1677

"HUMAN INTESTINAL AND MULTIVISCERAL TRANSPLANTATION"

Three years clinical experience at the Pittsburgh Transplantation Institute

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SUMMARY

I.- INTRODUCTION.

A.- Definition.

The general term **"Intestinal/Multivisceral Transplantation" (InMvTx)** refers to a *"new class of transplants involving the entire small bowel (jejunum + ileum), transplanted "en-bloc" with or without one or more segments of the gastro-intestinal tract (stomach, duodenum, colon), and with or withoutor one or more solid upper abdominal organs (liver, pancreas)".*

B.- Classification.

Based on the vascular anatomy of the intra-abdominal organs, which have been likened by Starzl to a large clump of individual grapes [1], the visceral and solid organ components of the intestinal/multivisceral graft may be transplanted in a variety of different combinations, as indicated by the specific requirements of the single candidates:

- **Isolated Intestine Transplantation (iInTx):**
  - small bowel **(SBTx)**
  - small bowel + colon **(InTx)**

- **Combined Liver and Intestine Transplantation (cLvInTx):**
  - liver + small bowel **(LvSBTx)**
  - liver + small bowel + colon **(LvInTx)**

- **Multivisceral Transplantation (MvTx):**
  - stomach + duodenum + liver + pancreas + intestine

The true **"Cluster Transplantation"** (liver + duodenum + pancreas)[1] [2] is not usually included among the many different multivisceral transplant procedures. Unlike intestinal/multivisceral transplantation, it is actually a real hepato-biliary-pancreatic graft, whose single visceral component (duodenum) works mainly as a conduit for the bile and the pancreatic secretions. Moreover, its main indication is not for intestinal failure, but historically it has been devised and performed after upper abdominal exenterations for upper abdominal malignancies.

C.- History.

The first experimental intestinal [3-4] and multivisceral [5-8] transplantations were performed over three decades ago, but only recently they have been successfully applied to human clinical practice[7-12].
For thirty years the intestine was considered to be a "forbidden organ" because of the high incidence of graft loss, either due to technical, immunological or infectious complications [9-12]. Wth more effective immunosuppressive protocols (Cyclosporine A, FK-506) [14-19], better surgical and preservation techniques, more advanced monitoring and sophisticated management of the patients, intestinal/multivisceral transplantation is currently considered to be a feasible therapeutic option for patients with end-stage gastro-intestinal failure, isolated or combined with coexistent terminal insufficiency of one or more intraabdominal organs (liver, pancreas).

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[1] **"Cluster" Transplantation**: as of November 1st, 1993, 61 transplants have been performed on 57 recipients [1-13]

Since 1964, in the pre-Cyclosporine A era, several clinical attempts of intestinal transplantation failed because of the ineffective immunosuppression.

After introduction of Cyclosporine A, despite the availability of more adequate immunosuppression and more appropriate antibiotic therapy, the overall clinical experience was unsatisfactory. According to the small bowel transplant registry, the cumulative intestinal graft survival under Cyclosporine A was less than 10%. The patient and/or graft loss was mainly due to rejection, sepsis and disseminated post-transplant lymphoproliferative disease.

As far as isolated intestinal transplantation, until 1990 there were only two long-term survivors [6,11,12]. In addition, 3 survivors out of 5 combined liver and intestine transplantations have been reported [8,10]. The first historical successful clinical multivisceral transplantation (including stomach, duodenum, liver, pancreas, small bowel and colon), with extended survival and intestinal graft function of 6 months, was performed in Pittsburgh on October 31, 1987 on a three years old baby girl with short gut syndrome and TPN-related end-stage liver disease [7].

The introduction of the new immunosuppressive agent FK-506 in 1989 triggered further clinical attempts of intestinal/multivisceral transplantation.

Compared to Cyclosporine A, FK-506 has several clinical advantages: more potent immunosuppressive effect and superior therapeutic index, more ability to reverse ongoing or established acute cellular rejection, more precise and easy dose adjustability, minimization of steroid dosage, decreased side effect (less incidence of hypertension, absence of gingival hyperplasia and of hirsutism, better intestinal absorption patterns with consequent better suitability for intestinal transplantation).

Since 1989, the true "Cluster Tranplantation" series (liver + duodenopancreatic complex + varying lenghts of jejunum)) proved the viability of the intestinal component as well as the evidence of regeneration after severe rejection-related injury [2].

In May 1990 a prospective clinical trial of InMvTx under FK-506 was initiated at the Pittsburgh Transplantation Institute in both adult and pediatric patients [19,26].

The purpose of this chapter is to summarize this three years-long clinical experience in human intestinal and multivisceral tranplantation [27], to discuss the indications, contraindications and risk factors [28], to report the pre- and post-operative management of the patients [29], to describe the operative strategies and the surgical techniques [30,32], to summarize the clinical results and complications and to outline the possible future trends [26,33].

II.- PATHOPHYSIOLOGY OF GASTRO-INTESTINAL FAILURE.

A.- Etio-pathogenesis.

Primary end-stage gastro-intestinal failure is defined as the inability to maintain a physiologic nutritional status (body weight; caloric and protein intake; fluids and electrolytes balance; micronutrients; somatic and visceral protein compartments; subcutaneous fat; physical, cognitive and psychosocial development; etc.) by use of the gastro-enteric tract alone without special nutritional support, due to the anatomic loss of absorptive gastro-intestinal surface or to the loss of digestive, absorptive, neural, endocrine and motor functions of the gastro-intestinal tract [27,34].

Etiol-pathogenesis of primary intestinal failure is age dependent and acknowledges different causes which can be anatomic or functional, acute or chronic, reversible or permanent. Precise identification of the causes of intestinal insufficiency and of its sequelae has implications in choosing the type and the time of the intestinal tranplant to be performed.

Patients with anatomic etiologies suffer from "short gut syndrome", which can be congenital or aquired. Congenital absence of a significant length of the gastro-intestinal tract include intestinal atresia and gastroschisis. Acquired short gut syndromes occurs after extensive intestinal resections, secondary to acute (abdominal traumas, infarctions consequent to volvulus or to vascular accidents of the celiac

and/or superior mesenteric pedicle, necrotizing enteritis) or chronic morbid events (Crohn's disease, inflammatory bowel disease, surgical adhesions from previous surgeries).
Non-surgical functional etiologies of intestinal failure may be due either to absortive/secretory enterocyte insufficiency (microvillus inclusion disease, autoimmune enteropathy, radiation enteritis, polyposis syndromes with chronic relapsing bleeding and protein-loosing enteropathy: familial polyposis coli, Gardner's syndrome and incarcerating intra-abdominal desmoid tumors), or to neuro-muscular motility disorders (myogenic and neurogenic intestinal pseudo-obstruction syndromes, Hirschsprung's disease, total intestinal aganglionosis). Patients with non-surgical etiologies may present with a normal intestinal lenghth and gross intestinal morphology.

B.- Adaptation.

In patients with "surgical" short gut syndrome, the residual intestine usually undergoes adaptive changes (widening of the intestinal lumen, increasing of the villous height), in order to counterbalance the loss of absorptive/secretory intestinal surface. This adaptation process is facilitated by intraluminal nutrients, entero-trophic factors (glutamine), biliary and pancreatic secretions, enteric hormones. Depending on the grade of "adaptation" of the residual gut, intestinal failure may be reversible and some patients may recover from their malnutrition status after a period of transient TPN support. The most significant, but not the single, determinant for the reversibility of surgical intestinal failure is the lenghth of the remaining intestinal tract. Its minimum lenghth, required to maintain adequate motility and absorption/secretion functions as well as a life-compatible nutritional status, has been empirically established on a clinical basis: 10-20 cm of small bowel with the ileo-cecal valve, or 40 cm without it [36-38]. Resection of more than 80% of the small bowel in continuity with the ileo-cecal valve is usually incompatible with intestinal adaptation and is commonly associated with irreverible intestinal failure. In addition to the lenghth of the residual intestinal stump, other important cofactors influencing the potential recover of the remaining small bowel are: the presence of the residual ileum (because of its greater capacities for adaptation), the presence of the ileo-cecal valve (for its ability in slowing down the intestinal transit time), the presence of the colon (for its increased water absorption properties), the macro- and micro-scopic morphology of the intestinal mucosa, the intestinal microflora, the biliary and fat metabolism, the gut hormones interrelationships, the GI motility functions.

C.- Total Parenteral Nutrition.

Management of patients with irreversible end-stage gastro-intestinal failure relies so far mostly on in-hospital and home-TPN [37], which provided a significantly improved outcome with a 65%-80% survival at 3 years, depending on the etiology of the intestinal failure [38-39].
However, the reliability, stability and duration of long-term TPN treatment will remarkably vary depending on several limiting and complicating factors: catheter-related sepsis; extensive venous thrombosis with consequent progressive exhaustion of venous access for cannulation; mineral deficiency with bone disease; metabolic derangements; TPN-induced advanced liver disease with cholestasis, cholelithiasis, steatosis, cirrhosis and portal hypertension; multiple hospitalizations for complications; psychiatric disturbances with incomplete personal and social rehabilitation; high costs (75,000-150,000 US$/year) [27,39,40]. Accpording to the OASIS registry [33], the mean incidence of TPN-related complications requiring hospitalization averages 2.6 complications/patient/year. In children on lon-term TPN therapy, cholestasis with liver failure is even more common, occurring usually in 30-40% of the pediatric population. Mortality secondary to TPN-related complications occurs in 6.7% of the north-american patients and in 28% of the european population under long-term TPN management, being line sepsis, thrombosis of major central veins and liver failure the main causes of death. For these reasons, transplantation of the intestine either alone or combined with one or more solid intra-abdominal organs (liver, pancreas, kidneys) may be beneficial and life-saving in these terminal patients.

III.- INDICATIONS.

A.- Indications.

In general, intestinal transplantation can be considered as a therapeutic option, alternative to long-term TPN management, in the following clinical situations:

- for patients with irreversible intestinal failure;
- for patients requiring simultaneous intestinal transplantation as an absolutely complementary surgical step, needed to replace other failed life-saving intra-abdominal organs (liver, pancreas).

The indications for the different types of InMvTx (iInTx vs. cLvInTx vs. MvTx), as well as the various allograft organ configurations rely on the anatomical integrity and on the functional status of the residual segments of the gastro-intestinal tract as well as of the intraabdominal solid organs (liver, pancreas).

a) Isolated Intestine Transplantation (iInTx).

Isolated Intestine Transplantation is indicated in patients with chronic irreversible intestinal failure alone, not associated with end-stage insufficiency of other solid intra-abdominal organs, with permanent need for long-term TPN, and with high incidence of relapsing TPN-induced complications (frequent line-related sepsis, extensive venous thrombosis of the major central veins with severe problems or even exaustion of the central venous access sites for TPN cannulation).

Surgical short gut syndrome, with loss of more than 80% of the small bowel, is the most common general clinical indication. In the adult population, the preminent morbidities include abdominal traumas, vascular accidents of the celiac and superior mesenteric pedicle, multiple extensive intestinal resections for surgical adhesions from previous surgeries, for Crohn's disease, for Gardner's syndrome and for incarcerating intra-abdominal desmoid tumors. Among children, the leading morbid evnts include gastroschisis, intestinal atresia, midgut volvulus and necrotizing enterocolitis.

A second but less frequent general indication for isolated intestine transplantation is severe gastro-intestinal dismotility, secondary to visceral myopathy, visceral neuropathy or extensive absence of the myenteric plexus (total intestinal aganglionosis), with resultant chronic pseudo-obstruction syndromes.

A third uncommon general indication for isolated intestinal replacement is severe enterocyte absorptive/secretory dysfunction (microvillous inclusion disease, autoimmune enteropathy, radiation enteritis, diffuse inflammatory bowel disease, massive intestinal polyposis syndromes with chronic relapsing bleeding and protein-loosing enteropathy).

Although usually presenting with moderate and reversible signs of hepatic insufficiency (persistent liver function tests abormalities without significant synthetic dysfunction) and mild histologic liver patterns (mild to moderate cholestasis, steatosis, fibrosis) reflecting TPN-induced injury, patients in this group are usually anicteric.

b) Combined Liver and Intestine Transplantation (cLvInTx).

The primary indication for combined Liver and Intestine Transplantation is coexistent intestinal and hepatic failure, usually due to long-term TPN-induced end-stage liver disease [41]. Guidelines in determining the need for a simultaneous hepatic replacement in these intestinal transplant candidates are based on clinical picture (jaundice, portal hypertension with hepatosplenomegaly, esophageal varices, ascites, hypersplenism), liver biopsy findings (fibrosis, cirrhosis) and on liver function tests (hyperbilirubinemia, elevated aminotransferases, abnormal synthetic function and coagulation tests).

A second general indication for combined liver and intestine transplantation is for liver transplant candidates with concomitant extensive thrombosis of the whole porto-mesenteric venous system, requiring total enterectomy of the otherwise normally functioning native intestine.

A third infrequent general indication for simultaneous liver and intestine transplantation despite a normally functioning liver, is for patient with end-stage intestinal failure secondary to extensive

thrombosis of the entire splanchnic vascular system, due to congenital coagulation defects (protein C, protein S and antithrombin III deficiency), which can be amended by replacing the native liver. Because of concomitant vascular insufficiency of other upper abdominal organs (stomach, pancreas), these patients preferably need multivisceral transplantation.

c) Multivisceral Transplantation (MvTx).

Multivisceral Transplantation is indicated for patients presenting with terminal failure of more than two segments of the gastro-enteric tract, always including the intestine. In these patients, intestinal as well as hepatic and pancreatic failure is usually secondary to extensive thrombosis of the splanchnic and/or inferior vena cava vascular systems, with consequent severe venous hypertension. In 2 out of the 5 adult recipients of MvTx for extensive thrombosis of the celiac-mesenteric and inferior caval vascular bed, congenital deficiency of protein C and protein S was reported in one case, and anti-thrombin III deficiency in the other one. Since these proteins are synthesized in the liver, these pathologies represent further indications for composite intestinal grafts including the liver, to provide for these defective coagulation factors [42].

MvTx is also indicated in patients with diffuse intraabdominal tumors (polyposis syndromes, desmoid tumors), potentially curable malignancies requiring upper abdominal exenteration (gastrinomas), severe GI motility disorders (myogenic or neurogenic pseudo-obstruction syndromes). In one pediatric MvTx recipient the native liver was not replaced, still being in satisfactory functional and pathological conditions. The patient received a modified multivisceral graft, in which the liver had been removed on the back-table and subsequently transplanted in a different recipient. Recently, a 5 years old baby girl (L.D., MvTx # 23) who had undergone more than 12 month before a LvSBTx for gastroschisis and presenting with chronic rejection of both organs and end-stage kidney disease, received a MvTx whose multivisceral *en-bloc* graft included also both kidneys (8-organs multivisceral graft: stomach + duodenum + liver + pancreas + jejunum + ileum + colon + kidneys).

C.- Timing for Transplantation.

The optimum time for transplantation is difficult to assess, because of the high variability in the clinical course and life expectancy of these critically ill candidates. TPN-induced cholestatic liver disease with deterioration of liver functions tests and of liver biopsy particularly in children, multiple relapsing line-sepsis episodes, extensive central venous thrombosis with progressive access site limitations, inability to continue TPN, are usually the determining indications which prompt to InMvTx.

D.- Contraindications.

Except for general aspecific contraindications (age $\geq$ 60 years, systemic active infections, advanced aggressive, incurable or diffusely metastatized tumors, severe systemic diseases, severe cardio-vascular and respiratory decompensation, severe autoimmune and immunodeficiency syndromes), there are no absolute contraindications for InMvTx.

At the beginning of our experience, localized infection of the peritoneal cavity, diffuse not-metastasized tumors of the intraabdominal organs and of the retroperitoneal space, extensive thrombosis of both the splanchnic and inferior vena cava systems, multiple previous intraabdominal surgeries with consequent abdominal volume contraction, diffuse adhesions and even a "frozen" peritoneal cavity, had been considered to be absolute contraindications for InMvTx. Although they still represent severe high risk factors, they are no longer considered as contraindications.

IV.- EVALUATION OF CANDIDATES.

Pretransplant evaluation of the candidates for InMvTx must establish the etiologic diagnosis of gastro-intestinal failure, the current anatomical and functional conditions of the GI tract, the nutritional status of the patients, as well as define and quantify the potential pathologic and functional involvement of other extra- and intra-abdominal organ systems which also could be in part replaced (liver, pancreas, kidneys).
In addition to the standard general transplant candidate work-up (neuro-psychiatric, cardiovascular, respiratory, renal and endocrine-metabolic evaluation; assessment of the hematologic and immune systems), an accurate history and physical examination of the conceivable candidates, as well a thorough nutritional, gastro-intestinal, hepatic and infection evaluation are paramount to successful transplantation [28], as well as to standardize the selection criteria and to investigate the potential risk factors among these unique patient population.

A.- Past Medical History and Physical Examination.

An accurate past medical and surgical history and physical examination, focusing on the surgical and non-surgical causes of GI failure, on possible associated anomalies in other organ systems (mainly vascular and tumoral), on previous surgical procedures, on the past and present nutritional and infectious status of the patients, are the first and most critical step in the process of InMvTx candidates evaluation.

B.- Nutritional Evaluation.

