MOTILITY AND ABSORPTION
IN THE
AUTOTRANSPLANTED CANINE JEJUNOILEUM

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To my parents

ABSTRACT

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Transplantation of the upper gut will soon become a clinical reality, yet little is known about the effects on enteric physiology. This study addresses relevant and complementary long-term objectives with respect to the physiology of the transplanted jejunoileum, particularly neural and humoral control of the upper gastrointestinal tract.

The study is divided into three parts:

1- Autotransplantation of the entire jejunoileum was used to assess the role of extrinsic and intrinsic innervation of the jejunoileum in the regulation of postprandial gastroduodenal motility by the autotransplanted jejunoileum.

Before transplantation, jejunal infusion of NaCl did not interrupt the characteristic interdigestive motor complex either in the

gastroduodenum or in the jejunoileum. However jejunal infusion of nutrients interrupted the migrating motor complex in the gastroduodenum and the jejunoileum for the duration of the infusion. After autotransplantation of the jejunoileum, the MMC continued to occur in the gastroduodenum and in the jejunoileum during the infusion of NaCl. Jejunal infusion of nutrients interrupted the MMC in both regions for the duration of the infusion. Because inhibition of the gastroduodenal and the jejunoileal MMC continued to occur during infusion of nutrients into the transplanted jejunum, it is concluded that jejunoileal regulation of postprandial inhibition of interdigestive motility in the stomach and duodenum is mediated by hormonal factors and does not require neural continuity.

2- Hormonal induction of the MMC by Motilin was studied in three groups of dogs. In group I which consisted of neurally intact control dogs, motilin induced a premature MMC which originated in the duodenum and migrated along the small intestine. In group II, where intrinsic neural continuity was interrupted, motilin induced a premature MMC which began simultaneously in the proximal duodenum and proximal jejunum. In group III, the autotransplantation group, motilin induced a

premature MMC in the duodenum but not in the jejunum; rather, a short, non-migrating burst of spike potentials occured simultaneously in all jejunal electrodes. These observations suggest that extrinsic innervation is necessary for motilin to induce Phase III activity in the jejunum. Extrinsic neural pathways appear to mediate motilin-induced MMC activity in the jejunum.

3- The effects of jejunoileal transplantation on jejunal absorptive functions were studied. A jejunal loop made from the autotransplanted jejunoileum was used. There were no differences between autotransplanted versus neurally intact jejunal loops in absorption (output of loop effluent) of H20, electrolytes, glucose, and folate or in transit at 2, 4 or 8 weeks postoperatively. Thus, autotransplantation does not decrease absorptive capacity or affect jejunal transit time.

These experiments are relevant to understanding the physiology of jejunoileal transplantation. Autotransplantation did not alter significantly the physiology of the upper gut. These findings are vital for the future clinical application of intestinal transplantation.

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CsA	Cyclosporin A
GVHD	Graft-Versus-Host Disease
HLA	Human Lymphocyte Antigen
MMC	Migrating Motor Complex
NEC	Necrotising Enterocolitis
NPY	Neuropeptide Y
PEG	Polyethylene Glycol
PIP	Porcine Ileal Peptide
PSP	Phenylsulfophtalein
SP	Substance P
TPN	Total Parenteral Nutrition
VIP	Vasoactive Intestinal Peptide

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CHAPTER I

GENERAL INTRODUCTION

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One could not approach the notion of transplantation without genuine humility, profound awe and utter bewilderment in the presence of the magnificent order and perfection that prevails in the entire creation and in each and every one of the creatures that populate the universe. In fact one becomes distinctly aware that the invisible Creator is using the visible hands of one of his creatures to put right what went wrong in the created order of things, with a view to protecting or prolonging life itself in one's fellow creatures.

Etymologically, Transplantation stems from two latin words "Trans" and "Plantare", meaning to plant across, i.e to remove and plant in another place.

In the book of Genesis 2:21-23 we read the account of the first transplant ever in the history of creation, a masterpiece, a remarkable feat that

surpasses all understanding and could only be performed by the Creator, the Master of our bodies Himself: "The creation of Eve", this is how it reads:

> "Immisit ergo Dominus Deus soporem in Adam; cumque obdormisset, tulit unam de costis ejus, et replevit carnem pro ea. Et aedificavit Dominus Deus costam, quam tulerat de Adam, in mulierem; et adduxit eam ad Adam. Dixitque Adam: 'Hoc nunc os ex ossibus meis, et caro de carne mea; haec vocabitur Virago, quoniam de viro sumpta est.'"

> "So the Lord God made the man fall into a deep sleep. And while he slept, He took one of his ribs, and enclosed it in flesh. The lord God built the rib he had taken from the man into a woman, and brought her to the man. The man exclaimed: 'This at last is bone from my bones and flesh from my flesh. This is to be called woman, for this was taken from man.'"

This account was written by man, many generations and civilisations ago, from his own

understanding, with his own abilities and limitations, in his own literary style, but....under the influence (inspiration) of the Creator's Spirit. In today's language it depicts a Transplant, a creative transplant though, performed by the Creator of the human race Himself.

It is undoubtedly the first case of Transplantation ever reported in the literature!

The study of the enteric physiology of the transplanted intestine is a new field. The rejection phenomenon and its control by immunosuppressive therapy have been studied extensively, however little has been written on the physiology of the transplanted small bowel. The object of this work was to study the physiology of the autotransplanted canine jejunoileum, including motility, regulation and absorption.

The history of transplantation in general and of intestinal transplantation in particular are reviewed and a background of the physiological changes after intestinal transplantation are discussed. The thesis includes three main

independent studies. The first deals with the effect of autotransplantation of the small intestine on the motility of the gastroduodenum. The second deals with the hormonal induction of the migrating motor complex in the autotransplanted jejunoileum, and the third deals with the net jejunal absorption of water, electrolytes, glucose, and folate in the autotransplanted jejunoileum, in the fasting and the postprandial states.

These experiments are relevant to understanding the physiology of jejunoileal transplantation and its clinical application in the not too distant future.

CHAPTER II

HISTORY OF TRANSPLANTATION

HISTORY OF TRANSPLANTATION

1- OVERALL REVIEW OF TISSUE TRANSPLANTATION

Introduction

The history of transplantation deserves mentioning as it is the start of modern clinical advance. The twentieth century has witnessed an explosion of discoveries in the knowledge of the human body and its pathophysiology, and transplantation has added a new chapter in exploration and clinical application for the benefit of the human race.

The history of transplantation is a tale of a science whose application could not be clearly predicted at the beginning of this century. It is the fruit of years of collaboration between clinicians and scientists contributing equally towards different parts of the puzzle. Public awareness and acceptance has extended the interest in that speciality. It is a fascinating story of

modern science which has and will change the outcome of numerous conditions.

The idea of grafting parts of the body from one person to another goes back many centuries. There is archeological evidence that teeth were transplanted in man in ancient Egypt, Greece, pre-Colombian North and South America, Rome and perhaps China. (Peer, LA, 1955). Transplantation of teeth was described by Arab writers around A.D. 1000, by Ambroise Pare in Paris in the sixteenth century, and by John Hunter in the eighteenth century.

The terms transplant and transplantation are used broadly in reference to any removal or partial detachment of a part of the body and its implantation into or onto the body of the same or a different individual. According to the genetic relationship between donor and recipient there are four classes of transplants: 1- autograft- donor and recipient are the same individual; 2- isograft- donor and recipient are genetically identical individuals of the same species; 3- allograft or homograft- donor and recipient are genetically dissimilar individuals of the same species; and 4- xenograft or heterograft- donor and recipient are

individuals of different species.

According to the site of implantation, transplants are orthotopic if surrounded by the same kind of tissues or located in the same part of the body after transplantation as before; otherwise they are heterotopic.

During the early years of this century it has been definitely established that autotransplantations were practically always successful, that homotransplantations, although excellent to start with, were nearly always ultimately unsuccessful, anti-immune therapy being unknown at that time, and heteroplastic transplantations were always unsuccessful.

Autotransplantation of the kidney was performed with success by Alexis Carrel (1908). At the Rockefeller Institute, both kidneys of a dog were extirpated and one kidney was replanted. It was found that in most cases the dog remained in good health. Pathological examination of the transplanted kidney showed it to be entirely normal. The complete interruption of its circulation for few minutes and the suture of its vessels and ureter did not interfere with its functions. From a surgical point

of view the grafting of the organ was a possibility.

Homotransplantation using the same technique gave different results. During the first days following the operation, the dogs which had undergone a transplantation of one kidney from another dog were in the same condition as dogs which had undergone an autotransplantation. After six or seven days the results were different, the kidneys became congested. After twenty five or thirty days and more there was a great deal of albumin in the urine and even haematuria. After seven or eight months the kidneys were found to be sclerotic. In several sites of the organ there were leucocyte infiltrations. Carrel sensed that something was causing the damage but he did not call it rejection. The concept of rejection was there, if not the modern term. (Carrel A, 1908).

After homotransplantation of the thigh or the scalp of the animal it was found that in a few cases the reaction of the organism against the organ did not take place. In one case of transplantation of the scalp and ear and in two cases of transplantation of the leg the member did not become swollen, and after more than twenty days the new parts which had healed by first intention were in

such a condition that it was impossible to believe that they were not the real property of the animal. The explanation of this phenomenon was almost certainly the HLA compatibility which was unknown at that time.

Alexis Carrel in his address to the International Surgical Association in 1914 (Carrel A, 1914) already predicted that the surgical side of the transplantation of organs was "complete" as it was technically possible to perform transplantations of organs with perfect ease and with excellent results, but these methods could not be applied to human surgery for the reason that homotransplantations were almost always unsuccessful because of organ failure following transplantation. Carrel was the first to recognise that blood vessel anastomosis was required in order to move major vascularized organs such as the kidney in the same animal or from one animal to another. His simple method of vascular anastomosis using fine needles and thread has been used ever since 1902, with few modifications. (Carrel A, 1902). It depends on careful dissection, exact identification of the several layers of the vessels to be joined, control of the bleeding from both ends, and sewing them together in a manner that everts the intima.

Other workers in Europe and the new world were performing similar work between 1900 and 1930. In almost all experiments, kidneys were used because of their simple vascular supply, the presence of the ureter, which gives a measure of function within minutes and the fact that it is a paired organ, allowing survival of the animal in case of failure of the graft.

2- CONCEPT OF REJECTION AND CLINICAL IMMUNO-SUPPRESSION

In 1951 David Hume at the Peter Bent Brigham Hospital in Boston started grafting kidneys from one subject to another. The recipients were patients in far-advanced, irreversible chronic uraemia. Donor kidneys were obtained during surgical procedures and from cadavers. The transplanted kidneys were placed in the recipient's thigh, with anastomosis of renal artery to the profunda and renal vein to the common femoral vein. Experiments showed that while the kidney was ultimately rejected, function was good for several weeks (1952).

It was soon realised that the loss of the

grafted organ was due to a process quite distinct from infarction, avascular necrosis, infection or inflammation. The term Rejection indicated a process "by which the new host was refusing to grant the right of abode to the transplanted organ".

Emile Holman, a surgeon at Johns Hopkins, carried out in 1921 a skin graft from a mother onto a badly burned child. When some days later, he put more skin on the child, the child not only rejected the mother's skin but in addition developed a severe necrotising inflammation exfoliative dermatitis of his own skin. This suggested shared antigens and the development of an autoimmune disease as the cause of the necrotising dermatitis. Three months after the first appearance of the dermatitis, all the original grafts, deeply imbedded in granulation tissue, were curretted away. Within ten days there was a tremendous improvement in the general condition and the exfoliative dermatitis disappeared. Holman saw the remarkable implication of this experiment but was unable to pursue it further. (Holman E, 1924).

a- THE SECOND SET RESPONSE

During the World War II the British Medical Research Council focused on the problem of skin

grafting. They asked Dr. Peter Medawar to work with a plastic surgeon, Mr. Thomas Gibson, in Glasgow to attempt to perfect skin grafting in man and to investigate the use of skin from donors.

Dr. Medawar soon observed that he could rely on one uniform laboratory finding. If an initial skin graft from Animal A was placed on Animal B, it survived for about 7 days. Then if a second set of skin was applied in exactly the same fashion between the same two animals, the second set of skin underwent a highly accelerated rejection, in about half that period of time. This was therefore called the "second set response". Its historic importance in transplantation science, histocompatibility, and immunogenetics can scarcely be overemphasised. (Medawar PB, 1945). Dr. Medawar proceeded to unravel many aspects of tissue immunology using the second set response as endpoint, and his contribution well deserved the Nobel Prize.

Since 1962, all transplantation of tissues between unrelated individuals have been performed under the cover of a chemical agent to suppress the immune response of the patient to the graft. Many investigators in the meantime have been studying whole-body irradiation as a means of

immunosuppression, irradiation of the whole graft itself, and the use of drugs as nitrogen mustard. (Moore FD, 1964). The breakthrough came when Schwartz and Dameshek of Tufts University made observations on the effect of 6-mercaptopurine on xenogeneic solute protein antigen. (1959). They used a laboratory model in which the antigen was bovine or human serum albumin given either to a rat or a hamster. By radioactive tagging of the albumin, it was possible to study its disappearance curve. Without immunosuppression, it very rapidly disappeared from the circulation, removed by circulating antibody, but when they gave the animals 6-mercaptopurine, the foreign protein had a normal half-life in the body fluids of the recipient. 6-mercaptopurine completely blocked the primary immune response to the solute protein antigen.

Professor Calne was then a young surgeon doing postgraduate surgical research in London. He applied 6-mercaptopurine to the kidney graft model. Within weeks of these first trials, it was evident that an entirely new era of experimental kidney transplantation had begun. Keen to pursue this work and collaborate with other transplant researchers, Mr. Calne went to the United States. He worked with Murray and his group at the Peter Bent Brigham

Hospital and the Harvard Medical School. (Calne RY, 1974). Soon a derivative of 6-mercaptopurine was found and was called Imuran. The results with Imuran were better than those with 6-mercaptopurine, the toxicity was less marked and prolonged kidney graft acceptance in the dog was evident. Amongst the first patients operated upon with immunosuppressive chemotherapy was a patient whose course after operation was smooth and who survived for a long period of time. (Murray JE, 1963). Between 1965 and 1975, kidney transplantation became a widespread practice for the treatment of renal failure.

b- IMMUNOLOGICAL SELECTION

Two genetic systems are of major importance in human organ transplantation: HLA on Chromosome 6 and ABO on Chromosome 9.

