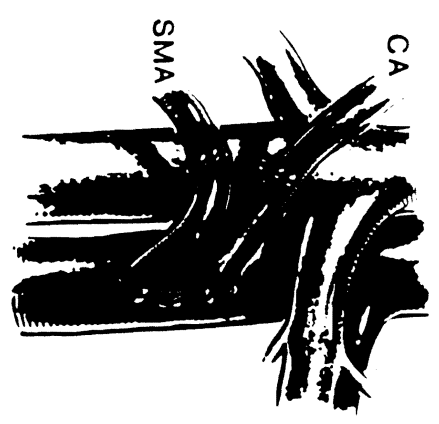
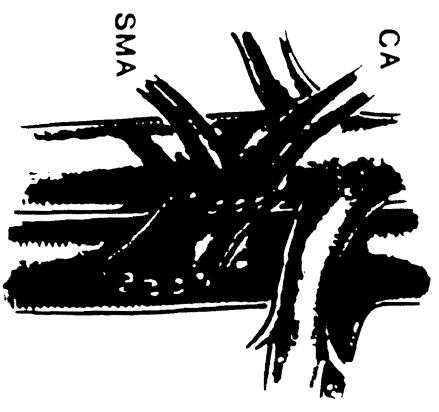
7

Figure 12

Fig. 5
F



Figure E





F 100000

Figure 1/b

F

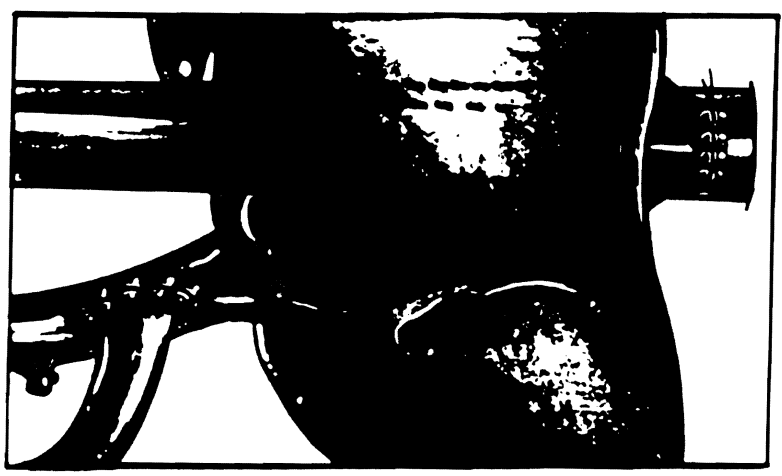
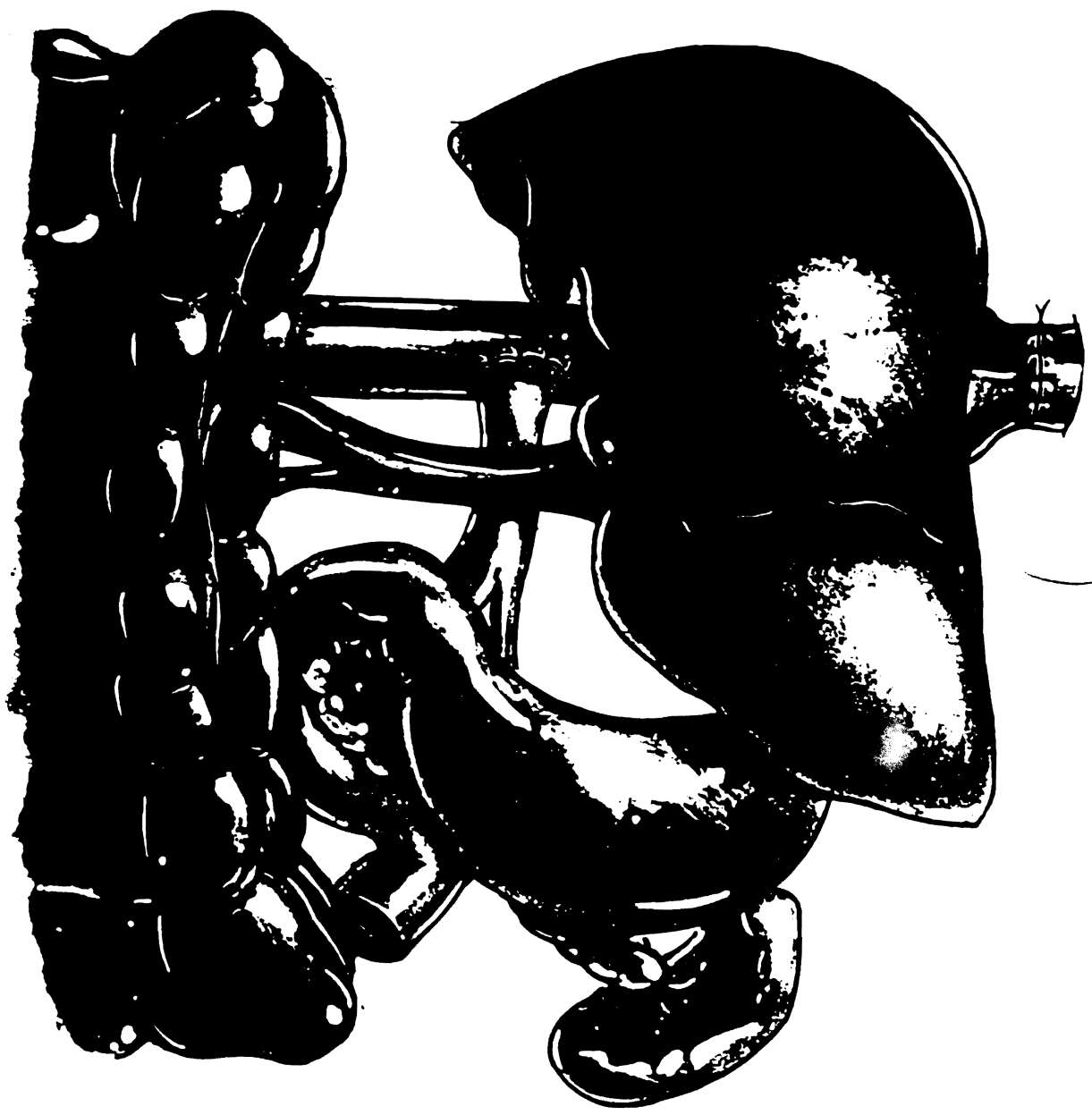


Figure 2



Figure 9



Figure 10