Nutritional evaluation is mainly based on a thorough nutritional history, anthropometric measurements and baseline malnutrition biochemical data. The nutritional history concentrates on duration of TPN-treatment, past and present TPN formulas, TPN-related complications, type and tolerance of residual oral feeding, oral diet formulas and oral supplementations, eating profile, volume and features of stools or of stomal output. Eating and nutritional profile is of paramount importance because many children never learnt how to feed or forgot what and how to eat; some pediatric and adult patients often associate unpleasant or adverse feelings while eating. These nutritional disorders may later affect posttransplant nutritional treatment and delay weaning from posttransplant TPN and from enteral tube-feeding support. Nutritional assessment is completed with baseline anthropometric measurements (height, weight, creatinine/heigt ratio, triceps skinfold, midarm circonference), and with biochemical measurements of malnutrition (serum levels of albumin, transferrin, thyroxin-binding pre-albumin, retinol-binding protein, Vitamis A, D, E, B_1, B_{12}, triglycerides, serum aminoacid analysis).
All transplanted patients, except two MvTx, were on pretransplant TPN treatment for 1 to 132 months. Each of them experienced one or more episodes of sepsis, cholestatic liver injury and other TPN-induced complications.

C.- Gastro-Intestinal Evaluation.

Assessment of the anatomic (both macro- and microscopic) and functional integrity of the residual GI tract segments is usually accomplished by routine upper and lower gastro-intestinal barium studies, by upper GI endoscopy and colonoscopy, by endoscopy-guided biopsies of the residual GI segments, with review of all previous available pathology specimens, by gastro-enteric motility studies (barium and radionuclide gastric emptying time, intestinal transit time, GI manometric and myoelectric studies) and by GI absorption tests (D-xylose absorption test, 72 hrs-fecal fat test).
More specifically, patients with primary chronic diseases of the gut (Crohn's disease, microvillous

inclusion disease, diffuse polyposis, radiation enteritis, Hirschsprung's disease) need full endoscopic, radiologic and pathologic evaluation of the residual segments of the native gastro-intestinal tract, in order to exclude any residual primary disease in the native gut, to anticipate a proper surgical plan with an adequate intestinal graft.
Patients with thrombotic disorders require accurate angiography evaluation along with complete coagulation profile including protein C, protein S and antithrombin III levels.
In patients with potentially curable intra-abdominal malignancies (desmoid tumors, gastrinomas), meticulous imaging evaluation of the extent of the tumor and of its relationship with the contiguous organs and tissues is mandatory.
Candidates with pseudo-obstruction syndromes require full gastro-enteric motility evaluation (barium and radionuclide gastric emptying time, intestinal transit time, GI manometric and myoelectric studies).

D.- Liver Evaluation.

Liver evaluation must be routinely performed in each InMvTx candidate. Pathology patterns and functional status of the liver are the major determinant factors in choosing the type of transplant (iIntx vs cLvInTx or MvTx). Assessment of the hepatic status follows routine standard liver transplant protocols, in order to quantify the functional hepatocellular reserve (serum levels of bilirubin, necrosis and cholestatic enzymes, proteins and albumin, ammonia; serum protein electrophoresis; coagulation profile; hepatic tumor markers; Child score), to evaluate liver pathology (steatosis, cholestasis, hepatitits, fibrosis, cirrhosis, tumors), to prove portal hypertension (bleeding esophageal varices, hypersplenism, ascites) as well as of patency of the portal vein and of the splancic venous system (Doppler ultrasonography, contrast CT and/or MRI of the abdomen, angiography and venous phase portography). Portal vein and splancnic venous system patency is required for drainage of the native abdominal organs (abdominal esophagus, stomach, duodenum, pancreas with or without the spleen, colon) which will remain in the recipient after iInTx and cLvInTx. Far from being a contraindication, a clotted portal vein and/or a thrombosed splancnic vascular system are specific indication for cLvInTx or MvTx, after excision of the native liver and intestine or total abdominal exenteratio, respectively.

E.- Infection Evaluation.

Each candidate is tested for baseline CitoMegaloVirus (CMV) and Ebstein-Barr Virus (EBV) titers, as well as for viral hepatitis (HAV, HBV, HCV, HδV) screen. Routine blood, sputum, urine, ascites and other biological fluids cultures for bacteria, fungi and virus are performed if clinically indicated, along with routine quantitative stool cultures. A meticulous history of previous infectious complications will lead pretransplant prophylactic antibiotic therapy and guide possible need for pretransplant selective gut decontamination.

Over the past three years, more than 200 potential candidates have been evaluated; 61% of them were appropriate for InMvTx. Of these, 43% have been transplanted, while 57% were put on the waiting list. Of this latter group, 25% died while waiting for transplantation. The major causes of death while waiting for transplantation were TPN-induced cholestatic liver failure and septic complications [82].

V.- SURGICAL TECHNIQUE.

A.- Donor Operation.

A perfect graft of good quality, adequate size and proper anatomic configuration is the key to successful InMvTx. The anatomic organ composition of the graft to be retrieved varies according to the type, extent and severity of the diseases involving the gastro-intestinal tract and the extra-enteric abdominal organs (liver, pancreas), the status of the splanchnic venous system, the degree of portal hypertension and the extent of liver damage in the recipient[1]. The anatomic configuration of the graft should be decided in advance and well known to the donor surgeons after the candidate evaluation has been completed. However there is always a low possibility for unperceived intraoperative findings, which may change the previously designated graft configuration. Therefore a close and continuous communication between the donor and the recipient teams is paramount, along with the harvesting surgical and back-table procedures which should be extremely flexible, complying with the ongoing requests from the recipient surgeons, and allowing for any final dissection and organ graft configuration to be fashioned at the back-table.
Intestinal harvesting should not interfere with the retrieval of other isolated extra-abdominal (heart, lungs) and intra-abdominal (liver, pancreas, kidneys) organs.

a) Donor selection.

Any donor, referred for potential liver harvesting, is also suitable for intestinal retrieval, without the need of any further anatomic and functional assessment of the intestine, whose adequacy is controlled by the donor team at the time of donor surgery. Nevertheless, young (less than 45 years old), hemodynamically stable, local donors are preferred.
Donor size should be similar or preferably even smaller than that of the recipient, whose peritoneal cavity, repeatedly violated by previous surgeries, has usually contracted to a reduced abdominal volume.
Donors should be brain-death heart-beating cadavers, with ABO blood type identical to that of the recipient, and with random HLA tissue-typing match. Although donors with positive lymphocytotoxic cross-matches have not been exluded in order to avoid any prolonged cold ischemia time while waiting for the results , our current policy is to exclude performing intestinal transplantation across a strong positive lymphocytotoxic cross-match, mainly for isolated intestinal grafts.
Because of the high incidence of CMV enteritis, which has been the most common morbid event in these patients, despite long-term prophylasis or aggressive therapy with more than one antiviral agent (gancyclovir, foscarnet, anti-CMV immunoglobuli "Cytogam"), the recently adopted policy at the Pittsburgh Transplantation Institute is to transplant CMV-seronegative candidates for InMvTx and particularly for isolated intestinal transplantation, only with grafts from CMV-seronegative donors.

b) Donor management.

In addition to the standard routine multiorgan donor management [43], preoperative treatment of the multivisceral donor involves systemic antibiotic coverage[2] and gut decontamination. Selective bacterial and fungal decontamination of the GI tract is performed by administering cathartics[3],

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[2] **Ampicillin**: 1 gm (25 mg/kg/dose) IV q 6 hrs; **Cefotaxime**: 1 gm (25 mg/kg/dose) IV q 8 hrs, starting immediately after acceptance into donorship; last doses at the time of donor operation.

[3] **Polyethylene Glicol - Electrolyte Solution (Go-Lytely)**; Adult donors:: 2000 mLs per NGT x 1 @ 30 mLs/min; Pediatric donors < 10 years age: 500 mLs per NGT @ 10 mLs/min; Pediatric donors > 10 years age: 1000 mLs per NGT @ 10 mLs/min.

enemas[4] and specific antibiotic solutions[5] through a naso-gastric tube [24].

No attempt is made to reduce the graft's immunogenicity by manipulating its lymphoreticular tissue with poly- or mono-clonal anti-lymphocytic immunoglobulins (ALS, ALG, OKT3) or with other immunomodulator agents (immunosuppressive drugs, irradiation), administered to the donor or to the graft.

c) Donor surgical techniques.

The basic surgical principle is to dissect, perfuse and cool the multivisceral graft and its organ components, preserving their vascular (both arterial and venous) as well as their parenchimal anatomical and functional integrity [1,20].

Surgical strategies and techniques for intestinal or multivisceral graft retrieval may differ according to the organ or organ combinations required by the recipient's pathology. Again, flexibility and compliance with the recipient team's guidelines are mandatory [19,21,24,25,44,46].

At the beginning of our experience, specific harvesting surgical techniques for the isolated intestine and for the combined liver+intestine graft have been devised and performed [30,31]. Subsequently, because of the possible need for additional organs to be transplanted at the time of the recipient's dissection and exploration, the current standard procurement procedure at the Pittsburgh Transplantation Institute is the removal "en bloc" of a multivisceral graft, including the abdominal esophagus, stomach, duodenum, liver, pancreas, small bowel, colon and sometimes the kidneys, regardless of the graft organ configuration the recipient is supposed to be transplanted with [32]. Subsequent dissectcion and isolation of the individual organs as well as tailoring of a composite multivisceral graft is performed later at the back-table, based upon the organs or combination of organs as needed.

The multivisceral harvesting procedure begins with an extensive midline sterno-laparotomy from the sternal notch to the pubis; an abdominal transverse subcostal cruciate incision is usually added to facilitate dissection of the abdominal organs and viscera from the peritoneal reflections. The intra-abdominal solid organs and viscera are then thoroughly explored to assess size and quality of each organ and looking for any vascular anomaly. After standard liver mobilization by dividing the round, falciform and left triangular ligaments, while the cardio-thoracic donor team is working within the chest dissecting the cardiac and pulmonary structures, the infrarenal aorta is dissected free and encircled, carefully identifying the origin of the IMA and exposing the aortic bifurcation, the common iliac vessels and the IMV.

The supraceliac infra-diaphragmatic aorta or the distal descending thoracic supra-diaphragmatic aorta is dissected and encircled by a transcrural or trandiaphragmatic approach, respectively.

The hepatic hilum and its components are thoroughly explored and identified but not dissected. Only the fundus of the gallbladder is incised and the bile is flushed out with saline.

Omentectomy is then performed by separating the greater omentum from the transverse colon and from the greater curvature of the stomach, carefully preserving the gastro-epiploic arcade; the short gastric vessels are ligated and divided.

The duodenal-pancreatic complex is then mobilized from the right kidney, infrahepatic IVC and suprarenal abdominal aorta below by an extensive Kocher manouvre, until the superior mesenteric pedicle is visualized and exposed, looking for the presence of a replaced aberrant right hepatic artery, which might subsequently entail an alternative transection of the SMA origin

Subsequently, the right colonic angle and the right portion of the transverse colon and mesocolon are dissected and mobilized from the duodenal-pancreatic complex beneath, by an extensive Cattel-Gregoire manouvre, dividing between ligatures the connecting venous loop of Henle.

The cecum, ascending colon and mesocolon, mesenterium along with the right portion of the transverse colon and mesocolon are then mobilized from their retroperitoneal fusions and from the right retroperitoneal organs (right kidney and ureter, duodenal-pancreatic bloc, right gonadal vessels, infrahepatic IVC), and gradually moved medially towards the midline. A similar manouvre is carried out on the left side, by mobilizing and separating the sigmoid and descending colon and mesocolon, the left colonic angle and the left half of the transverse colon and mesocolon from the left retroperitoneal fusions and structures beneath (left

[4] **Sodium mono- and di-phosphate (Fleet's enema)**: 118 mLs PR x 1; **tap water** enteroclysis x 1 until clear.

[5] **"The Mud"**: **Amphotericin B**: 500 mg or **Nystatin**: 2,000,000 IU + **Polymyxin E sulphate (Colistin)**: 100 mg + **Gentamicin**: 80 mg in 42 mLs of **distilled water**, per NGT q 4 hrs.

kidney and ureter, lower pole of the spleen, tail and body of the pancreas, left gonadal vessels and abdominal aorta).
Next, the spleen and the pancreas are completely dissected and mobilized from left to right, carefully preserving the spleno-pancreatic arterial and venous branches, as well as the IMV and its confluence with the splenic vein.
Dissection, isolation and mobilization of the gastric fundus, gastric-esophagel junction and abdominal esophagus is then performed by dividing the gastro-phrenic ligament and the posterior mesogastrium; the gastro-hepatic ligament is left intact thoroughly preserving the left gastric artery, a possible replaced left hepatic branch and the right gastric vein.
At this time, the whole gastro-intestinal tract, liver, pancreas and spleen are completely mobilized, leaving the abdominal aorta and the infrahepatic IVC as well as the origin and confluence of their major branches (celiac axis, SMA, renal arteries, renal veins, IMA, common iliac vessels) totally unroofed and freely exposed.
The abdominal esophagus at its gastric-esophageal junction and the sigmoid colon with its mesum at its rectal-sigmoid junction are transected next using the stapler technique.
The donor is then systemically given heparin[6] and the abdominal aorta is cannulated. The previously encircled proximal abdominal supraceliac aorta or the distal thoracic supradiaphragmatic aorta is cross-clamped, perfusion of the composite graft is started with cold Belzer-University of Wisconsin (UW) solution, venting the venous outflow of the graft by transecting the suprahepatic and sometimes the infra-hepatic suprarenal IVC. Topical intra-abdominal cooling is accomplished by using a slush mixture of iced saline.
The general principle is to cool the graft with a limited total amount of cold UW solution[7] infused only through the abdominal aorta, in order to avoid graft overperfusion and consequent intestinal and duodenal-pancreatic complications [43].
Although after this limited perfusion the intestine and the liver might not feel cold enough, there shouldn't be any major concern, provided they got satisfactorily blanched. Being a hollow viscus, the intestine will cool in the ice bath more easily than a solid organ. As to the liver, additional cold portal perfusion can be performed a few minutes later at the back-table.
At the end of the *in-situ* trans-aortic perfusion, an aortic Carrel patch is fashioned encompassing both the origin orifices of the celiac axis and of the SMA. Likewise, if the entire length of the colon down to the rectal-sigmoid junction is required for future "pull-through" colo-rectal reconstruction in pediatric recipients with familial polyposis or Hirschsprung's disease, the IMA is removed in a similar way, individually cutting its origin from the aorta using the Carrel patch technique, thoroughly preserving the marginal blood supply to the terminal colon (Drummond-Riolan vascular loop) including its distal segment (inferior mesenteric vascular arcade).
Next, if not yet done, the suprarenal infrahepatic IVC is transected, the diaphragm and the pericardial sac around and above the liver are divided and the composite multivisceral graft is removed *en-bloc* from the abdominal cavity.
The remainder of the procedure follows the standard multiple organ retrieval techniques [44-46].

B.- Back-Table Procedures.

The removed multivisceral graft is taken to the back-table and placed in a sterile basin, submerged in a cold UW solution bath for further *extra-situ* procedures. The common back-table procedures performed on an *en-bloc* composite multivisceral graft are: incidental liver reflushing, intestinal lumen wash-out, multivisceral graft dissection, tailoring of the graft organ configuration and simple cold storage preservation.

a) Liver reflushing.

If the liver didn't blanch and cool enough because of the limited volume of the *in-situ* trans-aortic perfusion, additional cold portal perfusion can be performed at this time through a venous portal cannula placed in the very peripheral end of the IMV or preferably of the splenic vein at the splenic hilum, diverting and confining the cold fluid to the liver by finger compression of the portal vein just below the tip of the portal cannula [9].

b) Intestinal lumen wash-out.

Initially in our clinical series, no attempt was made to wash out the small bowel, which was simply stapled at its proximal and distal ends. Later, flushing of the intestinal lumen with an antimicrobial agent very similar to that used for selective bacterial and fungal gut decontamination, became a standard procedure, mainly since the colon was retrieved and included as a distal segment of the intestinal graft. Back-table flushing of the intestinal lumen is performed by gravity irrigation

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[6] **Heparin Sodium**: 3.0 mg/kg = 300 IU/kg IV bolus.

[7] **Adult donors**: 1000-2000 mLs; **pediatric donors**: 50-100 mLs/kg; **temperature**: 5 - 10°C; **perfusion pressure**: 50 cmH_2O.

with a chilled lactated-Ringer antibiotic solution[8] until a clear effluent is achieved.

c) Multivisceral graft dissection.

The supra- and infra-hepatic stumps of the IVC are fashioned in the same way as for a standard isolated liver graft. The liver hilum should not be entered, thus avoiding any injury to its vascular and biliary components.
Dissection of the celiac axis is performed by removing periadventitial connective and ganglionic tissue, carrying it down to the origin of the splenic artery, carefully preserving the left gastric artery.
Likewise, dissection of the SMA is carried down to the origin of the middle colic artery, thoroughly protecting and saving the tiny inferior duonenal-pancreatic arterial branches.
If the descending colon has been retrieved and included as part of the intestinal graft, the proximal segment of the IMA is dissected and carried down to the origin of the left ascending colonic arterial branch.
Dissection and isolation of the celiac axis, SMA and IMA for such a lenght is performed in order to avoid displacement, distortion, twisting or kinking of these vessels.
If not already previously performed *in-situ*, splenectomy is done by careful dissection of the splenic hilum, taking care not to injury the tail of the pancreas.
The last steps of the multivisceral graft back-table preparation are a pyloroplasty or pyloromyotomy, along with the tailoring of a terminal antiperistaltic ileostomy loop, about 10 cm proximally to the ileo-cecal valve, usisng the Bishop-Koop technique. Both procedures can also be later performed *in-situ*, after implantation of the graft in the recipient.

d) Tailoring of the graft organ composition.