1- TISSUE TYPING

The discovery of tissue-typing is traceable to the work of Professor Dausset in Paris (Dausset J, 1969) (Rapaport FT, 1970). He showed that human lymphocytes had characteristic antigens designated as Human Lymphocyte Antigen (HLA). Finding the tissue type of donor and recipient enabled us to

understand how closely related two siblings or cousins, parent and child, really were, or how antigenically similar two unrelated individuals were. It was later shown that these tissue typed antigens had specific locations on the genome. The HLA locus is on chromosome 6 and is divided into several regions and subregions. Molecules coded for by HLA-A, -B and -C region genes are termed class I molecules and are present on all nucleated cells. In contrast, molecules coded for by HLA-D region genes (includes the HLA-DP, -DQ and -DR subregions) are termed class II molecules and are present on B cells, macrophages and dentritic reticular cells, and, under some conditions, on intestinal epithelial cells and other cell types. Matching, particularly for the combination of HLA-A, -B, and -DR, seems to correlate with graft success. In more than 8000 first cadaver transplants, very well matched grafts for DR and HLA-B (zero antigen incompatibility) had a 20% better graft survival than poorly matched grafts. (Opelz G, 1985). There was a highly significant influence of immunologic factors on graft outcome even in CsA treated patients. HLA matching and CsA treatment had additive effects.

2- ABO BLOOD GROUP

A better understanding of the quantitative and qualitative aspects of the molecular structure of A,B blood group determinants could facilitate transplantation across the ABO barrier. (Breimer ME, 1985). Donor-recipient ABO compatibility is an absolute requirement. (Hume DM, 1968). ABO antigens are on cells other than erythrocytes, and a graft must not contain either A or B antigens that are absent on the recipient. The exact role of other red cell antigens in graft rejection is unclear, however incompatibility for these antigens, seems to be adequately controlled by immunosuppressive drugs.

c- GRAFT-VERSUS-HOST DISEASE *

In Graft-versus-host disease (GVHD), donor lymphoid cells damage host tissue. This occurs when there is an immunodeficient host, an immunocompetent graft, and histoincompatibility between the graft and the host. Lymphocytes in the graft recognize the host as foreign. The process is mediated by T lymphocytes which secrete lymphokines. These soluble mediators can cause direct cell injury and may also act by involving other cell types, such as polymorphs and macrophages, in augmenting the immune reaction. The major factor determining the severity of the GVHD is the degree of disparity in

* The bone marrow and intestine contain many immunologically competent cells and an obvious complication is GVHD.

histocompatibility. GVHD is classified as acute or chronic. (McDonald GB, 1986). In acute GVHD, any region of the intestinal tract can be affected, but disease is often most severe in the distal small intestine, caecum, and ascending colon. Typically, acute disease occurs within two weeks to two months of the transfer of the allogenic lymphoid cells. (McDonald GB, 1986). Patients may experience large volume watery diarrhea and lower abdominal pain with or without upper gastrointestinal symptoms. Stool exam usually reveals faecal leukocytes, occult blood, and considerable cellular debris. Other early manifestations of acute GVHD can include skin (maculopapular rash) and liver disease (cholestatic jaundice). Chronic GVHD develops between 3 and 12 months. Intestinal symptoms in chronic GVHD differ markedly from those in acute GVHD. Small intestinal symptoms are not a major component of the syndrome. Chronic liver disease, skin changes (pigmentation, contractures, scleroderma), oral and occular sicca, oesophagitis, polyserositis, are seen in the vast majority of patients with chronic GVHD. (Shulman HM, 1984). Most patients with chronic GVHD have had preceding acute GVHD which has resolved or evolved into chronic GVHD. However, 20 to 30% will have a de novo, late onset of chronic GVHD without acute GVHD. The outcome is excellent in patients with the GVHD

limited to the skin and liver, but poor in patients with involvement of other organs. (McDonald GB, 1986).

3- EARLY CLINICAL EXPERIENCES

a- KIDNEY TRANSPLANTATION

During the early 1950s, several patients underwent renal transplantation in Paris and Boston; these all ultimately failed as immunosuppression was not used.

1954 was an important milestone year in the history of transplantation, a kidney transplant was carried out by Dr. Joseph Murray from a healthy twin to a sick identical twin. Function was excellent and there was prolonged survival. (Merrill JP, 1956). Murray's operation was soon to be repeated and has reached many hundreds of twin pairs worldwide. The twin experience presented a very simple and clear message: With the immunogenic barrier overcome, a transplanted kidney could give new life to a dying patient. The long-term success of renal transplants between monozygotic twins was followed by a great increase in clinical studies with renal allografts. It is interesting to note that Joseph Murray was

awarded the Nobel Prize in Medicine in October 1990, for the advances in transplantation he has made since his first successful transplant.

In 1959 Murray in Boston and Hamburger in Paris, each performed a renal allograft using nonidentical twins as donor and recipient as donor and recipient. The recipient was immunosuppressed with total-body irradiation. (Moore FD, 1964). As immediate and long-term success was observed in these two cases, there were numerous further reports of the use of living related donors and immunosuppressed recipients.

Successful use of haemodialysis to substitute for renal function temporarily during a period of acute renal failure was developed by Willem Kolff in the Netherlands during World War II. His first dialysis machine was made using sausage casing and some tomato cans. He later developed an apparatus consisting of a large horizontal cylinder revolving with its undermost segment in a tank of rinsing liquid. (Kolff WJ, 1944). All his dialysis patients died. As he said, "it was a good thing the boss was away"!. Following World War II, Kolff gave his apparatus to several countries and institutions for further experimentation and work.

It was George Thorn, at Harvard, who made dialysis a part of a standard therapy in the United States using a Kolff-type artificial kidney. (Merrill JP, 1950). With dialysis came a renewed focus on the kidneys. A patient could be maintained as long as necessary until a kidney for grafting became available.

b- LIVER TRANSPLANTATION

Modern concepts of transplantation of the liver were first explored by Welch, who experimented ectopic transplants of the liver in a different site in the abdomen. (Welch CS, 1955). Moore in Boston (1959), and Starzl in Chicago (1964) reported on animal experiments on orthotopic liver transplantation. When immunosuppressive chemotherapy became available, clinical transplantation of the liver was attempted. Calne became Professor of Surgery in Cambridge and continued to work very actively from 1965 onward. By 1975, transplantation of the liver was reported from two centers (Starzl in Denver and Calne in Cambridge). With the advent of Cyclosporin the operation became much more widespread.

Cyclosporin was a new drug, a small cyclic peptide, fungus metabolite (Trichoderma polysporum and Cylindrocarpum lucidum) introduced by Borel and associates (1977) in Switzerland. Cyclosporin binds to a specific cell protein called cyclophlin. Organs such as the kidney and liver have a high concentration of cyclophlin (Handschumacher RE, 1984). Transplantation of the liver has only recently received acceptance as a standard therapy. The results have improved with the 4-year graft survival in paediatric liver transplant recipients approximating 75%.(Shaw BW, 1985). It has been thought until only recently that the operation will never be as widely done as kidney transplantation because of the fact that the liver is not a paired organ and that cadaver donors must be used, however partial liver transplantations from live donors (family members) have been performed successfully with promising results. (Starzl in Pittsburg, PA 1989).

c- THE HEART

It was in 1967 that Barnard in South Africa carried out cardiac transplantation. (Barnard CN, 1982). Unlike the liver, the vascular arrangements of the heart are reasonably simple and involve large

vessels whose anastomosis do not present the challenge of small size. Open heart surgery has progressed in such spectacular fashion with the use of the pump-oxygenator that immunosuppressive methods learned from the kidney were entirely applicable to the heart. By 1980, various efforts to develop an artificial heart had been made, and by 1982 the artificial heart could be used in a widely publicised patient in Salt Lake City under the general guidance of Dr. Kolff, the man who developed the artificial kidney 40 years earlier. (De Vries WC, 1984).

The recent increase in the number of cardiac transplantations has been paralleled by a marked improvement in the one-year graft survival and the expansion of cardiac transplantation includes older patients. (Szentpetery S. 1987).

d- OTHER ORGAN TRANSPLANTATION

Transplantation of the lung has been the natural outgrowth of experience with the heart. Transplantation of both lungs is surgically no less complex than transplantation of a single lung. Hardy reported the first human pulmonary allograft. (1963).

Pancreatic transplantation for Diabetes Mellitus was first suggested by Ssobolew (1902). The first clinical pancreas transplantation was performed in 1966 at the University of Minnesota. (Kelly WD). Sutherland and Najarian at the same institution have carried forward the studies of pancreatic transplantation very aggressively, working both with islet cell and whole-organ transplants, and have reported encouraging results. (Sutherland ER, 1984). While transplantation of pancreatic islets has been uniformly unsuccessful, transplantation of the whole pancreas has been performed with reasonable success in many patients. The technique of implanting the pancreatic exocrine drainage into the bladder (pancreaticocystostomy) using a cuff of duodenum around the ampulla of Vater is a major technical improvement and has improved the survival rate of whole pancreatic grafts. (Sollinger HW, 1985, 1987). This drainage procedure is associated with fewer surgical complications than enteric drainage, and urinary amylase levels are a very useful indicators for the detection of early rejection episodes.

Transplantation of Bone Marrow is not a complicated procedure, simple aspiration and

reinjection are often sufficient. Its utility is greatest in patients suffering from bone marrow destruction as in certain forms of chemical toxicity and aplastic anaemia, or where bone marrow destruction is an essential aspect of tumor chemotherapy, as in some of the leukaemias. Since the marrow contains many immunologically competent cells, an obvious complication is GVHD, which can be of great severity. Peripheral blood monocytes have now been successfully used as stem cells in place of bone marrow to treat dogs with spontaneous lymphoma. This may widen the application of this approach in human patients. (Appelbaum FR, 1986).

During the period of 1925 to 1945 corneal transplantation emerged as a widespread and generally accepted therapeutic practice.

Nerve autotransplants are used to bridge defects in important motor nerves. It has been nearly a hundred years since it was demonstrated that a nerve autograft was capable of conducting impulses across a nerve defect. (Simmons RL, 1979).

4- ADVANCES IN TRANSPLANTATION

During the mid-1970s, there was relatively

little progress in transplantation. The clinical results in transplantation had not improved and in fact were deteriorating. However, more recently progress that has been made offers great promise in clinical transplantation.

The utilisation of donor-specific transfusions with living-related donors is one of the most important advances in clinical transplantation because it demonstrates that biological manipulation of the human adult was not only possible but could predictably improve graft survival. (Bowen PA, 1985). The recipient is transfused with the donor's blood prior to transplantation. The application of this technique is limited because of the relatively small and decreasing role of living-related donors in transplantation.

Monoclonal antibodies are being used to treat acute rejection episodes in renal transplantation. OKT3, a murine monoclonal antibody was highly effective in efficiently reversing acute cadaver kidney allograft rejection in a multicenter randomised study. (Kreis H, 1985). It reacts with human medullary thymocytes and all mature T Cells and blocks T Cell-mediated cytotoxicity directed at

antigens associated with HLA products.

An experimental anti-rejection drug, called FK506 was recently introduced (Hoffman AL, 1990, Thomson AW, 1990). It is a powerful new immunosuppressive agent that is synergistic with cyclosporin and which allows long term survival of recipients of cardiac, renal and hepatic allograft. The fact that FK506 and CsA are synergistic in their action as immunosuppressive agents prove to be clinically important since complimentary therapeutic effects may avoid much of the toxicity associated with the use of each agent independently.

5- DONOR PROCUREMENT AND ORGAN PRESERVATION

Grafting from the dead cannot hurt the donor but there are many difficulties in utilising organs from cadavers, the most delicate being goodwill in the community and the ethical problems surrounding the subject.

On the other hand, the major operation of removing a kidney from a family donor is not without risk. While only a very few, there have been donor deaths. The injury of one person to help the other is not new to medicine and surgery, as witness death

in childbirth or the widespread use of blood transfusion, but to remove an organ from one person to help another was a new concept. The procurement of a suitable number of viable cadaver organs has been a problem for organ banks. There is need for better public understanding of the fact that traumatic deaths in young people are the very ones that offer the greatest hope of salvage of others. Newspapers, magazines, radio, television and advertising could help the public to understand their own key role in the distribution of scarce but precious human resources.

Kidney preservation is adequate for the current clinical needs, however heart, pancreas and liver preservation is not optimal for the most efficient transplantation of these organs. The current methods of renal preservation by pump perfusion or cold storage, are reasonably comparable in terms of graft results. The capability of preserving the liver, lung, kidney, heart and intestine, for unknown reasons, differ. There is now evidence that hormonal depletion of the donor contributes to poor organ quality and that the administration to the donor of a combination of insulin, cortisol, and Triiodothyronine T3 improves the function of transplanted hearts and kidneys.

(Novitzky D, 1986). These new findings could improve the long-term preservation of organs, thus improving the possibility of transplanting sensitised patients and increasing the feasibility of successful immunologic manipulation of recipients of cadaveric grafts.

There continues to be great expansion of information on transplantation which is improving current graft survival. The side effects and the complications of immunosuppresive agents could be minimised, opening the door for an even wider clinical application of transplantation.

Success with renal, heart, liver and pancreas transplantation leads to the developing of techniques for small intestinal transplantation which is an alternative to total parenteral nutrition and the complications of the short bowel syndrome.

CHAPTER III

INTESTINAL TRANSPLANTATION

INTESTINAL TRANSPLANTATION

1- EXPERIMENTAL INTESTINAL TRANSPLANTATION

Organ transplantation as a feasible clinical discipline has related mainly to renal, cardiac, hepatic, pulmonary and pancreatic homotransplantation.

It was in 1959 that experimental small intestinal transplantation was attempted by Lillehei and associates at the University of Minnesota. (1959). Their interest in this concept was the result of their work on the relationship between irreversible shock and intestinal ischaemia. They were stimulated to inquire into the ability of small intestine to withstand varying degrees of ischaemia at varying temperatures, and the development of successful techniques of transplanting the intestine. Their efforts were directed at finding the maximum time that the small intestine of the dog could suffer partial or complete interruption of the circulation and still recover once normal

circulation was resumed.