Despite previous exhaustive candidate evaluation, detailed planning of the recipient operation and continuous communication between the donor and the recipient teams, back to the recipient's hospital, the recipient surgeons examine the graft, discuss the recipient's requirements based upon the patient's expected and unexpected intraoperative findings and take decision about the final organ graft configuration (MvTx vs. cLvInTx vs. iInTx).

1) isolated intestine graft: if only an isolated small bowel or intestine graft is required for transplantation, the hepatic hilum is entered and dissected in the usual way as for a standard hepatic graft. The distal common bile duct is isolated and transected close to the pancreas washing-out the bile with saline; the right gastric, gastro-duodenal, left gastric and splenic arteries are divided; the portal vein is exposed and divided above the confluence of its venous roots; the liver is removed, temporarily preserved with cold UW solution storage and subsequently transplanted into a different recipient.
As to the isolated intestinal graft, *if the pancreas is not required* for a pancreatic transplant, the portal and superior mesenteric veins are exposed by transecting the pylorus and the neck of the pancreas. The portal-mesenteric venous axis is dissected free from the pancreas and duodenum, by taking all the small lateral and posterior pancreatic and duodenal tributaries, by dividing between ligatures the splenic vein, and by separating and removing the duodenum and the pancreas from the intestinal graft.
If, conversely, the pancreas is required for a separate pancreatic transplant, both the SMA and SMV are dissected and divided below the inferior margin of the neck of the pancreas, just a few millimeters distal to the origin of the middle colic vessels. In this case, being the vascular stem of the intestinal graft usually too short, the stumps of the SMA and SMV are given more lenghth by anastomosing to them the iliac arterial and venous grafts retrieved from the same donor.

2) combined liver/intestine graft: in order to obtain a combined *en-bloc* liver/intestine graft, the pancreas must be sacrificed, being necessary to dissect and separate the superior mesenteric vessels from the duodenum and the pancreas.
The hepatic hilum is entered and partially dissected; the distal common bile duct is isolated and transected close to the pancreas; the right gastric, gastro-duodenal, left gastric and splenic arteries are identified and divided; the portal vein, unlike with the isolated liver graft, is dissected free and exposed, but not skeletonized nor divided, mantaining its continuity with the retro-pancreatic SMV, which is draining the venous outflow from the intestinal component of the composite liver/intestine graft. The remaining steps of the graft tailoring procedure are the same performed to fashion the isolated intestinal graft in a non-pancreatic donor (see above).
Being the double arterial stem of the composite hepatic-intestinal graft usually too short, the aortic Carrel patch including the origin orifices of both the celiac axis and the SMA is often anastomosed to a thoracic or abdominal aortic graft from the same donor, in order to achieve a longer common vascular arterial conduit.

e) Graft preservation.

Whichever the size and the organ configuration of the graft, if not immediately transplanted after the back-table procedures, the isolated intestinal or composite multivisceral graft is eventually placed in a double sterile plastic bag filled with chilled UW solution and ice and put down in an ice chest, for temporary simple cold storage preservation.

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[8] **Intestinal wash-out antibiotic solution: Amphotericin B**: 500 mg or **Nystatin**: 2,000,000 IU + **Polymyxin E sulphate (Colistin)**: 100 mg + **Gentamicin**: 80 mg, in 1000 mLs of **lactated-Ringer; flushing volume**: 2000 - 6000 mLs; **temperature**: 5 - 10°C; **perfusion pressure**: 50 cm H_2O.

In the present clinical series, no living nor non-heart beating donors have been used. All the grafts have been retrieved from heart-beating cadaver donors[9], with a mean age of 15.02 ± 15.32 years (range = 8 days - 48 years), similar in size to the recipient, with weight variations of 20% more (57%adult, 36% pediatric) or 20% less (43% adult, 64% pediatric) than the weight of the recipient.

All donors were ABO identical and random histo-incompatible for the HLA system; 2 cases presented a strong positive lymphocytotoxic DTT-crossmatch. No alteration of the donor or of graft's lymphoreticular tissue has been accomplished.

HAV, HBV, HCV, HδV, EBV, HSV, HZV, HIV serologies were negative in all cases; 14 donors had positive CMV serology tests.

The last 13 grafts of the present clinical series of 43 intestinal recipients included the colon, whose lenghth varied according to the lenghth as well as to the anatomic and functional integrity of the residual native colo-rectal stump. The colon was included as a part of the isolated or composite transplanted graft in order to improve fluid absorption and to preserve the ileo-cecal valve, attempting to decrease the incidence of diarrhea and of bacterial overgrowth, which occurred in recipients of small bowel without the colon.

Because of preoperative unperceived and intraoperative unexpected findings, the pre-planned harvesting procedure was upgraded from SB grafts to LvSB grafts in 2 cases (4.26%), from SB graft to Mv graft in 1 case (2.13%), and from LvSB grafts to Mv grafts in 2 cases (4.26%). Moreover, 2 additional upgrades from LvSB grafts to Mv grafts have been required but not performed, being the organs not available; in both cases, however, the combined LvSB grafts have been successfully transplanted.

Conversely, in 1 case the graft was downgraded from the preoperatively planned LvSB graft to an isolated SB graft, the separated liver having been successfully transplanted into a different recipient.

The procurement of intestinal or multivisceral grafts as well as the retrieval of grafts having organ configurations different from those previously preplanned, did not interfere nor jeopardize the successful retrieval of other extra- and intra-abdominal organs. In a continuous series of 35 intestinal donor operations, 19 hearts, 4 lungs, 64 kidneys, 11 livers and 1 pancreas were also properly retrieved, the remaining 24 livers and 4 pancreas having been harvested as part of either cLvIn or Mv grafts [31].

No significant post-transplant complications related to the harvesting techniques or to the preservation methods have been recorded, except for a case of acute hemorragic pancreatitis, secondary to severe harvesting injury in a MvTx recipient, who required emergency post-transplant total graft pancreatectomy.

The **total harvesting operative time** averages from 3 to 4 hrs; the **back-table operative time** varies from 2 to 4 hrs. **Cold ischemia time** should be kept less than 10 hrs in order to prevent preservation injury to the intestine. The relatively short mean cold ischemia time of 7.4 ± 2.2 hrs (range = 2.8-11.4 hrs) is mainly due to our adopted policy of using local donors along with optimizing the time coordination between the donor and recipient surgeries. In fact, in order to minimize cold ischemia time, the recipient operation usually get started as soon as the donor surgeon notifies the recipient team of adequate graft and satisfactory retrieval conditions.

[9] **Donor population (n = 47)**; 43 donors and grafts for primary transplants; 2 donors and grafts for retransplants; 2 grafts not used because of candidates intraoperative deaths.

C.- Recipient Operation.

a) Recipient pretransplant management.

As soon as an intestinal or multivisceral donor is available, in addition to the routine preoperative management as for standard liver transplant candidates, all InMvTx candidates are routinely treated with systemic infectious prophylaxis and with decontamination of the residual native gastro-intestinal tract segments. Preoperative infectious prophylaxis is done by administering systemic IV antibiotics[10]. Selective bacterial and fungal decontamination is performed by using the same antimicrobial agents used for the donor, administered through a naso-gastric tube[6] [24]. The residual native rectum and colon are flushed out with enemas[5] and antimicrobial agents[6]. In patients still retaining their entire native GI tract (Hirschsprung's disease, pseudo-obstruction syndromes, malabsorptive syndromes, polyposis syndromes), cathartics[4] are also administered.

b) Recipient surgical techniques.

Each of the recipient operations has its own individual peculiarities, requiring different surgical strategies and techniques, specific for each single patient. Although all InMvTx procedures technically differ from one another, nonetheless they can be technically grouped into three major different types: isolated Intestine Transplantation (iInTx), combined Liver/Intestine Transplantation (cLvInTx) and Multivisceral Transplantation (MvTx).

The final decision in choosing which type of InMvTx procedure should be performed is taken at the time of preliminary intra-abdominal dissection and exploration, focusing on the status of the liver and of the remaining native intestine, as already described.

The basic general surgical strategy of the recipient operation, which is common to each of the three different InMvTx procedures, consists of three subsequent main surgical stages: 1) intra-abdominal dissection and removal of the failing organs; 2) exposure of the native vascular anatomy with performance of the vascular anastomoses and graft reperfusion; 3) gastro-intestinal and biliary reconstruction [1,10,21,24,25,32,48].

The first surgical stage, in which **intra-abdominal dissection and removal of the native failing organs** is carried out, is usually the most difficult, hemorragic and time consuming step in the whole InMvTx procedure. As already described, except for candidates with pseudo-obstructive, malabsortive or polyposis syndromes, who may have a vergin normal abdominal cavity without previous forays, most patients who need intestinal or multivisceral replacement usually had previous multiple intra-abdominal surgeries for intestinal resections, lengthening procedures, intra-peritoneal obstructive or septic complications, resulting in contracted abdominal cavity volume and severe extensive intra- and retro-peritoneal adhesions ("frozen abdomen"). In addition, sequela of the patient's original disease and of the previous operations (enterostomies, peritoneal and biliary drains, internal and external intestinal fistulas, hepatic cirrhosis with portal hypertension, thrombosis of the splanchnic and/or of the IVC vascular systems) can further complicate dissection and removal of the recipient native failing organs.

The second surgical stage, in which **exposure of the native vascular stems, recipient/graft vascular anastomoses and graft reperfusion** are performed, differs in each of the three types of InMvTx procedures, based on the different site levels of the graft arterial inflow and venous outflow, as well as on the incidental need in cLvInTx of a temporary or permanent portal-caval shunt for the drainage of the splanchnic venous flow from the native remaining foregut organs (abdominal esophagus, stomach, duodenum, pancreas, spleen) which are not removed. Reperfusion of the graft is accomplished after the vascular anastomoses are completed. The arterial inflow is unclamped first, thus allowing the blood to completely perfuse the intestinal/multivisceral graft. In order to avoid complications related to the "reperfusion syndrome" (hypotension, hyperkalemia and acidosis), the blood initiallyy perfusing the graft is vented through the SMV (in iInTx) or from the infra-hepatic IVC

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[10] **Ampicillin**: 1 gm (25 mg/kg/dose) IV q 6 hrs; **Cefotaxime**: 1 gm (25 mg/kg/dose) IV q 8 hrs, starting immediately after the donor is pronounced; last doses just before the recipient operation, when the patient is taken to the O.R.

(in cLvInTx and MvTx), thus preventing the stagnant preservation solution pooled in the graft to enter the systemic circulation. After the graft is completely reperfused and adequately vented, the venous outflow clamp is released.

The third surgical stage of **gastro-intestinal reconstruction and venting** is common and basically the same in each of the three InMvTx procedures. What varies is only the site level of the proximal and distal intestinal anastomosis. In iInTx and cLvInTx, depending on the length and quality of the residual native proximal gastro-jejunal stump, proximal continuity of the alimentary tract is restored by anastomosing the most distal and accessible level of the recipient gastro-intestinal tract (stomach, duodenum or residual jejunal stump) to the proximal jejunal end of the graft (gastro- duodeno or jejuno-jejunostomy); in MvTx by anastomosing end-to-side the distal abdominal esophagus or the residual small fundal stump of the stomach of the recipient to the anterior gastric wall of the graft (esophago- or gastro-gastrostomy). The gastro-jejunal anstomosis is usually fashioned side-to-side; the duodeno-jejunal or jejunojejunal anastomoses are performed either side-to-side, end-to-side or end-to-end. According to the length and quality of the remaining native procto-colic stump in the recipient as well as to the inclusion of the colon in the graft, the distal intestinal anastomosis is fashioned between the distal intestinal end of the graft (terminal ileum or colon) and the most proximal level of the residual native enteric stump (terminal ileum, transverse, descending, sigmoid colon or rectum) of the recipient. By limiting the length of the graft colon, revascularization through the IMA is usually not required. Terminal ileostomy or colostomy is performed in patients who have lost their native distal recto-sigmoid colon. In two pediatric patients with familial polyposis and Hirschsprung's disease a colo-rectal "pull-through" procedure was performed, using the entire length of the graft's colon and preserving the recipient's functional ano-rectal sphincters. Different kinds of enetrostomies are fashioned for monitoring (inspection, digital and endoscopic exploration, biopsy) and decompress the transplanted gastro-intestinal allograft. Increasing consolidated clinical and surgical experience has gradually led to changes in the different types of external venting and enterostomies [20,33]. Initially, in the first 5 recipients of this clinical series, both ends of the transplanted intestinal grafts were exteriorized by temporarily constructing a proximal jejunostomy and a distal ileostomy, using the "chimney" technique [19]. Next (cases #6 through #29), only a distal "chimney" ileostomy was performed, the proximal "chimney" jejunostomy being replaced by a tube jejunostomy with or without a concurrent tube gastrostomy. Both external tube enterostomies were fashioned for gastrojejunal decompression as well as for early postoperative tube feeding. Later, in the first 10 of the 13 patients who received the colon in continuity with the small bowel, a "chimney" colostomy was done on the transverse colon of the allograft, which resulted in significant intestinal fluid losses through the stoma, necessitating IV fluid replacement; moreover it made endoscopic examination of the distal ileum very difficult or impossible to perform. For these reasons, the last 3 patients were given an end-to-end colonic anastomosis without any external colostomy, along with a reversed Bishop-Koop anti-peristaltic distal ileostomy using the terminal ileum. The Bishop-Koop distal reversed ileostomy has the advantage of decreasing the intestinal fluid loss through the stoma as well as making easier endoscopic examination of both ileum and colon. External enterostomies are taken down within 2 to 11 months after transplantation, by using an extraperitoneal approach. Biliary reconstruction is performed with a Roux-en-Y loop choledocho-jejunostomy only in cLvInTx. Temporary external common duct drainage through a trancystic cannulation as well a splenectomy and a pyloromyotomy or pyloroplasty are performed in MvTx. In order to minimize the risk of postoperatithe most distal and accessibleve acute infectious complications, appendectomy and cholecystectomy are performed on each native and/or grafted caecum and liver.

b_1) Isolated Intestine Transplantation (Fig. 1a).

1) preliminary intra-abdominal dissection and removal of the native failing organs: in iInTx intra-abdominal dissection and exposure of the vascular structures are usuallly facilitated by the absence of portal hypertension. The abdomen is entered and widely exposed through a midline xipho-pubic laparotomy, with incidental mono- or bi-lateral transverse extensions if needed. The extensive adhesions secondary to the original intestinal disease and/or from the previous multiple operations and complications are dissected. The residual segments of the native GI tract are identified and carefully dissected; usually they consist of the stomach, the duodenum in continuity with a short proximal jejunal stump and of a segment of terminal

ileum or colon of various length. Most patients with "short gut syndrome" already had previous intestinal resections: in these cases attempt is made to preserve as much as remaining native duodenum, small bowel and colon as possible, provided they are normal. In patients with residual portions of the native intestine still affected by the primary intestinal disease, resection of the remaining failing intestine is completed. In patients with pseudo-obstructive, malabsorptive and polyposis syndromes, usually still retaining their own native GI tract in its entirety, the whole length of small bowel and colon is resected.

2) exposure of the native vascular stems, vascular anastomoses and graft reperfusion: the residual main stumps of the recipient SMV and splenic vein as well as their confluence into the proximal portal vein below the pancreas are identified, dissected and exposed, along with the right postero-lateral side of the supra-pancreatic portal vein within the native hepato-duodenal ligament (Fig.1a, left insert). The recipient's infra-renal abdominal aorta, proximal to the IMA, is dissected and exposed, just before taking the graft into the operative field.

The arterial anastomosis is performed first, by suturing side-to-end the anterior wall of the recipient's infra-renal aorta to the isolated stump of the graft's SMA, with (Fig.1a, right insert) or without (Fig.1a, main figure) an arterial iliac interposition graft, when technically indicated [20].

The venous outflow of the donor intestinal graft can be drained either into the recipient's portal vein system or into the recipient's infra-hepatic supra-renal IVC. When technically feasible (n = 14 cases out of 15), the skeletonized stump of the graft's SMV or PV is anastomosed either end-to-end to the recipient's residual SMV stump, or end-to-side to the confluence of the recipient's SMV and SV (Fig.1a, right insert), or end-to-side to the right postero-lateral side of the recipient's PV at the level of the hepatic hilum ("piggy-back" technique) [47] (Fig.1a, main figure and right insert). Drainage of the graft's venous outflow into the recipient's portal system as opposed to IVC, is thought to be preferable because it provides the liver with hepatotrophic factors [1,48-49]. It might also have immunologic advantages [50-52]. If the graft's venous drainage into the recipient's portal system is not technically achievable because of size discrepancy or difficult anatomic relationships, the venous outflow of the graft is drained into the IVC system by fashioning a permanent end-to-side porto-caval shunt at the level of the suparenal infra-hepatic IVC (n = 1 case) (Fig.1a, right insert).