It was apparent from these studies that the small bowel of the dog surprisingly could recover successfully from a period of total ischaemia, especially if hypothermia was instituted to 5 C. Almost all dogs survived a five hour period of complete circulatory arrest. These studies showed that the anatomic arrangement of the superior mesenteric artery and vein was such that the entire small bowel could be removed, with the exception of a few centimeters of duodenum, preserving its vasculature in such a way that a single arterial and venous anastomosis would completely revascularise the bowel. After surgery, dogs with intestinal autografts developed severe diarrhea and steatorrhea during the first week. After three weeks an essentially normal appetite returned, and the dogs began to gain weight. By four to six weeks the stools of these dogs appeared normal. Lymphatic regeneration in the autotransplanted bowel was confirmed by reexploration of selected survivors at intervals of five to six weeks postoperatively. Sky blue dye, injected into autografted mesenteric lymph nodes, could be visualised within minutes of injection in the thoracic duct and lymphatic channels around the portal vein. Injected radiopaque

Renografin could be observed radiologically in the thoracic duct.

Kocandrle and colleagues (1966) confirmed these observations in dogs with intestinal allografts; fully regenerated intestinal lymphatics were demonstrated at the end of the fourth postoperative week. Normal sized channels delivered the lymph from the transplanted intestine into the thoracic duct.

Alican and Hardy (1971) demonstrated complete intestinal lymphatic regeneration from five months to a year postoperatively. Biopsies of the intestinal wall of these long-term autografts revealed normal histology.

It was quickly realised, that Lillehei's model could have great implications in the treatment of patients suffering from the short bowel syndrome.

Allotransplantation of the small intestine without immunosuppression invariably resulted in the death of the recipient, usually by the eighth postoperative day. (Goott B, 1959). Operating simultaneously on two dogs, Lillehei and associates removed the jejunum and the ileum of each animal and

immediately exchanged them with those of the other dog. Circulation of the allograft was restored by anastomosing the superior mesenteric artery and vein of the graft to the same vessels in the host. Gastrointestinal continuity was restored by anastomosis of the duodenum and terminal ileum of the host to the proximal and distal ends of the allograft respectively. Initially the allografted dogs followed an identical course to that previously seen in autografted dogs. Death before the sixth operative day was originally attributed solely to GVHD with profound metabolic disturbance in the host, because of the relatively normal growth and histologic appearance of the bowel. Hypertrophy of the mesenteric lymph nodes in the allograft further substantiated this hypothesis. The sites of vascular anastomoses were patent and healing of the intestinal anastomoses had proceeded normally. The characteristic picture of classic homograft rejection was not evident. (Manax WG, 1966).

Later experiments disclosed that both graft rejection and GVHD occured in small intestinal transplantation.

The small bowel is unique among vascularized organs in that it is rich in lymphoid tissue in the

form of mucosal/submucosal lymphocytes, Peyer's patches, and mesenteric lymph nodes. The presence of lymphoid tissue in the graft has two potentially negative consequences. It can increase the immunogenicity of the graft and the cells in the graft have the potential to induce GVHD. The length of the graft and its content of lymphoid tissue transplanted determine the dominant reaction.

Short intestinal segments, 10 to 15cm, were allografted into the neck of host dogs to allow frequent observation and biopsies of the graft. One week after surgery the allografted ileum became cyanotic, despite patent vascular anastomoses, biopsies showing the typical mononuclear and polynuclear cellular infiltration of the ileum signalling prompt and definite rejection. On the other hand, grafting of long segments with massive antibody and antigen potential caused mainly GVHD. (Lillehei RC, 1966).

Several investigators observed signs of GVHD after canine small bowel transplantation (Lillehei RC, 1967)(Cohen B, 1976), whereas no GVHD could be demonstrated after small bowel transplantation in the pig model (Hay JM, 1974)(Stauffer UG, 1978), and even recent reports give only an indistinct

description of GVHD in small bowel transplantation. Schraut (1986) compared the signs and symptoms of GVHD and transplant rejection, and found that most of the clinical signs and symptoms are similar (dermatitis, diarrhea, lymphadenopathy, and fever) except for the splenomegaly which is a feature only seen with GVHD. He concluded that the predominant reaction in animals in whom a total intestinal transplant has been performed is allograft rejection. Lear and colleagues (1989) have shown that GVHD and rejection can coexist and that a two-way traffic of lymphoid cells develops very rapidly after small bowel transplantation.

2- CONTROL OF ALLOGRAFT REJECTION

Attempts at overcoming rejection and GVHD with conventional immunosuppressive regimens proved more difficult than for the kidney or the heart. (Hardy MA, 1970). Antilymphocytic serum, prednisone, azathioprine, and several other immunosuppressive drugs were administered alone or in combination to dogs with short cervical jejunal allografts. Survival could be increased to a mean of 25 days. (Preston WF, 1966). Short intra-abdominal intestinal grafts were also used, with restoration of continuity and had an average survival of 59 days.

Low dose graft irradiation alone was shown to prolong survival in a canine small bowel allograft model. Excessive intestinal damage was produced by 2500 rads, but 750 and 1500 rads produced no detectable acute or chronic damage in dogs observed from 100 days to years. Histologic evidence of GVHD appeared in the native small intestine in dogs receiving a non-irradiated graft but in none of the dogs receiving irradiated grafts. It was postulated that a balance was struck between the allograft rejection reaction and graft-versus-host disease in the low-dose irradiation group, resulting in prolonged survival. (Williams, 1988).

Quint (1968) has assessed the function of short cervical intestinal autografts and allografts by daily measuring radioactivity in systemic blood following intraluminal infusion of the graft with 14 C d-glucose. In dogs with and without treatment with immunosuppressive drugs, impending rejection could be predicted by cessation of active transport of 14 C d-glucose, which occured concomitantly with destruction of villi and necrosis of the graft stroma. The initial absorption values of 14 C d-glucose in autografted and allografted short

intestinal segments were the same. These results, however, were not compared with normal control loops of the same length. Similar studies have been carried out in dogs with entire small intestine allografts in the orthotopic position. (Ruiz JO, 1972). These dogs showed an immediate, and considerable impairment in the ability of the allograft to absorb d-xylose. These changes were not statistically different from those seen in dogs with intestinal autografts or intestinal denervation, with or without administration of immunosuppressive drugs.

Crane and colleagues (1988), using a technique for microvascular imaging in small bowel transplantation, found a reduction in vascularity in the host intestine in the GVHD model. The quantitative evaluation of vascular changes in the graft and the host would provide a means for evaluating the effectiveness of protocols for the treatment of rejection and GVHD and may improve the understanding of the role of each process in the response to a small bowel allograft.

The immediate impairment of any intestinal graft function was thought to be primarily due to denervation. Immediate impairment in absorption of

an intestinal allograft is unlike transplantation of other organs such as kidney, the liver, the heart, or the pancreas, where normal or near normal function is resumed almost immediately, despite denervation. From these observations it appears that immunosuppressive drugs must be given parenterally when intestinal allografting is done in animals or in man because of impaired absorption.

The most important and significant progress in transplantation has been the discovery and utilisation of Cyclosporin A. Cyclosporin has been used experimentally and clinically in small bowel transplantation in dogs (Craddock, 1983), pigs (Grant, 1988), rats (Kirkman, 1984) and humans (Cohen, 1986). Cyclosporin has proved remarkably effective in preventing rejection and structural and functional defects.

Recent work by Grant and associates has demonstrated that massive doses of intravenous Cyclosporin followed by oral Cyclosporin can reliably prevent intestinal rejection in outbred Duroc-Hampshire pigs. (Grant D, 1988). None of the pigs treated with intermediate doses to high doses of intravenous CsA developed rejection. More than 50% of the animals treated with intermediate dose of

CsA survived at least three months, with strangulated intestinal obstruction being the most common cause of late death. Most important, the intestinal recipients grew and gained weight at the same rate as did laboratory controls. Similar results were obtained by Craddock (1983) in canine studies.

The addition of steroids has not consistently improved the results obtained in dogs given Cyclosporin alone. Diliz-Perez and colleagues (1984) reported on 4 of 12 dogs that lived more than one hundred days after treatment with Cyclosporin and prednisone given orally, and showed that it does not extend graft survival significantly over that seen when a standard daily regimen with Cyclosporin is employed.

It is expected that the combination of Cyclosporin with azathioprine, antilymphocyte globulin, prednisone and in addition, monoclonal antibodies (OKT3) will allow further improvement of results.

Zane Cohen and co-workers in Toronto (1986), have studied total orthotopic small intestinal transplantation in unmatched mongrel dogs treated

with cyclosporin as the sole immunosuppressant. The success of small bowel transplantation in dogs without cyclosporin, with oral cyclosporin, or with parenteral cyclosporin was 12, 34, and 104 days of survival, respectively.

The recent introduction of FK506 (Hoffman AL, 1990, Thomson AW, 1990) believed to be more powerful than cyclosporin, offers a potentially important advance in the most difficult problem of intestinal transplantation; effective immunosuppression of an organ in a non-bacteriologically sterile environment. Hoffman compared the effects of FK506 and CsA on host survival, graft rejection and GVHD in a rat small intestinal transplant. Specific doses of FK506, resulted in prolonged graft and host survival in all genetic combinations tested. FK506 showed to be a more effective single agent than CsA in the prevention of acute rejection and lethal GVHD.

The window for therapeutic immunosuppression after intestinal grafting may be very narrow compared with that of other organs. Inadequate immunosuppression will lead to rejection, with increased gut permeability and the absorption of toxins.

Splenectomy of the host, as a form of immunosuppression, has been considered, however it has only a minor ameliorating effect upon the rejection process and is therefore not an avenue for immunosuppression in future clinical small-bowel transplantation (Schraut WH, 1988).

3- PROBLEMS IN EXPERIMENTAL INTESTINAL TRANSPLANTATION

It is not always easy to diagnose rejection and to monitor the effect of rejection on allograft function. Fortner and associates (1972), described a technique of exteriorisation of isolated segments of grafts as blind loops, rendering the graft easily accessible for serial biopsies. The loops reflect the changes that develop in the intra-abdominal graft and are readily accessible to biopsy, even deep biopsy, with a much reduced risk of clinically significant perforation. Stauffer (1975) has monitored small-bowel grafts by sequential mucosal suction biopsies and quantitative morphometric analysis.

However, in view of the limitations in the

interpretation of graft biopsies, and the difficulties of obtaining biopsies if the graft is in intestinal continuity with the bowel of the recipient (no stoma allowing easy access to the transplanted bowel), several function tests have been proposed, to supplement random biopsies which may not conclusively reflect the overall status of the allograft. The evaluation of absorption of glucose (Cohn WB, 1969), maltose, glycine, and fatty acids has demonstrated impaired absorption during the course of rejection. Borgstrom and colleagues (1986) showed that the Porcine Ileal Peptide (PIP), a newly isolated protein from the gastrointestinal tract (Wider MD et al.1984), mainly found in the distal small intestine, represented a potential organ-specific marker for small-bowel rejection. Disruption of the mucosa may result in either a transient increase of PIP in the peripheral circulation or in PIP's total disappearance from the circulation.

Problems have been significant in dogs and pigs. There is an extremely high incidence (40-60%) of early arterial and/or venous thrombosis. Survival of less than five days is usually due to technical failures. The cause of the high incidence of thrombosis is unrelated to the technique or

anastomotic integrity. (Pritchard TJ, 1985). A low flow state possibly aggravated by inadequate bowel preservation may predispose to thrombosis. There has been very little information on preservation of the small bowel since the observation of Toledo-Pereyra and associates in 1974. Pulsatile perfusion of the small intestine allowed successful transplantation after 24 hours and was thought to be superior to cold storage in Collins' solution (which simulates the electrolyte concentration of intracellular fluid). (Toledo-Pereyra LH, 1974). More recently there has been interest in cryopreservation of the small intestine, particularly free foetal intestinal transplants. With cyclosporin, cryopreserved free allogenic foetal grafts are able to grow. (Guttman FM, 1985).

4- HUMAN INTESTINAL TRANSPLANTATION

Roux (1907), reported the first intestinal autotransplant in man when he used a segment of jejunum to replace a child's oesophagus resected for benign oesophageal stricture.

Several attempts at human small intestinal transplantation were performed, despite the rather poor experimental results documented in the past 30

years.

The first partial small bowel transplantation (ileum) was done by Detterling (mother to child) in 1964. (Stauffer U, 1975). The first complete intestinal allotransplantation was done at the University of Minnesota in 1967, (Lillehei RC, 1967) it was a 46-year-old white woman who suffered acute abdominal pain and on exploration was found to have an enlarged spleen of unknown aetiology and two feet of infarcted jejunum. The infarcted jejunum was resected. The following day she suffered shock and was reexplored, the entire small intestine was infarcted, along with the spleen and the greater omentum. A small bowel transplantation was performed using a cadaver donor. Soon after completion of the operation, the patient went into shock and died twelve hours after surgery. Extensive pulmonary congestion and multiple small pulmonary infarcts were observed at autopsy. The portal vein of the patient was completely thrombosed and there was evidence of early ischaemic necrosis of the liver. The transplanted intestine showed venous congestion, but both the arterial and venous anastomosis were patent. No cause was found for the orginal portal and mesenteric venous thrombosis.

Olivier G and associates (1966) performed an orthotopic intestinal allotransplantation in a 35 year-old male who suffered from colonic polyposis and mesenteric fibromas (a type of Gardner's syndrome). The recipient's jejunum, ileum, and right transverse colon were resected. The allograft consisted of the entire small intestine (except the duodenum) and the right and transverse colon. The graft mesenteric vessels were anastomosed to the host mesenteric vessels, the donor jejunum to the host jejunum just beyond the ligament of Treitz, and the distal end of the graft was brought out as a colostomy. Azathioprine, corticosteroids, and equine antilymphocytic globulin were administered. 26 days after the operation the patient died of septic shock. At autopsy there were copious amounts of peritoneal fluid, and the allograft was distended and cyanotic. The mucosa of both the small and large intestinal allograft was haemorrhagic and ulcerated. The intestinal wall and mesentry were thickened, and the mesenteric lymph nodes of the allograft were infarcted. The intestinal and vascular anastomoses were patent. Mononuclear infiltration, necrosis involving all layers of the graft, and capillary and venular thrombosis were present.

Alican and Hardy (1971) performed an

intestinal transplantation on a 10 year-old boy who was found to have a gangrenous small bowel from the ligament of Treitz to the ileocoecal valve secondary to strangulation by a mesenteric band. The donor graft was one meter of ileum taken from the child's mother. The patient was given azathioprine, prednisone, and antilymphocytic globulin. On the seventh postoperative day the stoma of the graft appeared necrotic, and the patient became septic. He was reexplored, and while the circulation of the graft was still intact, the graft did not look healthy. It was removed but the patient died 32 days after transplantation.

All patients who had undergone intestinal transplantation before cyclosporin became available died either because of technical problems or because of rejection and/or GVHD.

Within the last decade a number of reports have increased our understanding of the problems that surround small bowel transplantation. With the availability of Cyclosporin in addition to other effective immunosuppressive drugs, the prognosis has improved for patients who may undergo small-bowel transplantation.

Starzl (1984) reported transplantation of a pancreaticoduodenal segment in which two patients also received long jejunal segments in composite graft, and treated with cyclosporin and steroids. Intestinal cramps, watery diarrhea, and severe hypoalbuminaemia required reoperation and removal of the jejunum and distal duodenum.

In 1985, Cohen Z (1986) performed a small bowel transplantation on a 26-year-old patient using CsA, however the patient died on the eleventh postoperative day.

Goulet and associates (1987), at the Hopital des Enfants-Malades in Paris, performed a small bowel transplantation on a 9 year-old girl, the donor being a 17 year-old from the same blood group. The child died 206 days later from sepsis.

Grant D (1989) summarised intestinal transplantations with cyclosporin between 1985 and 1988, reporting 10 cases which included the Toronto and Paris transplantations. There have been no long-term survivors, rejection and sepsis being the major causes of graft loss.

Several centers have been able to detect

intestinal rejection and remove the graft before life-threatening complications had occured. Prevention of rejection requires methods to reduce the antigenicity of the graft (Irradiation, Portal drainage, Segmental graft, Multivisceral Transplantation) in combination with improved immunosuppressive protocols (Splenectomy, CsA, Transfusion, Multidrug therapy) (Grant D, 1989).

Corry and colleagues (1988) reported more than 20 patients with pancreaticoduodenal allografts with anastomosis of the main pancreatic duct to the bladder (pancreaticocystostomy) and who were treated with CsA, azathioprine, and prednisone. The duodenal stumps were viewed repeatedly by cystoscopy and the bowel remained viable, without signs of fibrosis or mucosal destruction, as long as rejection of the pancreatic graft was suppressed. This experience clearly indicates that the rejection of intestinal grafts can be prevented by present-day immunosuppressive therapy, and that these grafts remain morphologically intact.

The question is not whether intestinal allotransplantation should be attempted in man but how to make such transplants work. The study of graft function is therefore crucial in order to

determine future success of transplantation.

5- PRESERVATION OF SMALL INTESTINE

The small intestinal mucosa, more than any other structural layer of the bowel, is highly sensitive to ischaemia, but also possesses a great regenerative potential.

An effective method for preservation of the small bowel during the interval between harvesting and implantation is a key factor in the success of small-bowel transplantation. A method of small-bowel preservation that allows functional graft survival after intervals of ischaemia of up to 12 hours, is needed. Such a time interval is desirable to permit unhurried graft procurement from cadaver donors and recipient preparation, until the actual implantation is carried out.

Lillehei and associates directed their laboratory efforts toward finding the safe limits of a complete in vivo interruption of intestinal circulation. (Lillehei RC, 1959). The canine small bowel tolerated two hours of total ischaemia if the bowel was allowed to cool to room temperature (25 to 28 C). If the bowel was cooled to 5 degrees C, it

was safe to interrupt its circulation for at least 5 hours. Following these experiments, segments of small bowel allografts, which had been preserved in vitro under various conditions, were transplanted into necks of dogs. (Eyal Z, 1965). When the small bowel had been preserved for 24 hours by hypothermia alone, haemorrhagic necrosis occured after revascularisation. The addition of chlorpromazine, which is a phenothiazine having a general inhibitory effect on cellular metabolism, to the perfusate and the storage solution, allowed successful preservation at 4°C for up to 48 hours. The addition of hyperbaric oxygen resulted in further enhancement of preservation.

Lyons GW and associates (1965) tested the viability and function of canine ileal segments preserved for 24 to 48 hours by determining the intestinal absorption of chloride and glucose. No significant difference was found between the intestinal and fresh ileal segments stored under hypothermia and hyperbaric oxygen for 24 to 48 hours. Idezuki and associates (1968), showed that dogs can survive for 150 days after pancreaticoduodenal allografts which have been preserved in vitro for 22 hours at 4°C and 3 atmospheres of oxygen, thus proving the viability of

both the pancreas and duodenum. The intestine can therefore be preserved for 4 or 5 hours by hypothermia alone, but periods up to 24 hours are also possible with the addition of chlorpromazine and hyperbaric oxygenation.

Austen and McLaughlin (1965) showed that in vitro nonpulsatile blood flow to isolated canine small intestine segments resulted in impaired metabolic function and gross changes in the intestine and mesentry, within 6 hours. With pulsatile flow, these changes did not occur even after perfusion for 18 hours. Toledo-Pereyra (1974) showed that the intestine could be preserved for up to 72 h. using hypothermic pulsatile perfusion. Iijima and Salerno (1967) infused ileal segments with diluted blood at normothermia for 5 hours and autotransplantation proved these segments to be viable.

Ricour and associates (1981) showed that in the piglet, intravascular and bowel lumen flushing with a 4°C Collins' solution which simulates the electrolyte concentration of intracellular fluid, followed by cold storage allowed the preservation of the bowel up to 20 hours. However, Schraut (1988), using the rat model was only able to preserve the

bowel for up to 6 hours.

Guttman and associates (1985) showed that foetal rat intestinal segments previously frozen were able to survive and even grow normaly once reimplanted subcutaneously.

There are some encouraging accomplishments in small bowel transplantation. Long term survival in animals has been reported. Use of Cyclosporin has improved the outcome. However, bowel transplantation remains at an experimental stage, although clinical application has been attempted by many centres. It is hoped that results will improve in the same way as those of the transplantation of the kidney, heart, liver and lung.

While the rejection phenomenon and its control by immunosuppressive therapy are continuing to be studied extensively, the study of enteric physiology of the transplanted gut is a new field. It is still not well understood how the physiology of the transplanted bowel is affected, with respect to its motility and absorptive functions.

CHAPTER IV

RATIONALE OF INTESTINAL TRANSPLANTATION

RATIONALE OF INTESTINAL TRANSPLANTATION

Many patients die each year, lacking only a new bowel to survive. Talsma et al (Talsma SE, 1989) reviewed the registers of patients receiving home parenteral nutrition in the USA and the UK, and found that approximately 400 patients in the USA and 20 patients in the UK receive Home Total Parenteral Nutrition (TPN). However, for various reasons, only 58 persons in the USA and 2 persons in the UK were acceptable candidates for small-bowel transplantation.

The digestive and absorptive surface provided by the small intestinal mucosa in healthy adults is more than is needed to maintain adequate nutrition. The resection of small lengths of small intestine usually causes no clinical symptoms. The severity of symptoms after resection of large segments of the small bowel is related to the extent of resection and the specific level of the resected small intestine. Absorption of certain

physiologically needed substances is most efficient in either the proximal (Iron, folate, calcium) or the distal portion (bile salts, vitamin B12) of the small intestine.

Thus resection of 40 to 50% of the total length of the small intestine is usually well tolerated, provided the duodenum, the proximal portion of the jejunum, the distal half of the ileum, and the ileocaecal valve are spared. In contrast, resection of the distal two thirds of the ileum and ileocaecal valve alone may induce severe diarrhea and significant malabsorption even though 25% of the total small intestine is resected. Resection of 50% or more of the small intestine usually results in significant malabsorption, and resection of more than 70% of the small intestine often produces such catastrophic malabsorption that survival of the patient is threatened. The first report of survival after massive resection of the small intestine was by Koeberle (1881).

The most common clinical conditions that require resection of excessive portions of the small intestine to preserve the life of the patient are those compromising its blood supply, and these are:

a- Thrombosis, embolus or low flow ischaemia of the superior mesenteric arterial bed, and thrombosis of the superior mesenteric vein and its branches.

b- Mechanical conditions such as volvulus of the small intestine, and rarely strangulated internal or external hernias.

c- Necrotising enterocolitis (NEC), and connective tissue disease.

Other indications include Crohn's disease, neoplasm, trauma, radiation enteritis, atresia of the small bowel, and resections for congenital disorders. (Trier JS, 1989)

The minimum amount of small intestinal absorptive surface required to sustain life seems to vary from patient to patient. Prolonged survival with oral alimentation has been recorded in a number of patients with an intact duodenum and as little as 15 to 45 cm of residual jejunum (Winauer SJ, and Zamcheck N, 1968). However, without long-term total parenteral nutrition, prolonged patient survival is the exception rather than the rule, if in addition to the entire duodenum, less than 60 cm of jejunum or ileum remains. Preservation of the ileoceocal valve is important as it reduces contamination of the

residual intestine by the colonic flora, and its presence seems to increase the transit time of the small intestinal luminal contents (Fich A, 1990). Preservation of part or all of the colon significantly reduces fluid and electrolyte losses.

The syndrome resulting from the loss of bowel surface and/or function has been called the Short Bowel Syndrome. Chronic gut failure is present when the patient is unable to absorb enough nutrients from the intestinal tract to preserve health and a feeling of well-being. (Irving M, 1983). When the causes of short-bowel syndrome are considered, patients can be divided into three groups. The first group has an absolute decrease in absorptive surface owing to subtotal resection of the small intestine performed on account of mesenteric arterial or venous thrombosis. The remaining gut is seldom in a position to effect necessary absorption. The second group of patients has a relative decrease in small bowel surface caused by diffuse disease of small intestine, such as Crohn's disease or radiation enteritis. The third group of patients has an absence of gut motility, which in turn leads to chronic intestinal malabsorption. Scleroderma and ideopathic pseudo-obstruction are typical symptoms in this

group.

Reduction of absorption of all nutrients, including water, electrolytes, fat, protein, carbohydrate, vitamins, and trace elements, after massive resection of small intestine, creates an urgent clinical situation. If vigorous fluid and electrolyte replacement is not instituted promptly, life-threatening dehydration and electrolyte imbalance may develop. Severe malabsorption will take place, severe weight loss, from caloric depletion. Purpura and generalised bleeding may reflect impaired coagulation caused by malabsorption of Vitamin K. In time peripheral neuropathy will develop. Both fasting and postprandial gastrin levels may be elevated in patients months and even years after extensive intestinal resection. Gastric hypersecretion may follow, due to the loss of inhibitory agents, causing serious peptic ulcer disease. (Windsor CWO, 1969). Other complications include, anaemia, and osteopenia.

Treatment includes vigorous parenteral replacement therapy during the first few weeks after massive intestinal resection, to prevent development of cachexia and severe nutritional deficiencies, by providing glucose, amino acids, electrolytes, vitamins, trace minerals, and lipids. Therapy

immediately following extensive bowel resection requires intravenous nutrition and bowel rest. During the first two months of therapy, the main risk to the patient is from excessive fluid and electrolytes loss. In the transitional phase which follows, parenteral nutrition is continued during administration of enteral nutrition with chemically defined diets, given continuously by an infusion pump. The fat content of the diet has to be kept low in order to reduce stool frequency and to control steatorrhea. This also helps to reduce the loss of calcium, magnesium, and zinc. If the entire colon has been preserved, the amount of oxalate and lactose in the diet must be restricted. These dietary measures are supplemented by antidiarrheal preparations, H2 antagonists, cholestiramine and antibiotics. (Muller JM). It is usually clear within a year or two after surgery to what extent patients' oral nutrition requires supplementation parenterally. Home parenteral nutrition (HPN) is started as soon as extra medical or nursing assistance is no longer required. HPN is a well established method for treating intestinal failure. Several centres in Europe and North America provide this service and have experience with hundreds of patients (Irving M, 1981). The feasibility of parenteral alimentation with prolonged survival has

proved life-saving in patients with massive intestinal resection. (Heizer WD, 1977). Muller and associates (1986) reported their experience with short-bowel patients between 1978 and 1985. Out of 26 patients, 7 died postoperatively, 8 died between 3 and 13 months after discharge from the hospital. Of the remaining 11 patients, seven have returned to their former jobs, the remaining 4 were unable to work.

The ideal long-term therapy for patients displaying short-bowel syndrome, would be small-bowel transplantation. However, apart from a few exceptions, long-term parenteral nutrition is presently the only available method of preventing these patients from starvation, although there are relative contra-indications to TPN which include liver disease and severe depression, ultimately resulting in increased morbidity and mortality.

Home parenteral nutrition, leads to an improvement in the life-style of these patients, freeing them from the confines of the hospital and allowing most of them to resume an active life at home or at work. However, the nutritional management of these patients still requires close monitoring owing to the nonphysiologic route of

alimentation. Metabolic complications include deficiency states such as hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, calcium disorders and disorders in glucose metabolism. (Fisher JE, 1980).

In addition, long-term venous access can be associated with catheter complications at the time of insertion (pneumothorax, arterial laceration, haemothorax, mediastinal haematoma, injury to the nerves of the brachial plexus) and, later, bacterial contamination of the intravenous catheter can lead to a catheter-driven septicaemia which can be fatal within hours. Erosion of the catheter tip into a bronchus or other structures, thrombosis, and embolism add to the list.

Psychological limitations resulting from either the inability to eat or the dependency on an external means for survival are common. Such therapy impairs social and leisure activities and affects sexual and interpersonal relationships. Patients and their relatives must understand feeding schedules and follow aseptic technique in handling the catheters and the intravenous solutions.