3) intestinal reconstruction: the proximal end of the jejunum of the donor graft is anastomosed side-to-side Fig.1a, left insert), end-to-side or preferably end-to-end Fig.1a, main figure) to either the native stomach, duodenum or residual jejunal stump of the recipient. The distal end of the intestinal graft is anastomosed to either the remaining stump of the native terminal ileum, transverse, descending, sigmoid colon or to the rectum of the recipient. Terminal ileostomy or colostomy is performed in patients who have lost their native distal recto-sigmoid colon. A distal "chimney" ileostomy (Fig.1a, left insert), or preferably a Bishop-Koop distal reversed ileostomy (Fig.1a, main figure), with or without a "chimney" colostomy, as well as a tube jejunostomy (Fig.1a, mainfigure and left insert) with or without a tube gastrostsomy are fashioned in order to respectively monitor, decompress and tube feed the intestinal graft. A cholecystectomy and appendectomy complete the ilnTx procedure.

b_2) Combined Liver/Intestine Transplantation (Fig. 1b).

Unlike ilnTx, cLvlnTx entails the removal of the native liver with resultant anhepatic phase and consequent hemodynamic and physiologic changes. In addition, the native foregut organs (abdominal esophagus, stomach, duodenum, pancreas, spleen) should be preserved and their venous outflow needs to be drained since native hepatectomy is performed. Moreover, in cLvlnTx preliminary intra-abdominal dissection is usually more bloody and challenging because of the presence of extensive venous collaterals secondary to portal hypertension.

1) preliminary intra-abdominal dissection and removal of the native failing organs: in these patients, the native liver and intestine are removed, but the remainder of the foregut organs (abdominal esophagus, stomach, duodenum, pancreas, spleen) is retained (Fig.1b, main figure). The recipient's native residual intestinal segments (duodenal-jejunal junction, proximal jejunal and distal colorectal stumps) are identified, thouroughly dissected and carefully preserved if normal, or resected if still affected by the primary intestinal disease. Recipient's hepatectomy can be performed either by removing (standard technique) or preferably preserving ("piggy-back" technique) [53] the retro-hepatic IVC. If the "piggy-back' hepatectomy is performed, the need of a veno-venous by-pass [54] to channel the blood from the splanchnic and IVC systems to the right heart is eliminated. This technique has further advantage of not cannulating the recipient's major central veins, which might often be thrombosed from previous TPN-related complications, or if still patent, need to be carefully spared for postoperative maintenance TPN. After standard dissection of the native hepatic hilum, a temporary or permanent porto-caval shunt between the native portal vein and IVC is routinely fashioned in order to decompress and to drain the venous outflow from the recipient's native foregut organs which are not removed (Fig.1b, right insert)[55]. This temporary or permanent porto-caval shunt is usually performed in the early phases of intraabdominal dissection, in order to minimize the life-threatening blood loss due to the removal of the native liver and residual intestine in the presence of severe undrained portal hypertension.

2) exposure of the native vascular stems, vascular anastomoses and graft reperfusion: the infra-renal aorta is dissected and exposed as previously described. The subdiaphragmatic stump of the IVC or the entire suprarenal IVC is respectively exposed after the standard or "piggy-back' hepatectomy is completed. The venous outflow of the composite graft is reconstructed first. If the native hepatectomy was performed wit removal of the retro-hepatic IVC with the specimen, this segment of IVC is replaced with the graft using a standard liver transplant technique. If the recipient's hepatectomy was done preserving the native retro-hepatic IVC and the hepatic veins-IVC confluence, the venous outflow from the graft is accomplished by anastomosing end-to-side the graft's supra-hepatic IVC stump to the recipient's IVC at the level of the preserved native hepatic veins (piggy-back" technique). In this case, the infra-hepatic IVC of the graft can be ligated after graft venting and reperfusion (Fig.1b, main figure). Next, the arterial inflow of the graft is fashioned by anastomosing side-to-end the anterior aspect of the infra-renal aorta of the recipient to the aortic Carrel patch of the graft, encompassing both the orifices of the double

arterial stem of celiac axis and SMA. If not already done at the back-table, an interposition graft of thoracic or abdominal aorta (Fig.1b, main figure), or a bifurcated iliac arterial graft (Fig.1b, right insert) from the same donor may be required to fashion a longer common arterial conduit. After arterial unclamping and adequate venting of the graft through the infra-hepatic IVC, reperfusion is accomplished. In cLvInTx, the main portal vein axis between the donor's intestine and liver remains intact. Therefore, although the previously fashioned porto-caval shunt may last permanently (Fig.1b, right insert), it is preferable, after reperfusion, to take it down and to reconvert it to a porto-portal shunt, by anastomosing end-to-side the recipient's portal vein, which is draining the native foregut organs, to the left postero-lateral side of the graft's intact portal vein ("piggy-back" technique) (Fig.1b, main figure)[42]. This shunt reconversion provides the transplanted liver with the drainage of important hepatotrophic factors from the native pancreas, with consequent metabolic advantage [43,44,45]. The technical limiting factors which inhibit the reconversion from the temporary porto-caval shunt to a permanent porto-portal shunt are the lenght of the native portal vein and the size of the graft portal vein.

3) intestinal and biliary reconstruction: intestinal reconstruction is fashioned in a similar way as for ilnTx. Because the common bile duct of the graft has been transected as a surgical step of the cLvIn graft retrieval procedure, the biliary tract continuity of the new liver is peformed by a loop Roux-en-Y choledocho-jejunal anastomosis (Fig.1b, main figure).

b3) Multivisceral Transplantation (Fig. 1c).

Multivisceral transplantation can be envisioned as a modified extensive "cluster operation", by incorporating all or most of the gastro-intestinal organs.

1) preliminary intra-abdominal dissection and removal of the native failing organs: in all MvTx recipients extensive total abdominal exenteration is accomplished. Except for patients with pseudo-obstructive, malabsorptive or polyposis syndromes, who usually retain their own native organs inside a surgically non violated peritoneal cavity, total abdominal exenteration is an extremely difficult, challenging, bloody, life-threatening procedure. This is mainly true for patients who have Budd-Chiari syndrome, extensive thromboses of the splanchnic veins, hepatic veins and IVC, with consequent severe venous hypertension in the PV and IVC systems. Recipient hepatectomy is usually accomplished by using the "piggy-back" technique, thus avoiding the need of a veno-venous by-pass. Total abdominal exenteration entails the removal of the entire GI tract from the esophageal-gastric down to the sigmoid-rectal junctions, along with the removal of the duodenal-pancreatic-splenic complex attained by a total duodeno-pancreato-splenectomy.

2) exposure of the native vascular stems, vascular anastomoses and graft reperfusion: as for cLvInTx, the graft's venous outflow is reconstructed first by anastomosing end-to-side the supra-hepatic IVC stump of the graft to the recipient's IVC at the level of the preserved native hepatic veins, using the "piggy-back" technique. The graft's arterial inflow common conduit is anastomosed end-to-side either to the recipient's infra-renal or supra-renal periceliac aorta. Differently from the cLvInTx, in MvTx a temporary porto-caval shunt as well as its subsequent porto-portal reconversion are not performed since all the foregut organs in the recipient have been removed as part of the total abdominal exenteration procedure.

3) gastro-intestinal reconstruction and biliary drainage: proximal continuity of the alimentary tract is restored by anastomosing end-to-side the distal abdominal esophagus or the residual small fundal stump of the stomach of the recipient to the anterior gastric wall of the graft. If not already done at the back-table, a pyloromyotomy or a pyloroplasty is also done at this time, being the stomach totally vagotomized (Fig.1c). The distal continuity of the intestinal tract is re-established as in ilnTx and cLvInTx. In MvTx the hepatic hilum remains intact, with no need of biliary recostruction as for cLvInTx. However, in order to minimize the risk of acute biliary pancreatitis, a temporary diversion of the bile flow is accomplished through an external common duct drainage by a trancystic cannulation (Fig.1c).

c) Surgical technical variations and refinements.

As the surgical strategies and techniques for InMvTx evolved with increasing surgical and clinical experience [59], several technical variations and refinements have been introduced:

1) graft procurement: isolated intestine and combined liver/intestine grafts are not any longer retrieved. *"En-bloc"* harvesting of multivisceral grafts is our presently adopted procurement procedure, with subsequent back-table dissection and tailoring of the required organ graft configuration.

2) addition of the colon as part of the intestinal component of the graft: in order to minimize the severity of postoperative diarrhea and dehydration as well as the risk of ileal bacterial overgrowth, the colon with the ileo-cecal valve is now routinely retrieved and transplanted (n = 13 cases). Arterial blood supply to the colon, which must be carefully preserved, is based on the colic branches of the SMA and IMA as well as on the marginal arterial arcade (Drummond-Riolan arcade); venous drainage is through the venous tributaries of both the SMV and IMV.

3) preoperative arterial embolization: dissection of the recipient abdominal cavity and resection of the native or of the tranplanted organs, in face of severe venous hypertension secondary to thrombosed splanchnic and/or IVC systems, can entail catastrophic hemorrage, mainly due to the inability to promptly and effectively control the splanchnic arterial inflow by primary surgical clamping of the deeply hidden supplying arteries. After two MvTx candidates bled to death on the operating table, in order to minimize the risk of fatal intraoperative bleeding, a combined radiological-surgical approach was devised: in the anesthetized patient, the arteries supplying the organs to be removed (celiac axis and SMA branches) are radiologically embolized; thereafter, dissection and resection of the native organs are carried out in an almost bloodless operative field.

4) graft portal venous outflow: in ilnTx the graft venous outflow can be accomplished by anastomosing the skeletonized graft PV or SMV either end-to-end to the recipient SMV stump, or end-to-side to the confluence

of the recipient's SMV and SV, as well as to the right postero-lateral side of the recipient's PV at the level of the hepatic hilum ("piggy-back" technique) [57]. If this portal venous drainage is not technically achievable because of size discrepancy or difficult anatomic relationships, the venous outflow of the graft is drained into the IVC system by fashioning a permanent end-to-side porto-caval shunt at the level of the suparenal infra-hepatic IVC (n=1 case). In cLvInTx, if reconversion of the previously constructed porto-caval shunt to a porto(recipient)-portal(graft) shunt cannot be achieved because of technical hurdles, it can be safely omitted, although important hepatotrophic factors from the native pancreas cannot be provided to the transplanted liver.

5) intestinal anastomoses: initially in our clinical series, most of the intestinal anastomoses have been performed in a side-to-side or end-to-side fashion. Currently, based on experimental finding on the dog, our routine standard technique is to fashion end-to-end intestinal anastomoses as often as possible, in order to improve graft intestinal motility.

6) venting enterostomies: tube jejunostomy with or without tube gastrostomy, along with Bishop-Koop reversed distal ileostomy, with or most often without a "chimmney" colostomy, are the venting procedures at present routinely performed in all InMvTx recipients. The Bishop-Koop antiperistaltic distal ileostomy facilitates the endoscopic procedures in the ileum and colon, and decreases the intestinal fluid output through the stoma. A proximal tube jejunostomy with or without a tube gastrostomy is routinely used for gastro-jejunal decompression and for early postoperative tube feeding.

7) closure of the abdominal wall: patients with long-lasting "short gut syndrome" usually present with a contracted abdomen and a small peritoneal cavity volume. Consequently abdominal wall closure is sometimes not feasible due to lack of room and of strong usable abdominal wall tissues (fascia, muscles). In such cases simple skin closure is sufficient, by using wide skin flaps extensively dissected from the anterior and postero-lateral regions of the abdomen and the chest. If even skin closure is not possible, peduncolated myo-cutaneous flaps from the thighs can be used.

Total surgical time of the recipient operation is quite long, varying from 8 to 18 hrs; conversely, time required to fashion the vascular anastomoses (**warm ischemia time**) is relatively short, taking usually less than 30' minutes.

VI.- POSTOPERATIVE MONITORING AND CARE.

Postoperative course of InMvTx recipients is usually difficult and complicated, mainly in those patients who preoperatively presented deterioration of their physical performance status and various organ systems failures, which can persist in the postoperative period even in face of satisfactory allograft function. Postoperative course is usually more troubled in cLvInTx and MvTx than in iInTx patients, who generally present a lesser medical acuity [34,67].

Therefore, postoperative monitoring and management of these patients require a vrery aggressive and multidisciplinary approach by medical (surgeons, anesthesiologists, CCM physicians, internal medecine specialists, radiologists, pathologists) and nursing staff. It also requires, often for prolonged periods in the ICU, easy availability and access to diagnostic facilities (immunologic and infectious surveillance, sophysticated hemodynamic monitoring, bronchoscopy, TEGraphy, GI endoscopy, invasive a non-invasive radiology, histopathology, emergency lab tests) as well as timely and prompt therapeutic modalities (immunosuppressive and antibiotic treatment, mechanical ventilation and repiratory therapy, hemodialysis, fluid and nutritional support, emergency surgery for complications, thorough nursing care). Most important, however, is a continuous, dedicated, diligent committment to patient surveillance and care by both medical and nursing personel. Any subjective symptom or complaint as well as any new objective physical sign or change in the patient clinical picture must be aggressively followed and carefully investigated until the cause is found or it resolves [22].

Although sometimes difficult to achieve, early diagnosis of postoperative complications is a major determinant in successful InMvTx, being a *"conditio sine qua non"* for immediate, specific, effective therapy. Postoperative monitoring of InMvTx recipients is addressed to detect as early as possible the onset of post-transplant complications, mainly immunological (acute rejection, chronic rejection, GVHD) and infectious (opportunistic, bacterial, fungal, viral infections), as well as to assess the graft anatomic and functional integrity (absorption, motility, fluid and electrolyte balance, nutritional status). In recipients of composite grafts (cLvInTx, MvTx), post-transplant monitoring should also include assessment of the coexistent liver, pancreas and/or kidney grafts, according to monitoring protocols specific for each of these organs [68].

A.- Postoperative Management.

Early postoperative care of InMvTx recipients is provided according to standard transplant ICU protocols. Immunosuppression, prophylaxis of infection, nutrittional support and gastro-intestinal care, respiratory, renal and fluid management is preminent.

a) Immunosuppression.

The same immunosuppression regimen is used for each type of InMvTx (iInTx, cLvInTx and MvTx) [19,20,27,28,33].

a_1) Prophylaxis and maintenance immunosuppression.

Induction and chronic maintenance immunosuppressive prophylaxis involves the use of two and sometimes three drugs: FK-506, steroids and azathioprine [60,61,81,82].

1) FK-506: as the primary immunosuppressive agent, FK-506 is given, starting intraoperatively shorthly after graft reperfusion, at a dose of 0.15 mg/kg/day by continuous IV infusion over 24 hrs. One or two weeks after transplantation, once GI functions have recovered (resumption of GI motility and absorption, decreased stomal output) and after integrity of GI surgical anastomoses is confirmed by standard contrast barium studies, enteral FK-506 is given at 0.3 mg/kg/day either through tube jejunostomy or by mouth, in two daily divided administrations, with several days of overlap with gradually decreased IV doses and progressively increased enteral doses. Since FK-506 absorption is independent of bile enterohepatic circulation, adequate FK-506 plasma levels can be maintained on enteral dosage alone even in the early postoperative period [64-66]. Since the incidence of intestinal rejection episodes in InMvTx recipients is higher than the incidence of rejection in OLTx recipients, our current practice is to use higher doses of FK-506 to maintain higher concentration in InMvTx compared with OLTx recipients [68,87-89]. The mean FK-506 target 12-hours trough plasma level is 3-5 ng/ml in the perioperative and early postoperative period during continuous intravenous therapy; 2-3 ng/ml with oral administration during the late postoperative period (1-3 months); lower levels (1-2 ng/ml) are usually attained later in the long-term follow-up (3 month after transplantation). Continuous close modulation of FK-506 dosage is needed, based on plasma levels, cross-match and PRA%, hepatic and renal function tests, overdose-induced nephro- and/or neuro-toxicity, concurrent ongoing clinically suspected or histologically documented rejection and/or infection episodes.

2) steroids:

- ***IV steroids***: 1.0 gm of **Solu-Medrol (6-methyl-prednisolone sodium succinate)** (adult recipients, pediatric recipients > 30 kg) or **Solu-Cortef (hydrocortisone sodium succinate)** (pediatric recipients < 30 kg) is given by IV single bolus intraoperatively at graft reperfusion time. An IV steroid taper of Solu-Medrol is started on the first postoperative day at a daily dose of 200 mg (adults) or 100 mg (children), and gradually reduced over a period of 5 days to 20 mg (adults) or 10 mg (children) per day[11].

- ***enteral steroids***: after postoperative resumption of GI functions, IV steroids are replaced by enteral **prednisone (Deltasone)** at a dose of 20 mg/day (adults) or 10 mg/day (children). If graft tolerance with minimal rejection episodes is demonstrated and the recipient is clinically doing well, high perioperative and early postoperative prednisone dosage is gradually reduced to the minimum compatible maintenance doses or even discontinued, mainly in the pediatric recipients, who can be eventually managed only by reduced-dose monotherapy with FK-506.