Some patients feel overwhelmed by the

complexity of such programs and are therefore unable to benefit from this therapy.

Such a program is very costly; Intravenous solutions, catheters, dressings, repeated hospitalisations, and frequent biochemical and haematological assays often make such care prohibitively expensive on a long-term basis.

Surgical alternatives for the short bowel syndrome were summarised by Thompson and Rikkers (1987). They included slowing of intestinal transit (constructing intestinal valves, antiperistaltic intestinal segments, colon interposition, recirculating loops, and intestinal pacing), increasing area of absorption (intestinal tapering and lengthening, growing neomucosa), controlling gastric hyperacidity (acid reducing operations), however none of these operations are sufficiently safe and effective.

The only possible alternative, and the best method of treating the short-gut syndrome in any age group would be the transplantation of a healthy small intestine, which will allow patients to return to a normal life-style in the same way that the kidney grafting allows patients with chronic renal

failure to be freed from the restrictions of haemodialysis.

A living related donor with matching blood type and histocompatibility is ideal. The availability of such a donor allows scheduling operative procedures for harvesting and for transplantation, so that prolonged graft ischaemia and the need for organ preservation are avoided. The risk for the donor includes the loss of 150-200 cm of functioning small bowel, a loss which, in theory, should not lead to nutritional compromise but may do so in practice. (Schraut WH).

Techniques are available which permit removal of several abdominal organs, kidney, liver or pancreas, and the small intestine, from the same cadaver donor without jeopardy to any of the individual grafts. It is inevitable that the small intestine, because of its bacteria content, will be the last organ to be removed from the donor.

CHAPTER V

BACKGROUND AND AIMS OF THE STUDY

BACKGROUND AND AIMS OF THE STUDY

The study of the physiology of the transplanted intestine is a new field that will have direct clinical application, once transplantation becomes safely and successfully applicable in humans. Basic questions, concerning the effects of the transplantation procedure on intestinal motility, absorption, and secretion remain as yet unaddressed.

Factors controlling initiation and coordination of intestinal motility remain poorly understood, but must involve a regulatory mechanism via an interplay of extrinsic innervation, intrinsic innervation and humoral factors. The autotransplanted jejunoileum is denervated both extrinsically and intrinsically providing an opportunity to assess the neural control of gut motility.

The effect of intestinal transplantation on absorption has received little attention. The process of transplantation involves complete denervation, disruption of intrinsic myoneural continuity, and disruption of lymphatic drainage from the transplanted segment. All these may be expected to affect the absorptive ability of the jejunoileum either directly or via effects on intestinal motility and transit.

The following background is relevant to this study.

1- BASIS OF GASTROINTESTINAL MOTILITY

The movement of bowel contents through the small and large intestine is controlled by the activity of the smooth muscle contractions.

a- SLOW WAVES

The intestinal smooth muscle contractions are regulated by cyclic depolarisations in the muscle membrane, which are called slow waves (basic electric rythm): these are essential for rhythmicity and synchronisation of contraction. They are rythmic changes in voltage which occur whether or not the

muscle is working. Slow waves are pacesetter potentials which are generated by longitudinal muscle cells, which are therefore the pacemakers of the small intestine. (Connor JA, 1977).

The form of the slow wave depends on the location of the small bowel from which the recording is made. In the duodenum and upper jejunum, the configuration of each slow wave consists of a rapid upward, positive deflection followed by return to a somewhat positive plateau component that ends in a small negative component. In the middle third of the small bowel, the slow wave configuration is much more variable. The positive plateau and negative component characteristic of duodenal-jejunal slow waves are not always present. Irregular biphasic slow waves (a positive peak followed by a negative peak of varied amplitude) and symmetric sinusoidal waves are also observed. (Szurszewski JH, 1987). The amplitude of slow waves varies along the small bowel. Duodenal slow waves are larger than jejunal slow waves. Ileal slow waves are smaller than jejunal slow waves.

The mechanism responsible for the rythmicity has occupied the attention of many physiologists and clinicians. Each portion of the gastrointestinal

tract has its own intrinsic slow wave frequency that is affected by the adjacent intestinal slow wave activity.

The effect of the contiguous slow wave activity of neighbouring smooth muscle is called coupling (Sarna, 1985). The degree of coupling between adjacent portions of the intestine depends directly on the resistance between neighbouring smooth muscle cells. When intercellular resistance is maximal and coupling is minimal, each section of intestine has its own slow wave frequency.

b- SPIKE POTENTIALS

Spike potentials are rapid changes in smooth muscle membrane potential that initiate the rapid influx of calcium into muscle cell or its release from intracellular binding sites. It was Bozler (1938) who showed that spike potentials were action currents. The changes in intracellular calcium initiate contractile activity. Spike potentials can be recorded extracellularly at all sites along the small intestine. In the upper half, these potentials occur in brief bursts and are confined to a specific segment of the slow wave. They superimpose the slow wave. In the lower half of the bowel, particularly

in the ileum, spikes appear to occur on various parts of rather poorly defined slow waves. When spike activity is intense, spikes are superimposed over most or all of well-defined sinusoidal shaped slow waves. (Szurszewski JH, 1970).

The spike potentials always occur at one portion of the slow wave cycle. Thus the frequency of the slow waves determines the shortest interval between spike potentials and in this manner determines the frequency of intestinal contractions. Contractions may be irregular as not every slow wave contains spike potentials. The intensity of the spike potentials determines the strength of the contraction. Owing to these interrelations between slow waves and spike potentials, the rate and rhythm of the intestinal contractions depends on the characteristics of the smooth muscle membrane in that portion of the intestine. The pattern of these contractions then controls the movement of luminal contents in the intestinal tract.

The movement of material within the lumen of the small intestine is a complex phenomenon that depends on the interaction of multiple myogenic and neurohormonal factors. The slow waves in the small intestine are generated in adjacent cells of the

longitudinal muscle layer and are propagated by electronic spread to the circular muscle layer. Slow wave occur at regular intervals and are present continuously. Studies have shown that slow waves are nearly synchronous around the circumference of the intestine, (Bass P, 1961) providing a coordinating mechanism ensuring that the intestinal muscle around the ring becomes excitable more or less simultaneously.

The aborad movement of intestinal contents is controlled by a frequency gradient of slow wave activity that is present in the small intestine, and propagation of the slow wave activity through contiguous sites. There are three slow waves per minute in the stomach. Slow wave frequencies are faster in the duodenum (12 cycles/minute) compared with the ileum (8 cycles/minute), and large intestine (5 cycles/minute).

This oral to aboral gradient was first described by Alvarez in the rabbit small intestine (Alvarez WC, 1914). The faster contractile rate in the upper intestine pushes the intestinal contents forward. Large-amplitude slow waves may reflect a higher degree of synchrony than small amplitude small waves. Tight coupling of neighbouring sites is

prominent in the duodenum and proximal jejunum, giving a constant frequency in this segment. In this segment of the small bowel the propagation of the slow waves in an aborad direction controls the orderly movement of luminal contents. Beyond the proximal jejunum, the slow wave frequency decreases because the coupling between the slow waves becomes weaker.

Thus slow wave gradient determines intestinal flow, throughout the entire small bowel but is especially important distally where the gradient is greatest. Proximally, the prominent coupling of slow waves plays an important role in propulsion. It is suggested that the greater tone and irritability and the faster rythm of the upper part of the small intestine are associated with more rapid peristalsis in this region (Alvarez, 1914).

c- THE MIGRATING MOTOR COMPLEX (MMC)

Studies of the motor activity of the human and canine small intestine have shown as early as 1934 (Castleton KB, 1934) the occurrence of migrating motor complexes. Those observations were confined to short segments of the bowel. It was not until 1969 that Szurszewski at the Mayo Clinic

(Szurszewski JH, 1969), described a migrating electric complex that occurs during the interdigestive period.

During fasting the stomach and small intestine exhibit a cyclic pattern of motility that recurs with a period of 2 hours.

A characteristic cyclic pattern of motor and myoelectric activity develops in the stomach and then migrates caudally to the ileum, and as it terminates there, another starts in the gastroduodenum or upper jejunum and recycling continues.

The interdigestive motility pattern which has been called Migrating Motor Complex (MMC) is divided into 4 phases: (see Fig 5-A, 5-B).

Phase I- is a period of motor quiescence in which no spike or motor activity is seen, slow waves are without action potentials.

Phase II- is a period of intermittent contractions with randomly occuring bursts of spike potentials superimposed on slow waves, with the burst becoming more frequent and the action potentials larger in

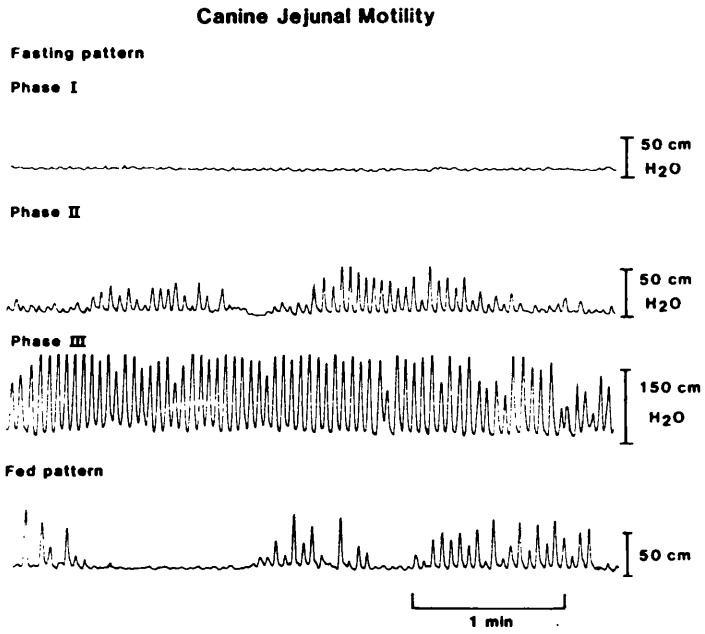
amplitude.

Phase III- a short 4 to 8-min burst of regular high amplitude contractions with every slow wave displaying an action potential of large amplitude, a recognisable complex of intense spike activity that begins in the stomach, duodenum, or upper jejunum and migrates in an orderly fashion caudally.

Phase IV- Short period of transition during which the activity returns to the quiescence of Phase I.

Figure 5-A.

Phases of the Migrating Motor Complex (MMC)

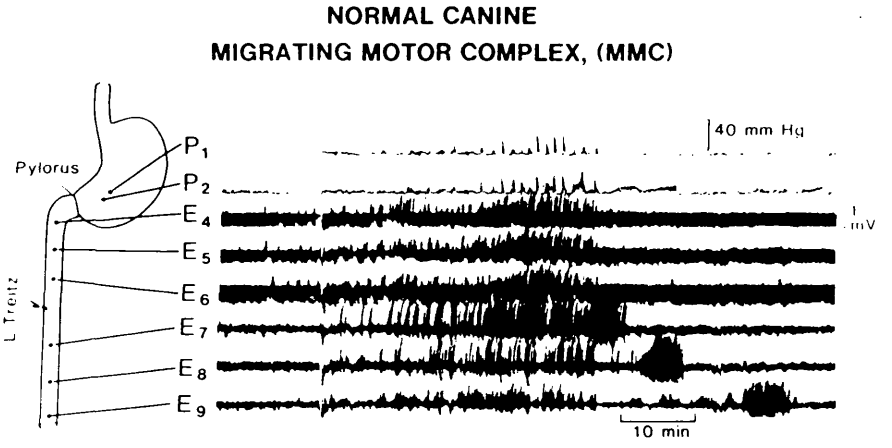


Jejunal motility in an intact dog. Phase I, period of motor quiescence. Phase II, period of intermittent contractions. Phase III, short burst of regular high amplitude contractions. Fed pattern, intermittent contractions.

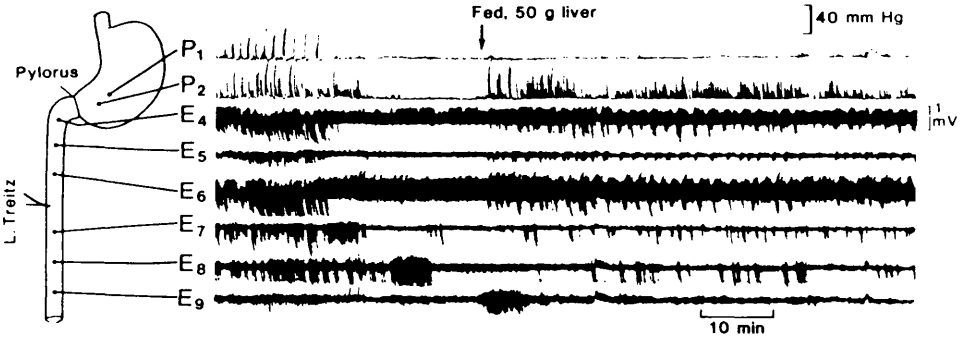
Figure 5-B.

Canine Migrating Motor Complex

5-B-a.



5-B-b.



Normal canine interdigestive and postprandial motility patterns. Fig 5-Ba. Phase III of the MMC. Fig 5-Bb Phase III of the MMC followed by a Fed pattern of intermittent contractions.

These electric complexes are seen only during fasting. Feeding interrupts this cycle and establishes a less-well defined postprandial pattern of intermittent contractions, best characterised by the absence of interdigestive pattern and the presence of random bursts of spike and motor activity. After a variable duration, depending on the type of meal and caloric load (DeWever I, 1978, Schang JC, 1978), the interdigestive pattern is restored.

Functionally, the MMC sweeps the upper gut clear of non-digestible debris, preventing stagnation and bacterial growth, and moving this material into the colon, thus it was concluded by Szurszewski that the motor complex was the interdigestive "Housekeeper" of the small bowel. In contrast, the postprandial motor pattern is believed to optimise mixing and absorption of ingested nutrients. (Code CF, 1974). Combined cineradiography and myoelectric studies show that intestinal contents are propelled ahead of the advancing Phase III activity (Cohen S, Snape WJ,Jr, 1989).

d- CONTROL OF INTERDIGESTIVE MOTOR ACTIVITY

The mechanisms of initiation of the motor

patterns of intestinal motility have undergone intense investigations. Three major mechanisms have been studied:

1- EXTRINSIC NEURAL CONTROL:

Carlson and co-workers (1972) suggested that extrinsic innervation controlled initiation and the orderly migration of the MMC in the small bowel. Studying a 30 cm jejunal Thiry-Vella canine loop (an enterically isolated jejunal segment with intact extrinsic innervation) (see later in Methodology, Chapter VI), they found that the MMC propagated along the segment proximal to the anastomosis, then passed distally to and along the jejunal loop and finally in sequence, to the portion of the bowel distal to the anastomosis. They concluded that the continuity of the bowel wall was not essential for the coordination and propagation of the interdigestive motor complex.