3) azathioprine (Imuran): is administered sometimes (22 recipients) at low doses (1-2 mg/kg/day IV or PO) as a supplementation of baseline maintenance immunosuppression, when

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[11] **Solu-Medrol (6-methyl-prednisolone sodium succinate) taper.** *Adults and Children > 30 kg:* 1st POD: 50 mg IV q 6 hrs x 4 doses; 2nd POD: 40 mg IV q 6 hrs x 4 doses; 3rd POD: 30 mg IV q 6 hrs x 4 doses; 4th POD: 20 mg IV q 6 hrs x 4 doses; 5th POD: 20 mg IV q 12 hrs x 2 doses; then 20 mg IV qd. *Children < 30 kg*: 1 st POD: 25 mg IV q 6 hrs x 4 doses; 2nd POD: 20 mg IV q 6 hrs x 4 doses; 3rd POD: 15 mg IV q 6 hrs x 4 doses; 4th POD: 10 mg IV q 6 hrs x 4 doses; 5th POD: 10 mg IV q 12 hrs x 2 doses; then 10 mg IV qd.

significant FK-506 dose reduction is needed because of nephro- or neuro-toxicity. Azathioprine titration is geared to the WBC count and maintained provided the WBC continue to be > 3,000/mm^3.

4) prostaglandin E_1 (PGE_1, Alprostadil, Prostin): in addition to the above double or triple drug immunosuppressive prophylaxis, prostaglandinE_1 is also currently delivered to InMvTx recipients in the very early postoperative course. Except for the first 8 recipients, intravenous PGE_1 is given starting intraoperatively immediately after graft reperfusion, as soon as permitted by recipient hemodynamic stability, at a dose of 0.2 mg/kg/hr, and gradually increased to 0.6-0.8 mg/kg/hr (adult recipients). PGE_1 administration is continued for 7-14 days until IV FK-506 is stopped. PGE_1 dose for children is 0.003-0.009 mg/kg/min for the first 5 postoperative days. PGE_1 is administered for its beneficial effects on renal perfusion and for its prevention of microvasculature thrombosis, which is the damage-mediating pathogenetic event of harvesting-ischemic injury, of reperfusion injury and of acute cellular rejection [18].

a_2) Immunosuppressive treatment of acute cellular rejection (ACR).

Immunosuppressive therapy of ongoing ACR of InMv grafts includes the same drugs used for induction and maintenance immunosuppression (Fk-506, steroids, azathioprine) with the occasional addition of monoclonal antibodies (OKT3). Drug dosage and administration way are adjusted on the severity of the rejection monitoring criteria and mostly on the rejection histological grading scale. Intestinal rejection can impair FK-506 absorption with resultant inadequate FK-506 trough plasma levels. Consequently, optimization of FK-506 trough levels, targeting 3-5 ng/ml, should be accomplished by either increasing the baseline enteral dose or by administering supplemental IV FK-506. **Mild ACR** is treated initially by giving a single 1.0 gm IV bolus of 6-methyl-prednisolone (adults) or hydrocortisone (children), and by increasing FK-506 enteral or IV dose as needed or tolerated. In case of **moderate ACR**, a 5-days 6-methyl-prednisolone taper is delivered, in addition to FK-506 increased dosage and steroid single 1.0 gm IV bolus. This augmented steroid therapy has been required in about 50% of our InMvTx recipients. If in despite of the above treatment, moderate rejection progresses to **severe ACR**, OKT3 (Orthoclone-OKT3, Muromonoab-CD3) is given at 5-10 mg/day (adult and pediatric recipients > 30 kg), or at 2.5-5.0 mg/day (pediatric recipients < 30 kg) by IV bolus, over a 7-14 days course. In addition to steroid-resistant ongoing ACR, OKT3 should also be considered as initial immunosuppressive agent in case of severe ACR, as documented by extensive mucosal sloughing and serious crypt injury. OKT3 to approximately 18% of our InMvTx recipients.

Adequate and prompt immunosuppressive treatment of ongoing acute cellular reiection of intestinal grafts is usually successful. If it fails, the only available option is total removal of the intestinal allograft (graft enterectomy).

b) Prophylaxis and treatment of infectious complications.

Post-transplant infectious prophylaxis starts preoperatively by administering systemic IV broad-spectrum antibiotics along with selective gut decontamination to all the InMvTx candidates. In addition, any recent pre-transplant infection and/or colonizing organism from coexistent enteral fistulas should be aggressively treated preoperatively with adequate specific antibiotics.

Empiric anti-bacterial prophylaxis by systemic IV broad-spectrum antibiotics[3] is continued for the first 5 days after transplantation. Subsequently, if clinically indicated because of occurrence of infectious complications, discriminate antibiotic therapy is given, based on the results of blood and body fluid cultures as well as on the patient's clinical course.

In addition to aspecific systemic IV antibiotic prophylaxis, selective bacterial and fungal gut decontamination[6] of the InMvTx recipient is continued postoperatively for 4-6 weeks, and later resumed in case of moderate to severe rejection as well as in patients with overt symptoms of bacterial overgrowth [29,34,92].

Fungal infection prophylaxis by low dose Amphotericin B[12] is routinely employed when

[12] **Amphotericin B** prophylaxis: 0.2-0,3 mg/kg/day IV slow infusion, for 2-4 weeks.

clinically indicated (heavy intra-abdominal contamination, GI leaks, multiple re-explorations, aggressive treatment for rejection). If established active fungal infection occurs, long-term full-dose antifungal therapy along with reduction or even discontinuation of immunosuppression is required.

Viral prophylaxis with Gancyclovir[13] and Acyclovir[14] is also administered to prevent viral infections. The very high incidence of severe CMV enteritis in recipients of CMV sero-positive grafts entails the prophylactic administration in these patients of Gancyclovir[15] for 3 months after transplantation. Sometimes neither Acyclovir nor Gancyclovir are effective in preventing CMV complications. If that happens, administration of phosphonophormate sodium[16] and/or CMV immunoglobulins (Cytogam)[17] are back-up therapeutic options. It should be emphasized, however, that the most effective way to control *"de novo"* CMV infections still remains avoidance of CMV sero-positive grafts and temporary reduction or even discontinuation of immunosuppression.

Lifetime long chronic protozoal prophylaxis for Pneumocystis Carinii (trimethoprim/sulfamethoxazole, pentamidine, dapsone)[18] is given in all InMvTx recipients.

While the basic general principle of infection treatment by reducing or even discontinuing immunosuppression is usually effective in any transplanted or immunocompromised patient, it may not be valid in InMvTx recipients. In this peculiar patient population, translocation of enteric microorganisms through the injuried intestinal mucosa, with resultant septic complications, is commonly precipitated by concurrent ongoing rejection episodes. This coincidence of infection and rejection represents a particular situation in transplantation: in fact, treatment must be addressed toward both the infectious and immunological fronts, focusing aggressive antibiotic therapy on the specific septic etiology without decreasing, but conversely, increasing immunosuppression.

c) Nutritional support and gastro-intestinal care.

In the perioperative period and early postoperative course, continuous IV fluids are thorougly administered to all InMvTx recipients in order to compensate the intravascular volume depletion, secondary to peripheral fluid accumulation, fluid shift into the allograft and development of ascites.

Postoperative nutritional support is initially accomplished by resuming preoperative standard balanced **TPN** solutions, using dextrose, crystalline amino-acids, lipids emulsions, electrolytes, vitamins and trace elements, thus providing about 1.5-1.8 gm proteins/kg/day and 30-35 kcal/kg/day.

After gastro-intestinal functions recovered (resumption of gastro-intestinal motility and absorption, decreased stomal output) and upper GI barium contrast studies confirmed the integrity of the gastro-intestinal anastomoses, **enteral feeding** is started via a jejunostomy tube (naso-gastric, naso-duodenal and gastrostomy tubes can also be used), usually around the 7th-10th postoperative day. At the same time TPN formulas are gradually tapered and eventually discontinued as enteral feeding is advanced according to the nutritional status of the recipient and the absorptive capacity of the

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[13] **Gancyclovir**: 5 mg/kg IV q 12 hrs for 14 days; then intravenous or oral Acyclovir; adjust to renal function.

[14] **Acyclovir**: 5-10 mk/kg IV q 8 hrs; 400-800 mg PO TID-QID for 6-12 months; adjust to renal function.

[15] **Gancyclovir**: 5 mg/kg IV q 12 hrs for 3 months; adjust to renal function.

[16] **Foscarnet sodium) (Phosphonophormate sodium** : *Induction*: 60 mg/kg IV slow infusion q 8 hrs; *maintenance*: 90-120 mg/kg/day IV continuous infusion; adjust to renal function.

[17] **Cytogam** (CytoMegaloVirus Immune Globulin Intravenous Human; **CMV-IGIVH**): 60 mg/kg/hr IV continuous infusion; total recommended dose/infusion: 100-150 mg/kg/infusion.

[18] **Pneumocystis Carinii prophylaxis**: **Trimethoprim/Sulfamethoxazole (Bactrim)**: 1.0 mg/kg/day IV; 80/400 mg PO qd; **Pentamidine ischionate**: 300 mg in 6 mLs sterile water by nebulizer once a month; **Dapsone**: 100 mg PO qd.

intestinal graft. Continuous enteral feeding with gradually increasing volumes is preferred over the bolus method. Enteral feeding is initiated by using an isotonic elemental dipeptide formula containing medium chain triglycerides and glutamine (Peptamen). Four to six weeks after transplantation, Peptamen is converted in pediatric recipients to Compleat B, a blenderized meat-based lactose and gluten free diet, containing dietary fibers to promote normalization of intestinal motility and functions.

Tube feeding is later progressively decreased and definitevely weaned by reducing the rate then the time of enteral feeding, as oral intake is proportionally increased to a normal oral diet. In the early postoperative course, most InMvTx recipients do not take appropriate amounts of calories and proteins when on oral diet, which is often quantitatively inadequate. This eating disorder, which is more evident in children, could be secondary to several etiologic factors: most pediatric patients never have been fed before and consequently never learnt to eat; both pediatric and adult recipients often associate the act of eating with disagreable, distastful or even painful feelings; a hypergag reflex from lack of eating could also be evoked [102]. For this reason they need to undergo long and intensive rehabilitation and long nutritional education in order to learn what and how to eat. Whenever oral intake is not adequate or the intestinal tract becomes not functional, periodical intermittent tube enteral **supplementation** is required [103,104].

Opioids[19], **antimuscarinic cholinoceptor blockers**[20], **adsorbents**[21], **bulk-forming agents**[22], **somatostatin**[23] and **oral antibiotics** are used, alone or in combination, in InMvTx recipients with diarrhea, high stomal output, intensive intestinal hypermotility.

Eukinetic drugs[24] are given to patients experiencing gastro-intestinal dismotility with or without nausea and vomiting.

Antacids[25], **H_2-receptors blockers**[26] and **mucosal protective agents**[27] are administered to all InMvTx recipients. A short course of **Omeoprazole**[28] may be helpful in controlling hypersecretory conditions or upper GI tract dismotility disorders. Still under investigatio are thre nutritional role and the eutrophic properties of IV and enteral **glutamine.**

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[19] **Opioids: Opium Tincture**: 0.6 mLs PO qid; **Opium Camphorated Tincture (Paregoric)**: 5-10 mLs PO q6-q24 hrs; **Diphenoxylate Hydrochloride with Atropine Sulphate (Lomotil)**: 1-2 tabs PO q6 hrs, 5-10 mLs PO q6 hrs; **Loperamide (Immodium)**: 2 mg (i caps) PO after each unformed stool.

[20] **Antimuscarinic Cholinoceptor Blockers: Atropine Sulphate**: 0.4-0.6 mg PO q8 hrs; **Belladonna Alkaloids Tincture**: 0.6-1.0 mLs PO q6-q8 hrs.

[21] **Adsorbents: Kaolin with Pectin (Kaopectate)**: 60-120 mLs after each unformed stool; **Bismuth Subsalicylate (Pepto-Bismol)**: 524 mg (2 tabs) PO q30-q60 min' prn (max: 8 doses/day), 30 mLs PO q30-q60 min' prn (max: 8 doses/day).

[22] **Bulk-forming Agents: Psyllium Derivatives (Metamucil)**: 5-10 gm powder PO qd-tid.

[23] **Octreotide (Somatostatin Analogue, Sandostatin)**: 100-400 mcg/day SC in 2-3 divided doses.

[24] **Eukinetic Drugs: Metoclopramide (Reglan)**: 10-15 mg PO q6 hrs, 10-15 mg IV prn; **Prochloroperazine (Compazine)**: 5-10 mg PO/PR q6 hrs, 5-10 mg IV/IM q6 hrs.

[25] **Antacids: Aluminum & Magnesium Hydroxide (Amphojel, Riopan, Maalox, Mylanta)**: 30 mLs PO q6 hrs.

[26] **H_2-Receptors Blockers: Cimetidine (Tagamet)**: 800 mg PO q24 hrs, 300-600 mg IV/IM q6 hrs; **Ranitidine (Zantac)**: 150 mg PO q12 hrs, 50 mg IV/IM q6-q8 hrs; **Famotidine (Pepcid)**: 20-40 mg PO q24 hrs, 20 mg IV q12 hrs.

[27] **Mucosal Protective Agents: Sucralfate (Carafate)**: 1.0 gm PO q6 hrs; **Mysoprostol (Cytotec)**: 200 mcg PO qid;

[28] **Omeoprazole (Prilosec)**: 60-120 mg PO q24 hrs.

d) Respiratory care.

Mechanical ventilation is commonly continued for 48 hrs. Withdrawal from mechanical ventilation and extubation should be cautiously accomplished only after careful assessment of the weaning parameters[29] for an adequate period of time on CPAP ventilation mode. Several ventilation compromizing etiologies can delay weaning from mechanical ventilatory support and extubation in InMvTx recipients: preoperative weakening nutritional status with resultant malnutrition and muscle wasting; donor/recipient size discrepancy with increased intra-abdominal pressure and ensuing compression of the thoracic cavity along with incidental occasional inability to close the abdominal wall; postoperative incisional pain; graft primary dysfunction; liver failure; sepsis; ascites and pleural effusions; postoperative IV narcotics; paresis or paralysis of the right hemidiaphragm [27,59]. These patients often need tracheostomy for prolonged respiratory support; they also commonly require intensive respiratory therapy to prevent reintubation and pulmonary complications, as well as repeated thoracentesis and paracentesis.

e) Renal and fluid management.

After InMvTx, with peak at 48-72 hrs, significant interstitial fluid accumulation usually occurs, mainly into the peripheral tissues, lungs and allograft. This anasarca-like condition, concurrently with extensive fluid volume shift into the transplanted intestine secondary to harvesting/preservation injury, along with development of ascites secondary to mesenteric lymphatic disruption and leakage, entails significant intravascular volume depletion with resultant prerenal insufficiency. Accurate hemodynamic monitoring and careful fluid management based on continuous measurements of the filling pressures (CVP, PCWP) are required to optimize graft perfusion and to mantain anatomic and functional integrity of the kidneys, which are also exposed to several potential nephrotoxic agents (FK-506, certain antibiotics and anti-viral drugs) [27].

B.- Immunological Complications.

a) Monitoring of intestinal acute cellular rejection.

Monitoring of intestinal graft rejection is mainly based on clinical, endoscopic, histo-pathological, radiological and immunological criteria [20,29,60-61].

1) clinical criteria: clinical monitoring of the intestinal graft rejection is accomplished by multiple daily clinical evaluations, focusing on the patient's general clinical status and on the patterns of the intestinal stoma. Acute intestinal allograft rejection may be asymptomatic, but usually presents an array of symptoms, including fever, weakness, mood changes, abdominal pain, abdominal distension, hypoperistalsis, nausea and vomiting, diarrhea or sudden increase of watery stomal discharge. The intestinal graft stoma is carefully examined for color, texture and friability; the stoma may become edematous, erythematous, pale, congested, dusky and friable. Stomal output is assessed for volume, consistency, presence of blood and of reducing substances tested by pH and clinitest and reflecting, besides rejection, also infection or malabsorption. In more severe episodes of acute graft rejection, erosions, ulcerations and sloughing of the intestinal mucosa may occur, with gastro-intestinal bleeding, graft paralytic ileus and absence of stomal output. Due to disruption of the normal intestinal mucosal barrier, bacterial and/or fungal translocation can develop, with consequent septic complications and/or ARDS-like syndromes.

Clinical criteria are the keystone for early diagnosis of acute rejection of the intestinal graft. Unlike rejection of other isolated solid organ allografts (heart, lung, liver, kidney, pancreas) whose diagnosis is mainly attained by biopsy and/or by funtional or lab tests, diagnosis of intestinal acute rejection has to be primarily based on clinical criteria, which usually present first. In InMvTx, endoscopic, bioptic,

[29] **Weaning parameters**: V_T (Tidal Volume) = > 5 mLs/kg; FVC (Forced Vital Capacity) = > 10 mLs/kg; SMV (Spontaneous Minute Ventilation) = < 10 L/min'; NIP (Negative Inspiratory Pressure) = > -30 mmHg.

radiological and metabolic parameters of acute rejection come often too late: they help to confirm, not to make the diagnosis of acute rejection. It would be a serious mistake and a waste of precious time waiting too long for these results to start immunosuppressive treatment, since only a few hours may be available for effectively and safely reverse the ongoing immunological injury.

2) endoscopic criteria: surveillance endoscopic evaluations, routinely associated with multiple selective, endoscopy-guided mucosal biopsies, are usually performed mainly by terminal ileoscopy (ileal biopsies), but also by upper esophago-gastro-duodeno-jejunoscopy (gastric and jejunal biopsies) and by pan- and lower colonoscopy colonic biopsies). They are done twice a week for the first month, once a week for the next two months, monthly for the next three months and every 3-6 months or whenever clinically indicated, thereafter. Endoscopic features of mild to moderate acute intestinal graft rejection are edema of the mucosa, which can progressively become focally or diffusely erythematous, hyperemic, congested and dusky. It can loose its fine velvety appearance and become hypoperistaltic, friable, with fine mucosal granularity and focal erosions. More severe rejection presents with submucosal nodularity, focal or diffuse ulcerations, sloughing of extensive areas of the mucosa with development of pseudomembranes, intestinal bleeding and absence of peristalsis. These findings have been recorded in more than 500 endoscopic evaluations performed in each of the 43 InMvTx recipients [62,63]. Differential endoscopic diagnosis should be made between acute intestinal cellular rejection and CMV enteritis (punctate erythema, erosions, ulcerations).

3) histo-pathological criteria: histologic monitoring of the intestinal allograft is performed by frequent endoscopically guided mucosal biopsies; undirected stomal or endoscopic biopsies may miss focal lesions of rejection and/or conversely may show non specific pictures mimicing rejection. Simultaneous biopsies of the jejunum and of the ileum showed the more susceptibility of the ileum to rejection: consequently, ileal biopsies are needed to confirm or exclude allograft rejection.
In mild to moderate rejection, histo-pathological patterns consist of widening of the lamina propria, with edema, mixed inflammatory mononuclear infiltrate and focal venulitis. The cellular infiltrate components are mainly activated lymphoblasts and small lymphocytes, along with macrphages, plasmacells, eosinophils and sometimes neutrophil granulocytes. The cellular infiltrate can traverse the muscularis mucosae as well as invade the basal membrane, with resultant infiltration of the mucosal epithelial layer. Enlarged Peyer's patches, cryptitis with apoptosis, goblet and Paneth cell depletion, epithelial cell necrosis and final crypt loss of various degree are further histologic findings of mild to moderate acute intestinal rejection. At a more advanced and severe stage, complete mucosal sloughing, focal ulcerations, crypt destruction, neutrophil plugging of capillaries in the lamina propria, replacing granulation tissue and inflammatory pseudo-membranes are found. In late acute cellular rejection (> 3 months after transplantation), in addition to the above described histologic features, fibrosis of the lamina propria can be present; the activated inflammatory cellular infiltrate is usually less severe. It should be outlined that histologic features of intestinal acute rejection can be focal [64-67]. Successfully treated acute cellular rejection is usually associated with resolution of the clinical symptoms and signs over a few days; conversely, histological improvement in the pathologic findings occurs 5-7 days after the clinical response. Healing and regeneration changes occur, overlapping the above histologic features, with accelerated mitotic activity and increased nuclear/cytoplasmic ratio in regenerating enterocytes, increasad crypt depth, doubling of the epithelial mono-layer, resulting in architectural disruption, distorted uneven cryptic lumen and villous blunting; decreased edema in the lamina propria and resolution of mononuclear inflammatory cell infiltrate is found.
Histologic differential diagnosis is often difficult and should be formulated for intestinal graft ischemic injury and CMV enteritis, which is the most common infection in intestinal grafts.
In case of ***ischemic (harvesting, preservation and reperfusion) injury*** of the intestinal graft, which usually occurs after 7.5 hours of cold ischemia time, pre-reperfusion biopsies of the intestinal allograft show separation of the villous epithelium from the underlying lamina propria, along with focal areas of epithelial denudation. Early post-reperfusion biopsies of the graft display focal epithelial denudation of the villi, capillary congestion or hemorrage of the lamina propria, neutrophilic margination in the submucosal veins. At a later stage, the histo-pathological features consist of neutrophilic inflammation and formation of granulation tissue in the lamina propria, and of luminal inflammatory pseudo-

membranes. These lesions usually heal within 10-14 days after the transplant [69], with complete epithelial regeneration. Compared to the small bowel, the colon seems less susceptible to ischemic injury.

Major histologic features of ***CMV enteritis*** are giant mucosal epithelial cells with pleomorphic nuclei, harboring basophilic nuclear and cytoplasmic inclusion bodies, mixed inflammatory cell infiltrate, cryptitis, epithelial cell necrosis, apoptosis and villous atrophy.

4) radiological criteria: based on gastro-intestinal contrast studies, CT scans and gastro-intestinal transit and emptying time evaluations, the radiological criteria for allograft ACR consist of dilatation of the intestinal lumen, edema and thickening of the intestinal wall, blunting and loss of the mucosal folds, paralytic ileus with increased transit and emptying times [69,70].

5) immunological criteria: in evaluating intestinal graft ACR some immunological features should always be considered: identity or disparity of donor/recipient gender; identity, compatibility or incompatibility of ABO and HLA systems, positive or negative cross-match and PRA%. Evaluation of donor/recipient chimerism, circulating lymphokines levels and enzyme microvillous "brush border" activity are still experimental preclinical methods.

b) Monitoring of chronic rejection.

The transition from acute to chronic rejection is a slow, treacherous and deceitful process. Chronic rejection of intestinal allografts has been recorded in recipients with persistent or recurrent intractable acute rejection episodes [71]. **Clinical presentation** consists of chronic progressive allograft dysfunction with intermittent fever, worsening malnutrition, declining weight loss, chronic long-lasting exacerbating abdominal pain, recurrent or persistent intractable diarrhea with dehydration, intermittent melena or enterorrhagia, relapsing septic episodes. **Endoscopic examination** shows a rigid, stiff, tubular, hypokynetic appearance of the intestinal loops, with thickening of the mucosa, flattening or atrophy of the mucosal folds, chronic ulcerations with pseudomembranes, intestinal bleeding. **Histologically**, on endoscopic mucosal biopsies, there is a progressive distorsion of the mucosal architecture, with villous blunting, widening of the lamina propria, scant cellular infiltrate, severe prominent cryptitis with cryptic cell apoptosis, depletion or loss of goblet and Paneth cells. In more severe and advanced stages, focal chronic ulcerations, intramural micro-abscesses, epithelial metaplasia, fibrosis of the lamina propria, of the submucosa and of the mesenteric lymphnodes along with obliterative arteriopathy of the intestinal arterioles occur, as demonstrated by full thickness intestinal biopsies. **Radiologically**, intestinal contrast studies show a stiff, rigid, tubular picture of the intestinal loops sometimes with strictures, with flattening or loss of the mucosal folds, paralytic ileus with extended transit and emptying times. CT scans exhibit the same picture as above with significant thickening of the intestinal mucosa. Angiography has revealed segmental stenosis of the mesenteric arterioles, validating the obliterative arteriopathy of the chronic rejecting intestinal graft.

A **classification and grading system** for intestinal allograft acute and chronic rejection (acute rejection: mild, moderate, severe; chronic rejection: early, late) has been devised, based on the extension of the inflammatory infiltrate, the severity of crypt cell damage and apoptosis, the focal or diffuse ulceration, the severity of intestinal mucosal architectural distortion [68].

c) Monitoring of Graft-versus-Host Disease (GVHD).

Monitoring of GVHD is by clinical examination (fever, skin rash, septic-like syndrome), standard histology, immuno-histochemical techniques (immuno-staining, sex identification after fluorecence-in-situ-hybridization-FISH) and PCR-karyotyping ("DNA fingerprinting"). With these procedures it is possible to differentiate migrating immunocompetent cells from the donor (donor "passenger leucocytes") from recipient cells, as well as to document the immunological injury of the recipient tissues by the donor infiltrating cells. Inadequate immunosuppression is a major risk factor for GVHD. In despite of the "historical" fear [33] of high incidence of GVHD documented in experimental intestinal transplantation [6,72-75], our clinical experience has actually shown a minimal GVDH occurence (n= only 1 pediatric case).

One of the most intriguing findings from the above analyses is the gradual replacement

of the donor hematolymphoid cells in the intestinal wall and mesenteric lymphnodes in the graft by immunocompetent hematolymphoid cells from the recipient, which rearrange the normal intestinal mucosal immune system architecture [76]. Conversely, donor migratory immunocytes ("passenger leukocytes") from the graft migrate at the same time ubiquitously into the recipient blood stream and tissues. This new immunological status ("systemic chimerism") could be the basis of gradual induction of future donor specific non-reactivity (tolerance) [16,77-80].

C.- Infectious Complications.

High incidence of infectious complications in InMvTx recipients is the major cause of significant morbidity and mortality in this patient population [67,80-81,90-92].

Aggressive immunosuppression, pretransplant abdominal, pulmonary and/or line sepsis along with preoperative end-stage liver disease (in cLvInTx and MvTx) are the major medical predisposing factors. Surgical etiologic cofactors are difficult and complex technical procedures, requiring extended operative time, high blood transfusion volumes amd the need of frequent post-transplant re-explorations.

Bacterial pathogens are most commonly Gram-positive staphilococci and enterococci, of which the recently emerging pan-resistant enterococcal strain is uniquely threatening; Gram-negative rods are usually responsible of polymicrobial infectioms. Common fungal pathogens are Candida Albicans and Torulopsis Glabrata. Fungal infections occur mainly after heavy immunosuppression for severe rejection, as well as after intestinal leaks and multiple re-explorations. The most frequent viral agent is CytoMegaloVirus (CMV), particularly in adult recipients; less common viruses, mainly affecting pediatric recipients, are Respiratory Syncytial Virus (RSV), adenovirus, influenza and para-influenza virus, and most important Ebstein-Barr Virus (EBV). Viral infections are all opportunistic and are usually secondary to the need of aggressive immunosuppression for rejection episodes [93].

Clinical presentation of infectious complications varies with the infectious etiologic pathogens. Bacterial infections clinically present mostly as line sepsis, pneumonia, wound and intra-abdominal abscesses. Sometimes either multiple mixed infections from the same source or separate multiple sources of infection may occur simultaneously. Fungal infections occur in the esophagus, peritoneal cavity, paranasal sinuses, upper and lower respiratory system. Viral infections present in adults mainly as CMV enteritis; other clinical pictures consist of CMV hepatitis, pneumonitis, gastritis, retinitis and diffuse CMV syndrome. Pediatric recipients seem to be more sensitive to EBV infections (PTLD and acute lymphadenitis).

Distinctive infectious physiopathologic features occurring in this unique patient population are microbial overgrowth and translocation [94-97].

Bacterial overgrowth occurs when quantitative cultures counts of the stools and/or of the ileostomy discharge are greater than 10^9 CFU/mL. Bacterial overgrowth seems to be a common finding in the terminal ileum of intestinal allografts. Promoting factors for ileal bacterial overgrowth could be: surgical manipulation and surgical injury with resultant ischemia and lymphatic disruption; absence of the ileo-cecal valve; postoperative ileus; high dose steroids and heavy immunosuppression; suppressed gastric acid barrier; temporary intravenous nutrition and enteral defined formula diet.

Microbial (bacterial and/or fungal) translocation occurs when identical microorganism/s are found at the same time in the blood and in the intestinal lumen of the patient, without any evidence of other obvious sources of infection. Translocation most commonly arises during acute rejection episodes which immunologically damage the normal mucosal barrier of the intestinal allograft.

Therefore, the high incidence of systemic infections found in the InMvTx population can be related to impairment of the host defenses (heavy immunosuppression), microbial translocation secondary to loss of the mucosal barrier (surgical manipulation, harvesting/preservation injury, rejection), and microbial overgrowth.

In addition to daily infectious surveillance tests routinely performed in any transplant patient, infection monitoring of InMvTx recipients should include frequent cultures of the blood,

sputum, bronchial and alveolar secretions, urine, surgical wound exudate and drains' fluid. Most important are quantitative cultures of the stools and of the stomal discharge in order to monitor significant changes in the intestinal microflora and to confirm direct correlation between onset of systemic infectious episodes and simultaneously ongoing microbial overgrowth and translocation processes.

D.- Gastro-Intestinal Complications.

a) Assessment of graft status.

Initial baseline clinical evaluation of the anatomic and functional integrity of the intestinal graft starts intraoperatively on the operating table after graft reperfusion and before closure of the abdominal wall. Normal appearance consists of an uniform pink color of the transplanted intestine and mesentery, absence of edema or congestion as well as of pale or dusky discoloration, presence of occasional peristaltic waves. Both arterial and venous anastomoses are carefully inspected to rule out any tension, redundancy, kinking or twisting. Each of the gastro-intestinal anastomoses and enetrostomies is thoroughly examined for adequate blood supply, anastomostic strictures, patency and leakages.

Postoperative assessment of the intestinal allograft status is accomplished by using the same evaluation procedures and criteria employed to assess rejection and infection, as previously described. In addition to clinical, endoscopic, histologic and radiological evaluation, functional assessment of the intestinal graft is also attained by **intestinal absorption tests** (D-xylose and Vit.E absorption test, quantitative fecal fat excretion, FK-506 pharmacokynetics) [64,68,98,100], **gastro-intestinal motility studies** (barium and radionuclide gastric emptying time, intestinal transit time, gastro-intestinal manometry and myoelectric studies) [69,70,101], and recipient's **nutritional profile** (anthropometric measurements, biochemical markers of malnutrition).

In LvInTx and MvTx recipients, standard liver, pancreas and kidney function tests, along with bioptical/histological and radiological studies (US, CT/MRI scan, PTC/TTC, ERCP, radionuclide flow scans, etc) are used to monitor the anatomic and functional status of these allograft components, according to specific hepatic, pancreatic and renal transplant monitoring protocols, or whenever clinically indicated.

b) Gastro-intestinal complications.

1) gastro-intestinal bleeding: is always a threatening sign, which requires prompt diagnosis by endoscopy, histology and radiology, as well as immediate therapy. Rejection is the most common etiology.

2) gastro-intestinal anastomotic leakage: leakages from any of the gastro-intestinal anastomoses and enterostomies are usually due to poor wound healing, secondary to inadequate blood supply, infection, high dose steroids. This complication is more common in pediatric recipients. Overt severe septic syndrome is the usual clinical presentation. Diagnosis must be aggressively pursued and confirmed by radiological contrast studies and often by diagnostic laparotomy, which should always be performed whenever sepsis without evidence of any obvious source of infection occurs.

3) native gastric atony and pylorospasm: are common minor self-limiting complications which can cause early satiety, nausea and sometimes vomiting in the early postoperative course [70,101].

4) dismotility of the intestinal allograft: can occur either as hypermotility or as hypomotility/paralytic ileus syndromes [69,101]. These intestinal motility disorders can arise in the early postoperative course and persist in the late postoperative period, but usually tend to spontaneously resolve in the long term. Sudden changes in intestinal motitlity, particularly when associated with paralytic ileus, abdominal pain and distension, nausea and vomiting, should always prompt an aggressive search for acute intestinal rejection.

E.- Technical Complications.

a) Hemorragic complications.

1) intraoperative bleeding: is the major intraoperative life-threatening complication, related to many different (anatomo-pathological, surgical, patho-physiological, iatrogenic) etiologic determinants. Anatom0-pathological factors consist of extensive thrombosis of the splanchnic and IVC venous systems, resulting in severe portal hypertension. Portal hypertension can also result from liver cirrhosis secondary to TPN-induced end-stage cholestatic liver disease, or from Budd-Chiari syndrome. Intraoperative bleeding can be further aggravated by diffuse highly vascularized adhesions from multiple previous surgeries in face of cohexistent portal hypertension. In cLvInTx recipients, intraoperative bleeding is further exacerbated by hypersplenism with quali- and quantitative platelets dysfunction, by anhepatic phase, but mostly by liver disease related coagulopathy [106,108]. Hepatic coagulopathy results from decreased or inadequate synthesis of liver-derived pro-coagulant[30] and coagulation-inhibitor[31]factors; from reduced or absent hepatic clearance of coagulation activated factors and fibrinolytic enzymes, with resultant DIC, consumption coagulopathy and fibrinolysis; and from Vit. K deficiency, secondary to intestinal malabsorption and to loss of hepatic storage and metabolism sites due to hepatocellular failure. Temporary graft reperfusion coagulopathy, mediated by plasminogen activators from the graft[32] [107], along with some potential iatrogenic factors (dilutional coagulopathy, consumption coagulopathy secondary to excessive infusion of concentrated prothrombin complexes and fibrinogen, citrate intoxication) may be additional contributing factors to intraoperative bleeding. The challenging management of intraoperative bleeding is by accurate coagulation monitoring (TGE, coagulation profile), normalization of the global aspects of coagulopathy with transfusion of blood and blood products, autologous transfusion and intraoperative autogenous blood salvage with a "cell saver", veno-venous by-pass in composite grafts recipients, preoperative splanchnic arterial embolization in MvTx candidates. Hemo-substitutive therapy is addressed to mantain adequate O_2-carrying capacity, intravascular volume and blood coagulability by delivering to the patients a mixture of blood and blood products[33] with a rapid infusion system (RIS). In addition to blood transfusion therapy, specific blood products (platelets, FFP, cryoprecipitates) and drugs (ϵ-aminocaproic acid, protamine sulphate, heparin) are administered alone or in combination as needed, according to the patient's TEG and coagulation profile.