Several other groups restudied this question and found that, although the MMC cycled in the Thiry-Vella loop, temporal coordination of the loop MMC with the MMC of the intact bowel was disturbed.

Bueno and colleagues (1979) studying dogs

with isolated jejunal loops found that the myoelectric complexes passed from the proximal intestine to the loop and then to the intestine beyond the site of anastomosis. However some complexes started on the loop or on the intestine beyond the anastomosis.

Ormsbee (1981) showed that the propagation time from the proximal jejunum to the loop was significantly increased, and activity fronts were observed to originate in the loop and the intestine distal to the anastomosis. They concluded that the hypothesis that extrinsic nerves solely control the migration of the MMC is incomplete and that the intrinsic and the extrinsic innervation of the gastrointestinal tract were both required for the precise pattern of the MMC.

Those findings complicated the understanding of neural control of motility. Subsequent studies have challenged the role of extrinsic innervation in the control of motor patterns:

Marik and Code (1975) showed that vagotomy was followed by a reduction in the temporal regularity of the cycles of the complex. Aeberhardt (1977) showed that no effect on coordination of

antral and duodenal motor activity was found after either proximal gastric vagotomy or truncal vagotomy, suggesting that the coordinating mechanism is not dependent on vagal innervation. Gleysteen (1985) using a system of reversible cooling of the vagus at the level of the diaphragm, showed that more than 90% of gastric motor cycles persisted during vagal cooling and concluded that the vagus may modulate the duration of gastric phase III but does not govern the initiation of gastric cyclic motor activity, or its duration. Weisbrodt (1975) found that bilateral thoracic vagotomy had little or no effect on the fasting pattern of myoelectric activity. Ruckebusch (1975) found that after vagotomy complexes still occured but the duration of irregular spiking activity was decreased suggesting that the ratio of irregular to regular activity is dependent on the influence of extrinsic nerves. Reverdin (1979) showed that fasting patterns were not significantly altered by truncal vagotomy, but however feeding did not stimulate an appropriate enteric motor pattern.

Marlett and Code (1979) found that the interdigestive myoelectric complex was present before and after ganglionectomy, but the variability in the duration of its cycles was increased. In dogs

with bilateral vagotomies and bilateral thoracolumbar sympathetic chain ganglionectomies, morphine initiated phase III activity in the duodenum, which then migrated distally. (Telford GL, 1985)

Heppell (1981) showed that transection of the extrinsic nerves induced the appearance of extra MMCs in the proximal jejunum concluding that the extrinsic nerves suppress the appearance of extra MMCs arising in the proximal jejunum. However, autotransplantation of intestinal segments, as means of assuring complete extrinsic denervation, did not abolish the MMC. Itoh (1981) studied extrinsically denervated segments of jejunum and found that all MMCs migrated distally through them. They concluded that extrinsic innervation was not essential for the initiation and aborad sequential propagation of periodic motor activity.

Telford and colleagues (1985) using a canine model, transected the spinal cord between the second and third thoracic segments and found that the myoelectric activity in fasted and fed dogs was not under the control of supraspinal sympathetic pathways. However studies done by Fealey et al (1984) on humans with high-cord transection showed

that the interruption of the cervical cord above the level of the sympathetic outflow to the gastrointestinal tract disturbed normal interdigestive antral-duodenal motor coordination and delayed postprandial gastric emptying of liquid meals.

Therefore, vagotomy, sympathectomy, ganglionectomy, transection of extrinsic nerves and cervical spinal cord transection all cause only a mild disorganisation of motor patterns of gastrointestinal motility, and the MMC in the stomach and the small intestine continues to cycle after denervation.

However while extrinsic innervation is not a requisite for initiation of the fasting and fed motor patterns, extrinsic nerves may carry messages from the CNS to influence motility.

Indeed, many gastrointestinal or neuroregulatory peptides when given centrally (intracerebroventricularly) in very low doses that have no effect when given peripherally (intravenously), will alter motor patterns of the upper gut. The central nervous system does not initiate MMC activity but does modulate this

activity; can trigger a premature MMC and delay or inhibit MMC activity.

Bueno and Ferre (1982) showed that sulfated Cholecystokinin-OP (CCK-OP) decreased the frequency of the MMC and that Somatostatin increased it when given centrally through an intraventricular catheter, however they had no effect when given peripherally.

Bueno (1983) showed that Neurotensin administered centrally inhibited the gastric and intestinal MMC however had no effect when given intravenously. Substance P given centrally decreased the time of postprandial inhibition of the MMC. Calcitonin restored fasted MMC to fed rats transiently.

Intracerebroventricular administration of Dopamine increased the duration of the interval between two consecutive migrating motor complexes. (Fioramonti J, 1984).

2- INTRINSIC NEURAL CONTROL:

The MMC migrates distally in an orderly fashion along the small intestine. Intestinal

transection, which interrupts intrinsic myenteric neural continuity, disrupts this migration. Matsumoto et al (1986) showed that the MMC cycled independently in each of the segments of the small intestine which were fashioned by simple transection and reanastomosis. The MMC occured distally but lacked the temporal coordination with the proximal bowel and cycled at a faster rate. As intrinsic nerves regenerate in 6 to 12 weeks, temporal coordination is reestablished completely.

Sarna and colleagues (1980) showed that close intra-arterial bolus injections of atropine, hexamethonium and tetrodoxin designed to disrupt the enteric nerves and therefore inhibit intrinsic neural function, blocked the propagation of the MMC, when given prior to the arrival of the activity front. They concluded that the intrinsic cholinergic network of neurones controls the propagation of the MMC.

Heppell (1983) found that after enteric transection and reanastomosis at the ligament of Treitz and at a site 75 cm distal to the ligament, fewer duodenal MMC migrated into the jejunum, however each MMC still arose in the jejunum. They concluded that an intact enteric wall aids in the

distal propagation of the MMC.

These studies suggest that the intrinsic nervous system alone can generate a cyclic MMC and control its orderly migration. The MMC cycling phenomenon is now believed to be regulated by the intrinsic neural plexuses in the small bowel. The cycling phenomenon is attributable to spontaneous oscillators residing in the enteric nervous system. Transection and reanastomosis of the small bowel disrupts the coupling of these oscillators. (Sarna SK, 1985).

3- HUMORAL/HORMONAL CONTROL:

Previous studies suggested a role for humoral initiation of the MMC. (Mukhopadhyay AK, 1975, Bueno L, 1976, Wingate DL 1976, Thor PJ 1982).

Motilin is a putative, regulatory gastrointestinal peptide, containing 22 aminoacids and synthesised in the enterochromaffin cells of the duodenum and proximal jejunum. It is unusual in that its release is maximal during fasting, reaching its greatest concentration during the activity front of Phase III. The plasma motilin concentration fluctuates during the interdigestive state and each

peak of concentration coincides precisely with the occurence of Phase III. However migration of the MMC along the small bowel seems to be independent of plasma motilin concentration since the plasma motilin concentration decreases when the migration of the MMC occurs.

Lee KY and colleagues (1977) determined serial canine plasma motilin levels while interdigestive myoelectric activity was recorded for a period of more than two hours. The increase in motilin levels paralleled the frequency of spike potentials on slow waves. Vantrappen (1979) showed that there was a cyclic rise in plasma motilin levels coinciding with the occurence of Phase III, and concluded that motilin was one of the factors involved in the production of the activity front of the migrating motor complex in man.

Studies have shown that exogenous motilin induces a Phase III activity in dogs and humans, but not in pigs. Itoh (1976) and others (Wingate DL, 1977, Poitras P, 1980) found that when motilin (0.1-2.7 microgram/kg/hr) was infused during the interdigestive state, it induced a pattern precisely like the naturally-occuring interdigestive contractions. Those contractions were strongly

inhibited by the ingestion of food or an intravenous infusion of pentagastrin or somatostatin. Motilin did not initiate phase III activity in the post prandial period.

Borody (1981) and Bueno (1982), found that motilin was unable to induce a migrating motor complex or to modify its frequency in the pig.

Lee and colleagues (1983) showed that antimotilin serum abolished the MMC in the upper gut. Following the administration of antimotilin serum in the dog, the occurrence of the MMC in the antrum, duodenum, jejunum and ileum was temporarily interrupted for varying periods depending on the amount of antiserum administered. When the higher dose of antimotilin was administered, a more profound and prolonged inhibition occured. The immunoneutralisation of motilin abolished the MMC.

Sarr (1983) found that intravenous infusion of motilin did not alter the interval between phase IIIs in an extrinsically denervated loop of proximal jejunum, and concluded that motilin can regulate the interdigestive motility in the intact innervated bowel but not in the extrinsically denervated jejunum.

There are other hormones which can initiate a premature MMC.

Morphine has been shown to induce a migrating motor complex during the interdigestive and digestive periods. Telford (1982) and Sarna (1984) showed that morphine initiated a premature phase III activity in the fasted state and it also initiated phase III activity in the postprandial state. The morphine-initiated phase III activity in both the fasted and fed states migrated faster than spontaneous phase III activity. Sarr (1986) has shown that the minimal effective dose of morphine needed to induce a premature MMC-like activity was identical whether given intravenously or intra-arterially at the duodenum and he concluded that MMC-like activity induced by morphine is not mediated solely by opioid receptors in the wall of the duodenum.

Serotonin (Ormsbee HSIII, 1984), dopamine (Marzio L, 1986), Insulin (Prasad KR, 1986), Somatostatin (Thor P, 1978), Erythromycin (Itoh Z, 1985), Substance P at small doses (Thor PJ, 1982), Histamine, and Metoclopramide have been shown to initiate a premature MMC.

Nelson et al (Nelson DK, 1988), have studied the effect of jejunoileal transplantation on gut neuropeptide concentrations. Using the same model of autotransplantation used in this work, he found that tissue concentration of vasoactive intestinal peptide (VIP), and Substance P (SP) increased steadily from 2 to 12 weeks following transplantation. In contrast neuropeptide Y (NPY) concentration was decreased. They concluded that disruption of intrinsic and extrinsic neural continuity by jejunoileal transplantation increased the net synthesis of VIP and SP in enteric neurons following loss of an inhibitory autonomic input, and decreased NPY due to loss of NPYergic innervation.

e- POSTPRANDIAL MOTOR ACTIVITY

Mechanisms controlling postprandial disruption of the fasting motor activity remain incompletely understood.

DeWever and colleagues (1978) found that the duration of interruptions was linearly related to the caloric content of a meal and the composition of a meal once a threshold for disruption is reached. Triglycerides were much more effective than an

equicaloric amount of carbohydrate or protein in disrupting the migrating complex. The type of food is perhaps even more important in determining the duration of the disruption of the interdigestive MMC (Cohen and Snape 1989).

One mechanism controlling the inhibition may involve the presence of chyme. Heppell et al (Heppell J, 1983) studying a Thiry-Vella loop of proximal jejunum, showed that a liver meal failed to inhibit the jejunal loop MMC, however perfusion of the jejunal loop with duodenal chyme from an other dog inhibited the jejunal loop MMC. They postulated an enteric phase of postprandial inhibition.

A second mechanism may involve the postprandial plasma hormonal milieu. Many peptides and neurotransmitters given exogenously inhibit the MMC and induce a fed-like pattern, such as Pentagastrin, CCK (Wingate DL, 1978), Glucagon (Wingate DL, 1978), Substance P at high doses (Thor PJ, 1982), and Neurotensin (Thor K, 1982). MMC activity can be disrupted by sight and smell of food.

Hormonal factors alone are not sufficient. Sarna (1986) found that cross-circulation

experiments between fed and fasted dogs, using a shunt device implanted between the carotid artery and the jugular vein of two dogs, did not lead to inhibition of the MMC in the fasted dog, making a hormonal regulation alone unlikely. In addition, total parenteral nutrition does not disrupt MMC cycling, which indicates that nutrients in the blood do not activate the mechanism that alters MMC activity.

Support for neural mechanism comes from a study by Sarr (Sarr MG, 1981), who found that feeding interrupted the MMC in the duodenum but not in an isolated autotransplanted segment of jejunum, postulating that innervation was necessary for postprandial inhibition of the MMC.

Therefore an interplay of neural, hormonal and enteric mechanisms is probably involved.

2- SMALL INTESTINAL TRANSPLANTATION AND ABSORPTION

The effect of intestinal transplantation on absorption has received little attention. Previous studies of intestinal autotransplantation (Heppell J, 1981), have shown that dogs lose weight and

develop a profound diarrhea that persists for four to six weeks. The mucosa of the autotransplanted gut is blunted for up to 6 months (Ballinger WF, 1962). Kocandrle and colleagues (1966) studying the transplanted small intestine found an increased size of regenerated lymphatic channels and a complete lymphatic regeneration at the end of 4 weeks following autotransplantation. Sarr and associates (1981) have shown that motility patterns change following autotransplantation. These changes may have marked effects on absorption.

Crude, uncontrolled measurements of d-xylose and fat-absorption were found to be normal by some groups and abnormal by others; Goott and colleagues (1960) concluded that fat absorption was normal simply because transplanted dogs had a prolonged survival, and regained their preoperative weight after recovery from the operation.

Reznick and colleagues (1982) found that xylose absorption curves in the allotransplanted dogs were normal. However Ruiz (1972) found that dogs with transplanted intestine had decreased d-xylose absorption which reversed to normality within four to six months. He claimed that the immediate impairment of the intestinal function

reflected the effect of denervation.