2) postoperative intra-abdominal bleeding: if coagulopathy has been properly corrected intraoperatively, postoperative intra-abdominal bleeding is most often technical, usually arising from vascular anastomoses or from extensively dissected raw peritoneal surfaces. Postoperative bleeding should be almost constantly considered surgical; its management is consequently by early exploration, evacuation of collected blood and clots, and surgical hemostasis.

b) Vascular complications.

1) arterial inflow thrombosis: is a fateful complication resulting in massive necrosis of the pertinent supplied organs. Clinical picture varies according to the different necrotic grafts or graft components, but most commonly consists of sudden clinical deterioration with acute septic syndrome and hepatic coma in cLvInTx and MvTx); intestinal stoma appears pale or dusky;

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[30] **Liver-derived coagulation factors:** fibrinoge, prothrombin, coagulation factors V, VII, IX, X, XI.

[31] **Liver-derived coagulation inhibitor factors:** protein C, protein S, antithrombin III

[32] **Plasminogen activators:** tPA (tissue plasminogen activator0, pUK (pro-urokinase), Hageman factor fragments.

[33] **Mixture of blood and blood products:** PRBC: 300 mLs (for oxygenation), FFP: 200 mLs (for coagulation factors), Plasmalyte: 250 mLs (for intravascular volume and hemodilution). Resulting values are: Ht = 27%, Fibrinogen = 130 mg%, Prothrombin = 0.59U/mL, Factor V = 0.21U/mL, Factor VII = 0.58U/mL, Factor VIII = 0.57U/mL.

hepatic function tests (mostly aminotransferases) are elevated. Diagnosis is usually obvious; it is confirmed by doppler ultrasound evaluation and/or by angiography. Prompt removal of the necrotic graft or graft component is the only therapeutic option. In ilnTx recipients, graft removal can be accomplished with a relatively good prognosis of patient recovery; conversely, in composite grafts the event is most constantly fatal.

2) venous outflow thrombosis: is less likely, since the SMV-PV axis is preserved in composite grafts; only ilnTx recipients have an outflow venous anastomosis which might potentially occlude (by kinking or twisting) or thrombose. Ascites and stomal congestion are pathognomonic signs; diagnosis is verified by doppler ultrasound examination. Treatment consists of graft removal.

3) stenosis of the arterial and venous anastomoses: in absence of rejection and infectious complications, a presumptive diagnosis is suspected on clinical, bioptic and laboratory evidence of graft dysfunction. Diagnostic confirmation is by angiography. Treatment consist of surgical correction of the anastomotic stricture if interventional radiology balloon dilatation fails.

c) Biliary complications.

May occur only in cLvlnTx recipients who require a Roux-en-Y choledocho-jejunostomy, since biliary tract continuity is maintained in ilnTx and MvTx recipients.

1) biliary leaks: technically defective biliary anastomosis and arterial thrombosis are the most common etiologies. Bile leaks are disclosed by bilious fluid discharge from the wound and/or from the abdominal drains, usually within 2 weeks after cLnlnTx, and/or by unexplained sepsis. Diagnosis is confirmed by CT scan and PTC. Treatment is by immediate surgical exploration and by revision of the bilio-enteric anastomosis. Biliary PTCD is not adequate because of immunosuppression which inhibits wound healing and suppress antiseptic immunity.

2) biliary obstruction: heralded by cholestatic and/or cholangitis syndromes, this is usually a late complication secondary to anastomotic stricture. PTC substantiates the diagnosis. Attempted and most costantly failed PTC balloon dilatations are usually followed by surgical correction or new reconstruction of the Roux-en-Y biliary anastomosis.

As of postoperative complications, in all case of sepsis of unexplained origin in any lnMvTx recipient, the basic general principle of radiologically exploring each of the surgical anastomoses (vascular, gastro-intestinal, biliary) by ultrasound, doppler-ultrasound, CT scan, angiography, barium contrast series, PTC, etc., is paramount and should always be promptly considered.

VII.- CLINICAL EXPERIENCE.-

A.- Patient Population.

At the Pittsburgh Transplantation Institute, during a three years period, from May 2, 1990 through April 15, 1993, 45 transplants (lnTx = 16, LvlnTx = 22, MvTx = 7) have been performed on 43 recipients. Two additional candidates for MvTx, who died intraoperatively from massive bleeding during preliminary intraabdominal dissection, have been excluded from the total number (n = 43) of the transplanted patients as well as from analysis. Two retransplants (lnTx = 1, LvTx = 1) have been included in the total number of grafts (n = 45).

Of the 43 transplanted patients, 22 were pediatric (mean age = 3.5 ± 3.7 years; range = 0.5-15.5 years), and 21 were adult (mean age = 33.3 ± 10.2 years; range = 19.1-58.0 years).

The male/female ratio was 1.05 (♂ = 22, ♀ = 21); 33 patients were caucasian, 4 hispanic-american, 4 afro-american, 1 native american, 1 oriental.

Preoperatively, all patients, except two candidates for MvTx, were on Total Parenteral Nutrition (TPN) since 1 to 132 months (mean = 40.9 ± 41.9 months); each of them experienced more than one episode of TPN-related complications.

Serum total bilirubin level averaged 11 ± 13 mg/dL in the total patient population (ilnTx = 1.0 ± 0.6 mg/dL; cLvlnTx = 19 ± 14 mg/dL; MvTx = 5.0 ± 9.0 mg/dL).

Out of the total number of 43 recipients, the first 30 patients received grafts without the colon (SBTx = 10; LvSBT = 17; MvTx = 3), while the last 13 had the colon included in continuity with the small bowel component of the InMvTx grafts (InTx = 5; LvInTx = 4; MvTx = 4).

The most common indication for iInTx was short gut syndrome secondary to Crohn's disease; perinatal intestinal complications with consequent long-term TPN-induced liver failure were the major indications for cLvInTx; congenital coagulation defects with consequent thrombosis of the celiac/mesenteric vascular bed were a common indication for MvTx.

As of November 1, 1993, the mean follow-up time considering the total patient population was 15 ± 10 months (iInTx = 14 ± 7; cLnInTx = 16 ± 12; MvTx = 11 ± 8)[34]. The following results refer to 45 InMvTx performed on 43 recipients, with a mean follow-up for the 30 current survivors of 17 ± 9 months (range = 6-39 months) [33].

A.- Mortality and Survival.

a) Recipient survival.

Out of 43 recipients, 13 (30.23%) died (iInTx = 4/15, 26.67%; cLvInTx = 8/21, 38.10%; MvTx = 1/7, 14.29%), while 30 (69.77%) are currently alive.

Actuarial survival curves for the 43 recipients at 3, 6, 12 and 24 months are respectively 88%, 84%. 81% and 74% (Fig. 2a).

Actuarial survival curves for the three different types of transplantation (Fig. 2b) are for iInTx, cLvInTx and MvTx respectively:

- at 3 months =	100%	81%	86%
- at 6 months =	93%	76%	86%
- at 12 months =	93%	71%	86%
- at 24 months =	83%	65%	86%

b) Causes of death.

Causes of death were usually multiple, but the primary etiologies were: infectious complications (n = 5; iInTx = 3, cLvInTx = 2), technical complications (n = 4; iInTx = 1, cLvInTx = 3), disseminated PTLD (n = 2; cLvInTx = 1, MvTx = 1), uncontrolled rejection (n = 1; cLvInTx = 1), chronic rejection (n = 1; cLvInTx = 1).

Six recipients died within or shortly after 3 months following surgery, while 7 more patients died about 1 year after transplantation.

The 4 patients who died after iInTx were adults: 3 died from septic complications following removal of the rejected graft; the fourth one died of respiratory failure with a functioning graft.

Conversely, 6 of the 8 deaths after cLvInTx were pediatric recipients: 3 of them died from sepsis secondary to technical complications (biliary and/or enteric leaks); 3 more succumbed to respiratory syncitial viral pneumonia, refractory acute rejection and disseminated PTLD. Hepato-renel failure combined with chronic rejection in one case, and disseminated coccidiomycosis contracted during a community epidemic in the other case, were responsible for 2 adult cLvInTx deaths.

In the MvTx series, one single death was caused by PTLD which was misdiagnosed as rejection, leading to wrong immunosuppression overtreatment.

c) Graft survival.

Estimated actuarial survival curves at 3, 6, 12 and 24 months for all the 45 grafts show values of 80%, 78%, 72% and 59% respectively Fig. 3a).

In the early postoperative period (3 months), iInTx presented the best survival figures (88%), compared to cLvInTx (73%) and MvTx (86%). However, by six months and during the subsequent late

[34] As of November 16, 1993, **18 additional transplants** have been performed, attaining a total number of 63 InMvTx (InTx = 23, LvInTx = 27, MvTx = 13) on 59 patients. Four retransplants (InTx = 1, LvInTx = 1, MvTx = 2) are included in the total number of InMvTx grafts (n = 63). The last 18 InMvTx cases have been excluded from the present analysis because of their too short follow-up.

postoperative period, MvTx showed the best graft survival (86%) compared to ilnTx (64%) and to cLvlnTx (62%) at 18 months after the transplant (Fig. 3b).

d) Causes of graft loss.

Out of the total number of 45 transplants, there were 16 cases of graft loss (ilnTx = 6, cLvlnTx = 9, MvTx = 1), of which 6 were secondary to graft removal (ilnTx = 5, cLvlnTx = 1, MvTx = 0), and 10 were due to patients death (ilnTx = 2, cLvlnTx = 7, MvTx = 1).

The major cause in each of the 6 cases of total graft removal was rejection, secondary to inadequate immunosuppression, which had been reduced for different reasons: drug non-compliance by the patient; reduced or discontinued immunosuppressive therapy because of intection (CMV enteritis, RSV pneumonia), neurotoxicity (neurological demyelination syndrome), diagnostic error and consequent immunosuppressive mismanagement.

Two cases of partial graft removal were also recorded: one case of total duodeno-pancreatectomy due to severe irreversible preservation injury of the pancreas in a MvTx adult recipient, and one case of total hepatectomy secondary to hepatic artery thrombosis in a cLvlnTx pediatricrecipient. The first case is still alive, while the second one, who had a liver replacement, died for sepsis in the early postoperative course.

B.- Rejection.

a) Acute cellular rejection.

Out of 45 grafts, 43 (95,56%) experienced rejection of the intestinal component, while only 12 (42,86%) of the 28 combined intestinal grafts including the liver[35] showed hepatic rejection.

The average frequence of rejection episodes per graft was 4.1 episodes/graft for the intestinal component, and 0.6 episodes/graft for the liver. The number of rejection episodes per graft was similar in each of the three types of lnMvTx.

Clinical diagnosis of rejection was done in 95% of cases, but it was histologically confirmed only in 72%. There was a higher incidence of histological diagnosis of rejection in ilnTx (93%) than in cLvlnTx (62%) and in MvTx (57%).

The mean postoperative time to the onset of the first rejection episode in the whole series was 19 ± 28 days (range = 3-138 days) after transplantation. The postoperative onset time for the first ACR episode was 11.7 ± 6 days for ilnTx, 22 ± 34 days for cLvMvTx, and 15 ± 7 days for MvTx. Rejection may also occur at a later time: about 50% of the lnMTx recipients experienced acute cellular rejection episodes more than three months after transplantation. This relatively high incidence of late rejection episodes is partly due to attempts to reduce immunosuppression, usually because of septic complications (opportunistic infections, CMV enteritis, PTLD) [89].

The severity of rejection episodes was usually mild to moderate.

Little more than half (51.11%) of the 45 grafts (n = 23: ilnTx = 10, cLvlnTx = 10, MvTx = 3) required one or more steroid recycles, and 18% (n = 8: ilnTx = 5, cLvlnTx = 1, MvTx = 2) required immunosuppression with OKT3 [89].

There was no statistically significant difference among the three transplantation groups as to incidence, frequency and severity of rejection episodes. Therefore, the presence of the transplanted liver as part of the graft apparently does not protect the other graft components from the immunological injury [5,56,67,108,110].

Out of the 13 grafts which included the colon, 5 (38.46%) showed histological evidence of colonic rejection. In multivisceral grafts including the stomach and the pancreas, there was no gastric rejection, but 2 episodes of acute pancreatitis have been recorded in one patient who responded to increased immunosuppression.

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[35] One case of MvTx whithout the liver has been excluded.

b) Chronic rejection.

Histopathology of full thickness sections of the 6 removed grafts (ilnTx = 5, cLvlnTx = 1) showed evidence of chronic rejection in 3 cases (ilnTx = 2, cLvlnTx = 1). Moreover, the recipient of a combined liver + intestine graft, who showed strong positive cross-match, developed chronic rejection in both organs [89].

c) Rejection and graft loss.

Eight (50%) out of the 16 grafts (ilnTx = 6, cLvlnTx = 9, MvTx = 1) which were lost because of graft removal (n = 6) or because of recipient's death (n = 10), showed histopatological evidence of acute rejection (n = 5), chronic rejection (n = 2), or both (n = 1); of these 8 removed rejected grafts 5 were ilnTx (in 4 recipients) and 3 were cLvlnTx (in 2 recipients).
Graft removal (n = 6) with or without subsequent retransplantation, usually did not avoid recipient's death: only 1 ilnTx recipient (16.67%) out of 6 patients (ilnTx = 5, cLvlnTx = 1) survived.

d) Graft-versus-host disease (GVHD).

GVHD was seen in one single case of pediatric cLvlnTx. In this recipient, immunosuppression was substantially reduced because of a Pneumocystis Carinii pneumonia and a concurrent enteric anastomotic fistula. Onset of GVHD occurred on the tenth day after transplantation, with a severe septic-like syndrome and an extensive skin rash.
Standard histological and immuno-histochemical techniques (karyotyping, in situ hybridization), which differentiate donor cells from recipient cells, showed infiltration and immunological injury by the donor immunocompetent cells against the skin cells of the recipient.

C.- Infections.

a) Bacterial infections.

114 episodes of bacterial infection occurred in 38 (88.37%) (ilnTx = 12, cLvlnTx = 20, MvTx = 6) of the 43 lnMvTx recipients. The highest incidence was in the cLvlnTx recipients (95.24%), compared to ilnTx (80%) and MvTx (85.71%).
The average frequency of relapsing infectious episodes per patient in the whole series was 3.1 episodes/patient (ilnTx = 1.8, cLvlnTx = 3.7, MvTx = 3.7).
These infectious episodes consisted in order of: line sepsis, pneumonitis, wound and abdominal cavity infections, UTI, colitis, arthritis and cryptogenic bacteremia.
The isolated bacterial agents were mainly enteric microorganisms (Enterococcus Fecalis, Enterococcus Fecium, Enterobacter Cloacae, Clostridium Difficile, Clostridium Perfrigens, Klebsiella, Acinetobacter Anitratus), coagulase-positive and -negative staphilococci and Streptococcus Viridans.

b) Fungal infections.

Mycotic infectious episodes by Torulopsis Glabrata, Candida Albicans, Trichoderma Koningii and Coccidiodes Immitis occurred in the paranasal sinuses, trachea, lungs, esophagus and peritoneal cavity in 19 (44,19%) (ilnTx = 6, cLvlnTx = 8, MvTx = 5) of the 43 lnMvTx recipients. The highest incidence was seen in MvTx recipients (71.43%), being significantly lower in the ilnTx (40%) and in the cLvlnTx (38.10%) recipients.
The average number of mycotic infectious episodes per patient was 1.2 episodes/patient in the whole lnMvTx series (ilnTx = 1.0, cLvlnTx = 1.3, MvTx = 1.2).

c) Viral infections.

1) CytoMegaloVirus (CMV) infections: "De novo" or reactivated CMV infectious episodes (n = 18) were seen in 16 (ilnTx = 9, cLvlnTx = 5, MvTx = 2) of the 43 lnMvTx recipients. The average incidence of CMV infection in the whole lnMvTx series was 37.21% (ilnTx = 60%, cLvlnTx = 23.815, MvTx = 28.57%0.

The mean number of CMV infectious episodes per patient was 1.5 episode/patient considering the whole InMvTx series (iInTx = 1.8, cLvInTx = 1.6, MvTx = 1.0).
The clinical-pathological picture included enteritis (n = 11), hepatitits (n = 2), pneumonitis (n = 2), gastritits (n = 1), retinitis (n = 1) and diffuse CMV syndrome (n = 1).
"De novo" CMV infections were seen in 10 CMV sero-negative patients who received CMV sero-positive grafts (iInTx = 8, cLvInTx = 1, MvTx = 1). No CMV infection occurred in CMV sero-negative recipients of CMV sero-negative grafts.
Reactivated CMV infections were recorded in the remaining 6 pretransplant CMV sero-positive patients (iInTx = 1, cLvInTx = 4, MvTx = 1), of which only 2 received CMV sero-positive grafts.
The average onset time for CMV infection was 72 ± 63 days after transplantation (range = 21-128 days).