Toledo-Pereyra and colleagues (1975) studied absorption ability of the entire small bowel for carbohydrates and vitamins after preservation for 24 hours and allotransplantation. A significant impairment in the intestinal absorption of d-xylose and vitamin A was observed in the first weeks after preservation and transplantation . Functional recovery was only observed in long-term survivors, usually transplanted dogs that lived more than 5 weeks. There was no impairment in the absorption of vitamin B12.

As interest in intestinal transplantation grew, absorption from small segments of transplanted gut was studied but specifically as a parameter of rejection, and not as a functional quality of transplanted bowel.

Cohen WB (1969) monitored absorption of simple nutrients requiring active transport using 14C-D-glucose, and passive transport using 14C-D-arabinose and found that loss of active absorption occurred concomitantly with late histological rejection. Billiar (1984) found that maltose absorption was impaired before the clinical

appearance of rejection, and concluded that maltose absorption test effectively predicts rejection and monitors the function of the intestinal graft.

Another approach has been to study the effects of selective nerve stimulation, or pharmacological manipulation on absorption. Sjovall (1983a, 1983b, 1985), Redfors (1984), and Brunsson (1979) found that sympathectomy decreased net intestinal absorption independent of changes in total blood flow or flow distribution within the bowel wall; sympathetic stimulation increased net absorption. After total small bowel denervation, sympathetic activation had little effect on absorption. Pharmacologic studies in man and rat, showed that parasympathomimetics decrease and sympathomimetics increase net absorption of water and electrolytes. Cholinergic and anticholinergic drugs influence salt and water transport and these responses support the possibility of a role for the nervous system in the control of intestinal transport.

The mechanisms of initiation and regulation of the migrating motor complex are still unclear as findings were contradictory. Some studies giving support for neural mechanisms, others for hormonal

control. Previous studies had crude uncontrolled measurements of absorption yielding to conflicting results. The overall aim of this study was to try to clarify the neural and hormonal mechanisms of regulation of intestinal motility, and the effects of transplantation on the absorptive function of the gut.

3- SPECIFIC AIMS

The specific aims of our work were to investigate:

1- The role of extrinsic and intrinsic neural continuity in the jejunal regulation of the postprandial gastroduodenal motility, by studying the regulation of gastroduodenal motility by the autotransplanted jejunoileum.

2- The individual roles of extrinsic and intrinsic neural continuity in the initiation and migration of motilin-induced MMC activity in the duodenum and in the jejunum.

3- The transit and jejunal absorption of water, glucose, electrolytes and folate in the autotransplanted jejunoileum during fasting and

feeding.

An established model of autotransplantation of the entire canine jejunoileum has been chosen to determine the early and late effects on specific enteric functions, to expand our understanding of neurohumoral control of upper gastrointestinal physiology and explore new fields in the transplant physiology. Autotransplantation was used in order to avoid confounding effects of immune rejection or immunosuppressive drugs needed with allotransplantation.

CHAPTER VI

PLAN OF THE STUDY AND METHODOLOGY

PLAN OF THE STUDY AND METHODOLOGY

1- PLAN OF THE STUDY

The objectives of this study address relevant and complementary objectives with respect to:

1- the physiology of motility regulation of the gastroduodenum by the autotransplanted jejunoileum.

2- the hormonal induction of the MMC in the autotransplanted jejunoileum.

3- the net jejunal absorption of water, glucose, electrolytes and folate in the autotransplanted jejunoileum.

In the first part of the study five dogs were prepared with a proximal jejunal infusion catheter and with gastric manometry catheters and

serosal intestinal electrodes. After two weeks, fasted dogs were studied during jejunal infusion of either isosmolar NaCl or isosmolar mixed solution. After completion of baseline studies, the dogs underwent autotransplantation of the entire jejunoileum and identical studies were repeated.

In the second part of the study three groups of dogs were studied. Group I consisted of neurally intact control dogs. In group II, intrinsic neural continuity between the duodenum and the jejunum was interrupted by transection and reanastomosis of the distal duodenum. Dogs in group III underwent jejunoileal autotransplantation. Serosal electrodes were sewn to duodenum and jejunum in all dogs. After a 2-week recovery, fasting myoelectric activity was recorded. Motilin was given 30 minutes after a spontaneous duodenal Phase III.

In the third part of the study, six dogs underwent jejunoileal transplantation. An 80 cm modified jejunal Thiry-Vella loop fashioned with a neuromuscular bridge with the proximal jejunum was made from the autotransplanted jejunoileum. Six neurally intact dogs with identical jejunal loops served as controls. Dogs were studied at 2, 4 and 8 weeks after surgery. At each time-point, in the

fasted dogs the loops were perfused on 3 occasions for 3 hours with a warmed isosmolar solution of NaCl, KCl, NaHCO3, Glucose and 14C-PEG. Loop output was collected in 15-min intervals. Transit was assessed at 1-hour and 2-hour with Phenolsulphophtalein marker. Net absorption was assessed by differences in volume infused and volume collected. The same experiments were repeated after a meal of 500 g of liver.

All experiments involved the use of female mongrel dogs aged 6-60 months, weighing 12 to 18 Kg. Study of pure bred dogs was specifically avoided to prevent any bias to a specific breed. Dogs were selected because their physiology of intestinal motility and absorption mimics that of humans.

2- EXPERIMENTAL MODELS

a- MODEL OF JEJUNOILEAL AUTOTRANSPLANTATION

The model of jejunoileal transplantation used in this study is a modification of a previously established technique. (Sarr MG, Kelly KA, 1981). Attempts at complete autotransplantation of the jejunoileum, as described by Lillehei (1959) and more recently by Cohen (1986) and Williams (1987),

have been met with a very high mortality (>50%) due to a high incidence of mesenteric arterial thrombosis. The procedure consisted in freeing up and dividing the mesenteric vessels and removal of the entire small intestine. Once removed the bowel is cooled to 5°C and replaced as an autograft by resuturing the mesenteric vessels and anastomosis of the bowel to the duodenum proximally and colon distally. Sarr has developed a model of autotransplantation whereby all neural, myogenous, lymphatic, and connective tissue continuity with the jejunoileum is transected except for the superior mesenteric vessels. This model is equivalent to models used in cardiac autotransplantation studies.

After transecting the ligament of Treitz, the duodenum is fully mobilised and transected just distal to the region supplied by the inferior pancreaticoduodenal artery, thereby interrupting intrinsic myoneural continuity with the proximal, innervated duodenum. The mesentery is then transected in radial fashion back to the superior mesenteric artery and vein just distal to the inferior pancreaticoduodenal vessels at the base of the small bowel mesentery. Similarly, the terminal ileum is transected and its mesentery divided in radial fashion back to the same region of the

superior mesenteric vessels. Next, all extrinsic nerves, lymphatics, and connective tissue at the base of the mesentery are ligated and in doing so the superior mesenteric artery and vein are skeletonised and their investing adventitia meticulously stripped off using optical magnification for a length of one cm. At this point, the distal duodenum, the entire jejunum, and the entire ileum are completely isolated from any continuity with the body except for the walls of the superior mesenteric artery and vein. Intestinal continuity is restored by reanastomosis of the duodenum and ileum by a two-layered technique using 2/0 chromic cut gut and 2/0 silk, the respective mesenteric defects are reaproximated, and the base of the mesentery of the autotransplanted jejunoileum is sewn to the retroperitoneum to afford stabilisation of the base of the mesentery. This prevents torsion around the skeletonised mesenteric vessels by the weight of the autotransplanted small bowel. (Fig 8-A,B).

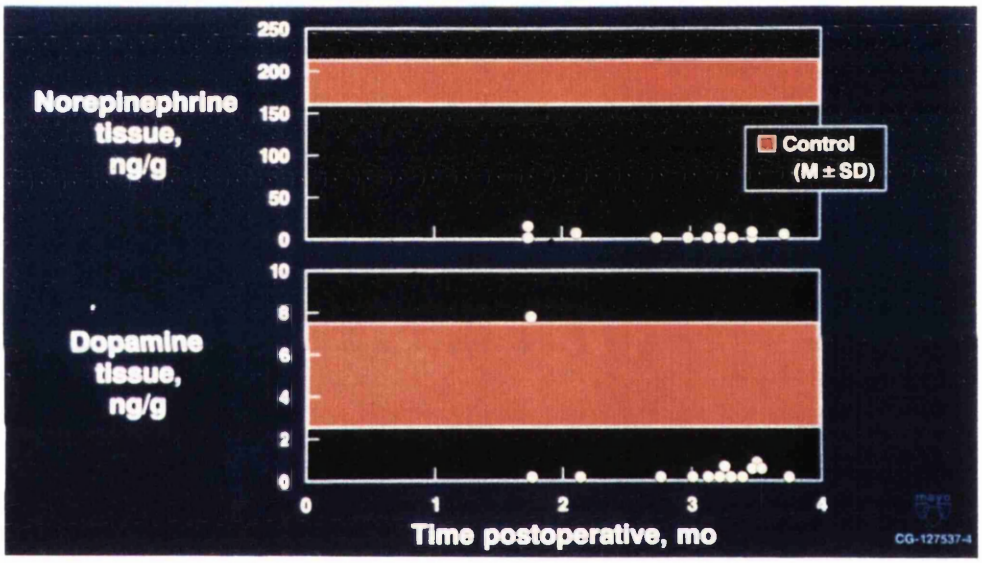
One might question whether our model of jejunoileal autotransplantation is appropriate. The motility patterns in this model agree with previous reports in a fully transplanted bowel. (Sarr MG, 1980). Sarr and colleagues (1987) have measured

tissue catecholamine concentrations before and after this technique of autotransplantation. In the normal jejunum, the concentrations of noradrenaline and dopamine were 187±10ng/g and 4.4±1 ng/g tissue, respectively and 3 months after this model of autotransplantation, the concentrations decreased markedly to <5 ng/g and <0.1 ng/g, respectively. Thus this is an excellent model of autotransplantation with a markedly decreased operative mortality (<10%). Figure 6 shows the changes in tissue concentrations of noradrenaline and dopamine after this model.

Formal autotransplantation carries too great a mortality to make it economically feasible for this type of study.

Figure 6.

JEJUNAL TISSUE CATECHOLAMINE CONCENTRATIONS AFTER JEJUNOILEAL AUTOTRANSPLANTATION



Changes in tissue concentrations of noradrenaline and dopamine after the model of autotransplantation. Catecholamines fall to low or unmeasurable levels and remain decreased for at least three months.

b- MODIFIED THIRY-VELLA LOOP (NEURO-VASCULARLY INTACT)

L. Thiry (Austrian Physiologist 1817-1897)

L. Vella (Italian Physiologist 1825-1886)

In the study of jejunal absorption, each dog underwent, in addition to the autotransplantation of the jejunoileum, the construction of an 80-cm modified Thiry-Vella loop of the proximal jejunum beginning 50cm distal to the pylorus. Enteric neural continuity with the duodenum and proximal jejunum was maintained by preserving a wide bridge of tunica muscularis, 2 cm wide by 3 cm long, between the proximal jejunum and enterically isolated jejunal loop. The mucosa and submucosa was excised. This bridge maintained myoneural continuity with the proximal gut as evidenced by maintenance of normal myoelectric patterns in the enterically isolated loop. A metal perfusion cannula was inserted into the proximal end of the jejunal loop, the proximal end was oversewn, and the distal end was brought to the skin as an end-jejunostomy. Intestinal continuity was re-established by an end-to-end anastomosis of the jejunum proximal and distal to the loop.

c- DUODENAL TRANSECTION

Each dog underwent a transection and end-to-end reanastomosis of the duodenum 5 cm proximal to the ligament of Treitz. By doing so, the area distal to the anastomosis was intrinsically denervated, however the extrinsic innervation remained intact. This model allows the study of the effects of intrinsic denervation on intestinal motility.

3- CONDUCT OF OPERATIVE PROCEDURES:

Animals were prepared after approval from and according to criteria set forth by the Animal Care Committee of the Mayo Foundation in accordance with the guidelines of the National Institute of Health. (USA).

Operative procedures were performed using a sterile technique according to standards set forth by the American Public Health Service Policy on humane care and use of laboratory animals. Dogs were anaesthetised using sodium pentothal (25 mg/Kg) and Fluothane (1%) maintenance to insure a rapid recovery from anaesthetic. All animals received antibiotic prophylaxis (Penicillin M, 250 mg IM) at

induction. Subcutaneous analgesia (Torbugesic 0.2 ml 4 to 6 hours) was administered to each dog in the postoperative period to minimise pain and discomfort.

Animals were housed in metabolic cages for the duration of the experiment period.

Method of euthanasia used at the end of the study was Pentobarbital intravenously.

4- CONDUCT OF EXPERIMENTS:

A two-week recovery period was allowed after all operative procedures before the study was started. All experiments followed a fast of at least 18 hours. Dogs rested comfortably in a Pavlov sling for the duration of the experiment. A urinary catheter was placed in the bladder at the start of each experiment to assure decompression of the bladder during the experiment.

Dogs were weighed weekly. Appetite, and bowel function assessed daily, by examining the cages and dishes.

The design of each experiment is detailed in

the chapter related to the specific study.

5- MOTILITY STUDIES:

Recording of gastric contractile activity was obtained from intraluminal polyethylene manometry catheters (Outside diameter 2.25mm, Inside diameter 1.25 mm). Manometric recordings of gastric motility were utilised preferentially in the stomach for determining patterns of motility because they give more easily recognisable patterns. Myoelectric activity in the small bowel were obtained from silver chloride (Ag/AgCl) unipolar serosal electrodes. Both electrodes and manometry catheters were embedded within flanged stainless steel cannulas implanted within the abdominal wall of the dog. Manometry catheter were perfused at a slow rate (0.1 ml/min) using strain gauges in series with a minimal compliance, pneumohydraulic perfusion apparatus. Recordings were made on Grass Model D Polygraphs using alternating current amplifiers and a time constant of 1 second. These techniques of recording motility are well-established and have been used in the Gastroenterology Unit at the Mayo Clinic for over 21 years. (Szurszewski JH, 1969).

All interdigestive motility recordings were

analysed by visual inspection of the specific phases of the migrating myoelectric complex according to the criteria established by Code and Marlett (3). (Refer to Chapter V)

The mean duration of Phase I (motor quiescence), Phase II (intermittent contractions), Phase III (regular bursts of high amplitude contractions), and Phase IV (transition period back to Phase I), was determined separately in the stomach, in the duodenum, and in the jejunum based on the actual tracings.