2) Ebstein-Barr Virus (EBV) infections: Post-transplant lymphoprolipherative disease (PTLD) was histologically confirmed in 4 iInTx recipients (pediatric = 3, adult = 1) at 49, 252, 287 and 383 days after transplantation. PTLD was multifocal, involved both transplanted and native organs and resulted in 2 fatalities.
Acute EBV lymphadenitis occurred in 2 more recipients (1 pediatric cLvInTx, 1 adult MvTx). The adult recipient experienced at the same time a concomitant acute cellular rejection episode in addition to the severe EBV infection, which was successfully treated with a triple anti-viral therapy (Gancyclovir, Foscarnet, α-interferon) despite the increased immunosuppression, due to the simultaneous ongoing graft rejection.

3) Other viral infections: in addition to CMV and EBV infections, other viruses (adenovirus, influenza and para--influenza virus, respiratory syncytial virus, rotavirus and herpes symplex virus) occurred on 17 episodes in 12 pediatric recipients, who seem to be more susceptible than adults to viral infectious agents.

d) Microbial translocation and bacterial overgrowth.

In 11 recipients (iInTx = 4, cLvInTx = 7), 13 episodes of isolated or combined bacterial translocation (Enterococcus Fecalis, Enterococcus Fecium, Clostridium Perfrigens, Klebsiella, Enterobacter Cloacae, coagulase-negative staphilococci), and/or mycotic translocation (Candida Albicans, Torulopsis Glabrata), were reported. Each of these 11 patients recovered.
The median onset time for the translocation episodes was 98 days (range = 2-303 days) after tranpslantation.
Out of the 13 episodes of translocation, 10 (76.92%) were associated to intestinal allograft rejection, with endoscopic and histological evidence of pseudomembranes and submucosal microabscesses.

Bacterial overgrowth with quantitative microbial cultures counts of the terminal ileum greater than 10^9 CFU/ml occurred at least once in 90.70% of the InMvTx recipients, and in 34% of the quantitative stool cultures (n = 532). Identified micro-organisms were bacterial (92%; Gram + :28%, Gram-:6%, Gram + and Gram-:58%) and fungal (8%).

Composition and concentration of the small bowel flora, very similar among the three types of InMvTx, seem to be influenced by selective gut decontamination, rejection and CMV enteritis. With active selective gut decontamination in the early postoperative period, microbial counts $> 10^9$ CFU/ml occurred in 19% of the quantitative stool cultures, whose composition was 67% Gram + and 33% Gram-. After discontinuing gut decontamination in the late postoperative period, microbial counts $> 10^9$ CFU/ml increased up to 38%, with decreased concentration of Gram + and increased concentration of Gram- counts. With severe ACR or CMV enteritis episodes, the total count raised both for Gram + and Gram- bacteria.

D.- Graft Function.

a) Nutrition.

In all InMvTx recipients, TPN was discontinued 59 ± 49 days (range = 18-210 days) after transplantation, while tube feeding enteral nutrition was started 16 ± 11 days (range = 3-54 days)) after transplantation, with an overlapping time between the beginning of enteral feeding and the discontinuation of TPN of about 1 month. The commencement of enteral nutrition was tolerated by ilnTx recipient at a significantly earlier time (8 ± 4 days) than by cLvlnTx (20 ± 9 days) and MvTx (24 ± 18 days) patients.

Of the 29 surviving non-explanted recipients, 25 (86.21%) (ilnTx = 9/10, cLvlnTx = 12/13, MvTx = 4/6) are definitively off TPN and their nutritional support depends solely on their well functioning grafts. The remaining 4 recipients (13.79%) (ilnTx = 1, cLvlnTx = 1, MvTx = 2) still need intermittent partial parenteral nutrition because of CMV enteritis (n = 1), gastric atony secondary to relapse and progression of primary pseudo-obstruction syndrome (n = 1) and gastro-intestinal dismotility (n = 2).

All pediatric InMvTx recipients, with one exception, showed significant weight and height increase. Although 7 adults recipients (ilnTx = 1, cLvlnTx = 2, MvTx = 4) showed weight losses of between 3% and 27% of their pretransplant weight, current weight of all adult patients is within normal limits of their ideal calculated weight [103].

b) Absorption.

The results of Vitamin E absorption and fecal fat excretion tests showed moderate impairment in intestinal fat absorption. This was more evident in the early postoperative period, but could also continue for up to one year after transplantation.

In most of the investigated patients, the D-xylose absorption test showed delayed absorption (peak = 90 min) during the first 4 weeks after transplantation; however it tended to return to normal in the long term. D-xylose absorption test was also decreased and delayed in cases of moderate to severe rejection, CMV enteritis and severe preservation injury.

Pharmacokynetic studies of enterally administered FK-506, on the other hand, showed adequate drug absorption, which was already evident before the end of the fourth week after transplantation, and was able to maintain satisfactory therapeutic plasma levels.

c) Gastro-intestinal motility.

In 17 of the 20 investigated cases, gastric emptying time in the early postoperative period was moderately prolonged (> 3 hours) in 6 patients, and significantly delayed (> 6 hours) in the remaining 11 recipients. Administration of natcotics in the perioperative and early postoperative period may be a determining factor of such gastric hypoperistalsis. Later, gastric motility tended to spontaneously return to normal in each recipient, within 4-6 months after transplantation.

Mean radiological intestinal transit time for the transplanted bowel (4.1 ± 5.8 hours), was abnormal in 13 (61.90%) (ilnTx = 7, cLvlnTx = 4, MvTx = 2) of the 21 studied recipients: in 6 patients an accelerated intestinal transit time (0.5 ± 0.2 hours, range = 0.33-0.83 hours) was found, while in the reamaining 7 recipients it was significantly prolonged (9.4 ± 7.2 hours, range = 3.25-24 hours). Intestinal transit time also tends to spontaneously normalize in the long term.

Myoelectric intestinal activity was evaluated in 9 adult recipients by measuring the "migrating motor complex (MMC)" in the native and transplanted gastro-enteric tracts. There was abnormal antral motility with decreased amplitude and frequency of the contraction waves. MMC showed transmission of the peristaltic waves from the native to the transplanted intestine, although it was often uncoordinated. Propagation of the contraction waves seems to occur more easily in MvTx than in ilnTx and in cLvlnTx recipients [101].

E.- Hospitalization, Readmissions and Costs.

Compared to isolated solid organ (kidney, liver pancreas, heart, lung) transplantations, lnMvTx require longer initial posttransplant hospitalization as well as more frequent readmissions [111]. Te median initial hospital stay for the entire clinical series was 11 weeks (range = 3-45 weeks); there was no significant difference between adult and pediatric recipients. Conversely, MvTx recipients were hospitalized longer (16 ± 7 weeks) than cLvlnTx (12 ± 9 weeks) and ilnTx (11 ± 6 weeks) recipients.

Median ICU stay was 11 days (range = 2-300 days); for ilnTx recipients it was shorter (13 ± 18 days) than for cLvlnTx (36 ± 67 days) and MvTx (48 ± 39 days) recipients.

Following the initial discharge, all patients, except one, required one or more readmissions. The median number of readmissions per patient was 3 (range = 0-14). Adult recipients were readmitted more frequently and for a shorter time than pediatric patients. Readmission frequency for cLvlnTx recipients (5 ± 4) was higher than for MvTx (4 ± 4) and ilnTx (3 ± 3) recipients; ilnTx patients experienced the longest median duration per readmission (11.5 days).

The leading causes for readmissions were opportunistic infections (mainly line sepsis and CMV enteritis, but also EBV infections and PTLD), allograft rejection episodes and dehydration for increased stomal output or diarrhea without evidence of rejection or enteritis. Other readmission reasons were routine follo-up, stomal closure, central catheter replacement.

Adult recipients presented a higher readmission rate due to rejection and CMV infection; conversely pediatric recipients had more readmission due to line sepsis and dehydration. Recipients of ilnTx experienced more frequent readmissions for CMV enteritis; MvTx recipients for line sepsis and dehydration. Readmission rates for rejection and dehydration tend to decrease over time; conversely frequency of readmissions for infection does not decline in the long term.

At present, 26 (81.66%) out of the 29 currentlu surviving lnMvTx recipents, still retaining their graft, are at home and fully functional.

Long initial hospitalization and ICU stay, high frequency of readmissions, extended total hospitalization time emphasize how difficult, complex and demanding is the early as well as the late postoperative hospital course of lnMvTx recipients. The resultant cumulative outlay for cost of human and technological resources, time expenditure and financial burden is consequently impressive.

VIII.- CONCLUSIONS.

Intestinal transplantation is thought to be the ultimate therapeutic option for patients with irreversible end-stage intestinal failure and for those with intolerance to long-term TPN.

Although intestinal [3-4] and multivisceral [5-8] transplantation were among the first experimental transplant models, they were the last to be successfully engrafted in humans. The strong immunogenicity of the intestine, the high incidence of infections and the compromised functional status of the intestinal graft long after the transplant, still hinder clinical lnMvTx as an established definitive therapy. Recent advancements in surgical techniques, in preservation methods (University of Wisconsin solution) and mostly in immunosuppression (FK-506) have significantly improved both experimental and clinical results, but rejection, infection and lymphoprolipherative complications still are major hurdles to be taken. Although the short-term (< 12 months) results of the Pittsburgh large clinical series are promising, long-term outcome is hinting some limitations to the extensive clinical application of lnMvTx, the main problems still being the very complicated post-operative course with extended hospitalization and the high incidence of late immunological and infectious complications.

Clinical lnMvTx still remains a demanding and sometimes a frustrating procedure from a technical, pathophysiological and immunological point of view; it is still an "unfinished product" far away from being a completely developed and a perfectly defined clinical procedure; more experimental preclinical animal research is needed and recent clinical lnMvTx results must be thoroughly and critically evaluated. Nonetheless, from this perpective, by merging further experimental knowledge with clinical

experience, InMvTx is expected to become, hopefully in a near future, the ultimate therapeutic treatment for patients with irreversible intestinal failure.

InMvTx is indicated for patients with irreversible intestinal failure and for those requiring simultaneous intestinal transplantation as a complementary surgical step, needed to replace other failed life-saving intra-abdominal organs (liver, pancreas). However, while indications for cLvInTx and MvTx are well established for patients suffering of combined terminal hepatic and intestinal failure, indications for iInTx are conversely still questionable and must always be evaluated with careful critical discrimination. TPN in fact should be considered as the primary treatment for patients with end-stage intestinal failure alone, keeping iInTx as the ultimate alternative therapeutic option only for those patients with end-stage intestinal failure combined with high incidence of relapsing TPN-induced complications (frequent line-related sepsis, extensive venous thrombosis of the major central veins with severe problems or even exaustion of the central venous access sites for TPN cannulation).

Despite significant advances in the understanding of intestinal preservation injury, currently there is yet no agreement about the optimal perfusion and preservation methods (chemical composition of the perfusion medium: NSS, LR, extracellular fluids, UW solution, modified UW soilutions; role of several additives: heparin, fructose, allopurinol, naloxone, superoxide-dismutase; perfusion flow: continuous vs pulsatile; effects of intraluminal irrigation; etc).

Although the general surgical strategies and techniques for InMvTx are currently well established and almost ubiquitously accepted, some technical details are still questionable and under investigation. In human recipients, the real need to direct the venous mesenteric outfloww from the intestinal graft or the venous splanchnic outflow from the remaining native foregut organs into the recipient portal system as opposed to the recipient systemic circulation, has yet to be studied and evaluated, as well as the hemodynamic, hepatotrophic, metabolic and immunologic effects of this portal drainage.

Microbial overgrowth and translocation are distinctive infectious physiopathologic features occurring in this unique patient population. Bacterial overgrowth seems to be a common finding in the terminal ileum of intestinal allografts. Refinements in our surgical technique with preservation of the ileo-cecal valve and inclusion of the colon as part of the intestinal graft are attempts in order to minimize this morbid condition. Microbial (bacterial and/or fungal) translocation most commonly arises during acute rejection episodes which immunologically damage the normal mucosal barrier of the intestinal allograft. Therefore, the high incidence of systemic infections found in the InMvTx population can be related to impairment of the host defenses (high dose immunosuppression), microbial translocation secondary to loss of the mucosal barrier functions (surgical manipulation, harvesting/preservation injury, rejection), and microbial overgrowth. New methods to prevent and to treat infectious complication and to enhance the barrier functions of the intestinal mucosa against translocation of luminal pathogens and its toxins should be attained. In this perspective, new antibacterial agents (Synercid) more active against tne drug-resistant enteric flora (Vancomycin-resistant enterococcus), selective gut decontamination, early enteral (tube or oral) feeding, modified TPN formulas might play an important role. Still under investigation are the functions of several additives to enteral or parenteral nutrition formulas (glutamine, polyamines, short-chain fatty acids), which could present potential beneficial eutrophic effects on the intestinal mucosa and its barrier functions.

Compared to other solid organ allografts (heart, lung, liver, kidney, pancreas), intestinal allotransplants are more susceptible to rejection. Consequently, continuous heavy immunosuppression is needed in order to attain a perfect and constant immunological control of the intestinal graft, thus preserving the barrier functions of the enteric mucosa. However, the need of continuous, long-term, heavy immunosuppression is potentially self-defeating, as confirmed by the high incidence of non-enteric borne opportunistic infections and of post-transplant lymphoproliferative disease.

In spite of prolonged high-dose immunosuppression, the risk of rejection remains extremely high even long after transplantation, as proved by the fact that about 50% of the intestinal graft recipients in each of the three transplant groups experienced rejection far beyond 3-6 months after transplantation. Since in cLvInTx and MvTx the simultaneously transplanted liver apparently doesn't protect the

intestinal component of the composite graft from rejection, there is no clinical nor immunological indication to replace normal native livers in recipients of isolated intestinal grafts.
Immunological monitoring of the intestinal graft is of paramount importance to early diagnose and prevent rejection and to minimize its complications. Since standard histological monitoring has several disadvantages (sample errors, risk of intestinal bleeding and perforation, non-accessibility of some distal jejunal and proximal ileal segments), more early, sensitive and specific functional tests (electrophysiological parameters of the intestinal mucosa), biochemical/metabolic markers (serum N-acetyl-hexosaminidase NAH, brush-border maltase activity in mucosal biopsies), and immunological indicators (evaluation of donor/recipient chimerism, circulating lymphokines levels) are needed to promptly detect rejection episodes.

Future experimental and clinical research in the intestinal transplantation should be addressed to a better understanding and to a more effective prevention and treatment of acute and chronic rejection. The high incidence of acute cellular rejection, the almost constant, gradual progression to chronic rejection, the need for extended, continuous, heavy immunosuppression with its consequent sel-defeating infectious and lymphoproliferative complications, force upon the urgency for a new immunological treatment strategy with a better therapeutic index. This goal could be attained either by developing and using new improved (combinations of) immunosuppressive agents, by MHC matchcing, which might also open the new perspective of living-related intestinal transplantation, or by inducing and amplifying the naturally occurring phenomenon of systemic mixed allogeneic micro-chimerism, with concurrent gradual development of donor specific tolerance.
Starzl hypothesizes that the general basis of immunological acceptance (tolerance) of all kinds of transplants is systemic micro-chimerism. Systemic micro-chimerism is naturally accomplished by the ubiquitous bi-directional migration of "passenger leukocytes" of bone marrow origin from the graft into the recipient and vice-versa. In intestinal transplantation, donor migratory immunocytes ("passenger leukocytes") from the graft migrate ubiquitously into the recipient blood stream and tissues. Conversely, at the same time a gradual replacement of the donor hematolymphoid cells in the intestinal wall and mesenteric lymphnodes of the graft occurs, accomplished by migratory immunocompetent hematolymphoid cells from the recipient, which rearrange the immune system architecture of the intestinal mucosa [76]. Migration of bone-marrow derived dendritic and hematolymphoid immunocompetent cells may be associated with graft acceptance (donor specific tolerance) rather than rejection and/or GVHD, depending on the immunological substrate of the graft, donor/recipient histocompatibility, type and power of immunosuppression. Tolerogenic systemic micro-chimerism can be amplified by performing combined bone-marrow and intestinal transplantation from the same donor. Bone-marrow enhanced micro-chimerism might minimize and even cancel the recipient immunological reaction against graft antigens. With consequent lowered risk of intestinal allograft rejection, there is no more need for continuous heavy immunosuppression, and unrestricted immunosuppressive drug weaning could eventually be accomplished [16,77,80]. The above described tolerogenic therapeutic approach has been included in the new revised protocol for InMvTx at the Pittsburgh Transplantation Institute, and is currently under evaluation.

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FIGURE LEGENDS.

Figure 1a.- Isolated Intestine Transplantation (iInTx): SBTx (jejunum + ileum) (left insert), and InTx (small bowel + colon) (main figure). For explanation, see text.

Figure 1b.- Combined Liver and Intestine Transplantation (cLvInTx): LvSBTx (liver + small bowel) (left insert), and LvInTx (liver + small bowel + colon). For explanation see text.

Figure 1c.- Multivisceral Transplantation (MvTx): for explanation see text.

Figure 2a.- Patient survival curves (entire patient population of 43 recipients).

Figure 2b.- Patient survival curves (according to type of transplantation).

Figure 3a.- Graft survival curves (all 45 transplants including 2 retransplants).

Figure 3b.- Graft survival curves (according to type of transplantation).