The period of the MMC was determined as the time elapsed between the beginning of two successive Phase IIIs at each point.

Coordination of the motor patterns of the MMC between the stomach, the duodenum, and the jejunoileum was examined by evaluating the mean durations and serial patterns for each phase in each region. Comparison of the durations and serial patterns between sites were used to evaluate coordination of the MMC between the different anatomical regions.

The frequencies of the slow waves were

measured over 5-min intervals during Phase I at one duodenal and one jejunal electrode.

Postprandial motility recordings were examined for the presence and duration of the inhibition of the MMC (presence or absence of a non-cyclic fed-like pattern of intermittent spike activity) individually in the stomach, duodenum, and jejunum.

6- ABSORPTION STUDIES:

Radionuclide (3H, 14C) activities were determined using a standard dual-counting liquid scintillation technique.

In the loop effluent, sodium and potassium concentrations were measured by a flame photometry (Beckman Klina Flame). Sodium and potassium emit characteristic spectra when excited by the flame. The flame is monitored by three photomultiplier detectors which view the flame through an optical filter specific for narrow band of wavelengths common to the individual ion. The light emitted by sodium and potassium is isolated and focused upon a photocell and is in direct proportion to the concentration of Na or K in the solution.

(Reliability Na±2.0 mEq/l, K±0.2 mEq/l).

Chloride was measured by chloride silver electrode (Corning Chloride Meter 920M). Chloride standard 100 mEq/l.

Glucose concentration was assayed with an enzymatic spectrophotometric technique (Sigma Diagnostics Glucose HK Kit).

Steady state dynamics were assessed by analysing recovery of a nonabsorbable 14C-Polyethylene Glycol (PEG) marker. Net recovery per 15-minute interval was determined in each dog for each separate experiment. A steady state for each dog was determined when the mean net recovery of marker in the effluent reached at least 95% of the mean marker infused for the 15-minute interval. In addition mean total net recovery for the duration of the steady state period was determined for each dog.

Net absorption of water, electrolytes, glucose, and folate was then calculated as the difference between the amount infused and the mean amount recovered. Net recoveries of water, electrolytes, glucose and folate were calculated for

each 15-minute period by correcting the amounts recovered (volume of effluent x concentration of substance) for 14C-PEG recovery assuming steady state dynamics.

7- TRANSIT STUDY

Transit time was expressed as the mean time needed for 50% of the corrected Phenolsulphophtalein (PSP) to traverse the perfused segment. The concentration of PSP was measured with a modification of a colorimetric analysis, to study the transit time. Transit times at one and two hours were similar and were thus combined. Net absorption and transit during fasting and after feeding at two weeks, four weeks, and eight weeks following surgery were compared.

8- STATISTICAL ANALYSIS

Because of the small number of dogs, more chance variation must be allowed and therefore comparison of mean values was performed using the Student's t test (parametric test) for paired data, with each dog serving as its own control. Summary values in the text are presented as mean values ± standard error of the mean (X ± SEM).

The Kruskal-Wallis test (non-parametric test) useful for analysing designs that involve more than 2 groups, was used to test for differences among three groups for duodenal latency.

The Wilcoxon Rank Sum test (non-parametric test, 2-sample rank test) was used to test if one group of dogs had a longer jejunal latency than the other in the motility study. Those data do not conform to a normal distribution and therefore require a non-parametric test.

Statistical significance was accepted if the p value was less than or equal to 0.05.

CHAPTER VII

REGULATION OF GASTRODUODENAL MOTILITY BY THE AUTOTRANSPLANTED JEJUNOILEUM

REGULATION OF GASTRODUODENAL MOTILITY BY THE AUTOTRANSPLANTED JEJUNOILEUM

1- INTRODUCTION

Characteristic cyclic patterns of motility of the upper gastrointestinal tract of man, dog, and most other mammalian species have been described (Szurszewski JH, 1969, Carlson GM, 1972, Code CF, 1975, Ruckebusch Y, 1977, Sarna SK, 1985). During fasting, the stomach and small intestine exhibit a cyclic pattern of motility that recurs with a period of about 2 hours. This cyclic motor activity begins in the lower oesophageal sphincter and stomach and then, in a very orderly fashion, migrates along the entire small intestine, hence the name, interdigestive migrating motor complex (MMC) (see Chapter V). Feeding interrupts this cycle and establishes a less well-defined, fed pattern of intermittent contractions. After a variable duration, depending on the type of meal and its caloric content, the interdigestive pattern of the MMC is restored (DeWever I, 1978).

The mechanisms controlling postprandial inhibition of the MMC and establishment of a fed pattern remain incompletely understood. One mechanism may involve the presence of enteric chyme and intraluminal nutrients (Heppell J, 1983). A second control mechanism may involve changes related to the postprandial plasma hormonal milieu. For instance, many putative regulatory peptides, such as cholecystokinin (Mukhopadhyay AK, 1977), pentagastrin (Weisbrodt NW), and others (Mukhopadhyay AK, 1975, Bueno L, 1976, Wingate DL, 1978, Thor K, 1982, Thor PJ, 1978), when given exogenously, inhibit the MMC and induce a fedlike pattern. The role of neural factors in this regulation has not been investigated in detail. The present study was conducted in the canine autotransplanted jejunoileum to investigate the role of extrinsic and intrinsic neural continuity in the jejunal regulation of postprandial gastroduodenal duodenal motility.

2- MATERIALS AND METHODS

a- PREPARATION OF ANIMALS:

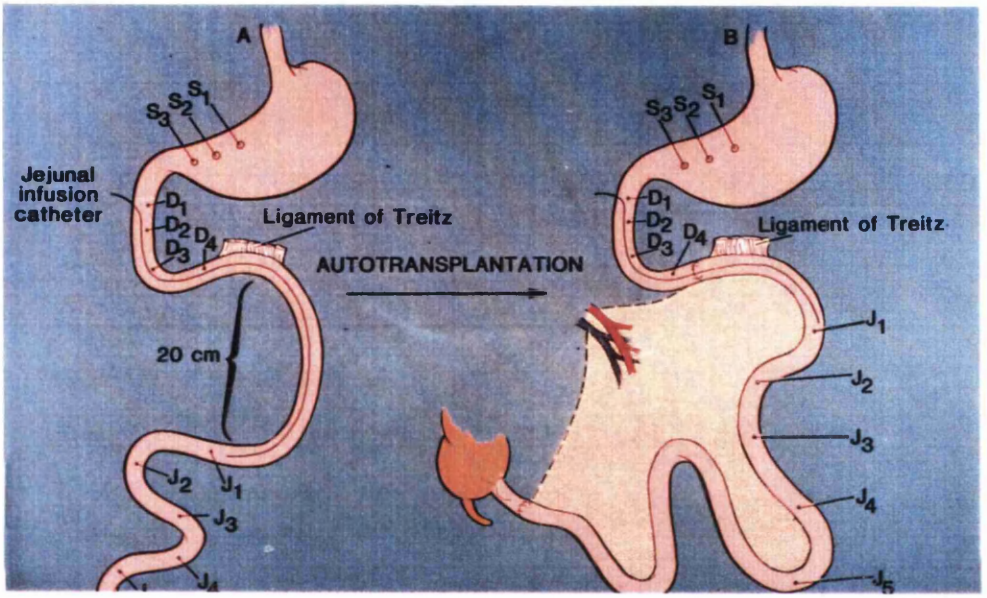
Five healthy female mongrel dogs (14-18Kg) underwent a laparotomy. A polyethylene catheter

(Outer diameter 2 mm) was introduced via a proximal duodenotomy and threaded 20 cm distal to the ligament of Treitz (Fig 7-A). Three polyethylene manometry catheters (Outer diameter 2.3 mm, Inner diameter 1.3 mm) were implanted into the gastric antrum, and nine serosal monopolar Ag/AgCl electrodes were positioned along the duodenum (at 2 cm interval) and the jejunum (at 10 cm interval, starting 10 cm distal to the ligament of Treitz). The gastric and jejunal catheters and the wires from the electrodes were cemented in two flanged metal cannulas implanted within the abdominal wall.

Soon after completion of the baseline control studies, the dogs underwent a jejunoileal autotransplantation (Sarr MG, 1987), whereby all neural, myogenous, lymphatic, and connective tissue continuity with the jejunoileum was transected, except for the superior mesenteric artery and vein, as described in chapter VI. (Fig 7-B).

FIGURE 7-A.

AUTOTRANSPLANTATION OF CANINE JEJUNOILEUM



Preparation of dog model.

(A) Manometry catheters (S1-S3) were positioned in the antrum, and serosal electrodes were sewn to the duodenum (D1-D4) and jejunoileum (J1-J5).

A jejunal infusion catheter was placed through a duodenotomy and threaded into the proximal jejunum.

(B) The entire jejunoileum was autotransplanted (shaded areas).

b- CONDUCT OF EXPERIMENTS:

All dogs were allowed at least two weeks to recover after each operation and had normal oral intake and bowel habits.

All studies were performed in fully conscious, fasted dogs resting comfortably in a Pavlov sling. A urinary catheter was placed in the bladder at the start of each experiment to assure decompression of the bladder during the experiment. Gastric contractile activity was measured continuously by perfusing the gastric manometry catheters (0.1 ml/min) via a minimal-compliance, pneumohydraulic capillary perfusion apparatus. Myoelectric activity was recorded continuously using alternating current amplifiers and a time constant of 1 second. In several separate days, a radiocontrast agent (Hypaque) was added to the infusate into the jejunum and visualised by fluoroscopy to exclude any reflux into the stomach and test the accuracy of the technique used; no contrast was ever observed in the duodenum.

Studies were performed identically before and at three to six weeks after jejunoileal autotransplantation. Each experiment was performed

randomly on at least four occasions in each dog, in order to get enough values for statistical comparison.

For the control studies, Sodium chloride (154mM), warmed to 39°C, was infused into the jejunal catheter at 2.9 ml/min for the duration of each day's experiment. Motility was recorded for 6-8 hours or for 3 complete cycles of the MMC. On days when nutrient was infused, warmed NaCl (154 mM) was infused at the start of the experiment at 2.9 ml/min. Thirty minutes after one complete cycle of the duodenal MMC, the jejunal infusion was changed to an isosmolar solution of warmed 50% Meritene (Sandoz, Parsippany, NJ 07054), a mixed nutrient solution (0.48 kcal/ml) consisting of 24% protein, 46% carbohydrate, and 30% fat. The infusions were continued at a rate of 2.9 ml/min for 5 hours (total 668 kcal) with continuous monitoring of motility.

c- ANALYSIS OF DATA:

All motility records were analysed by visual inspection. Manometric recordings from the stomach were specifically used because motor patterns are more easily recognised (Tanaka M, 1988) than gastric myoelectric recordings. Phases of the MMC were recognised according to criteria set forth by Code and Marlett (Code CF, 1975). The records were evaluated for the presence or absence of the MMC in each region during the jejunal infusions of NaCl or nutrient. In each dog, the mean period of the MMC in the stomach, duodenum, and jejunum was determined separately. The latency of inhibition of the MMC by the jejunal infusion was measured between the time the infusion was started and the first appearance of a fed-like pattern in the gastroduodenal region. The frequencies of the slow wave were measured over 5-min intervals during Phase I at one duodenal and one jejunal electrode.

d- STATISTICAL ANALYSIS:

Comparison of mean values was performed using Student's t test for paired data with each dog serving as its own control. Summary values in the text are presented as mean values ± standard error of

the mean (X±SEM).

3- RESULTS:

a- GENERAL ASPECTS:

All five dogs survived both operations and were alive and well at two to three months after transplantation. Although all dogs developed a profuse, watery diarrhea immediately after autotransplantation, they remained healthy with good appetites. The diarrhea lasted up to six weeks and was associated with loss of 9±1% body weight. At the time of sacrifice about 8 to 12 weeks after autotransplantation, the gut looked normal without evidence of dilatation, bowel obstruction, or ischaemia.

b- MOTILITY:

NaCl Infusion.

The infusion of NaCl into the jejunum did not interrupt the MMC in the gastroduodenum or in the jejunoileum either before or after the jejunoileal transplantation. In the intact dogs, before transplantation, all gastroduodenal MMCs

migrated distally in sequential fashion in to the jejunum (Fig 7-Ba). As expected, there was complete temporal coordination between MMCs in the duodenum and those in the jejunum. The period of the MMC was virtually identical in the stomach (116±5 min) and duodenum (114±6 min) (Table 7-1-a). In contrast after jejunoileal transplantation, although the characteristic MMC persisted in each region, there was complete lack of coordination between the MMCs in the innervated gastroduodenum and in the transplanted jejunum. The MMC cycled independently in each region (Fig 7-Bb). The periods of the MMC in the stomach (138±6 min) were different from that in the transplanted jejunoileum (95±5 min, $P<0.05$) (Table 7-1-b). The periods of the MMC were each different in the stomach, in the duodenum, and in the jejunoileum before compared to after jejunoileal autotransplantation ($P<0.05$).

Table 7-1-a.

CHARACTERISTICS OF INTERDIGESTIVE MOTILITY
BEFORE AND AFTER
AUTOTRANSPLANTATION OF CANINE JEJUNOILEUM

Before autotransplantation (intact dog) *

Characteristic	Stomach	Duodenum	Jejunum
Duration of Phases (min)			
Phase I	45±5	43±7	43±5
Phase II	53±4	61±3	64±3
Phase III	16±1	9±1	6±1
Phase IV	2±1	2±1	2±1
Period of MMC (min)	116±5	114±6	114±6
Slow-wave frequency (Cycles/min)		20±0.1	17±0.5

* Mean ± SEM, N=5 dogs.

Table 7-1-b.

After autotransplantation *

Characteristic	Stomach	Duodenum	Jejunum
Duration of Phases (min)			
Phase I	41±2	42±2	28±4 **
Phase II	73±9	75±9	53±4
Phase III	18±2	10±1	7±1
Phase IV	2±1	2±1	2±1
Period of MMC (min)	138±6**	135±7**	95±5***
Slow-wave frequency (Cycles/min)		19±0.5	14±0.5*

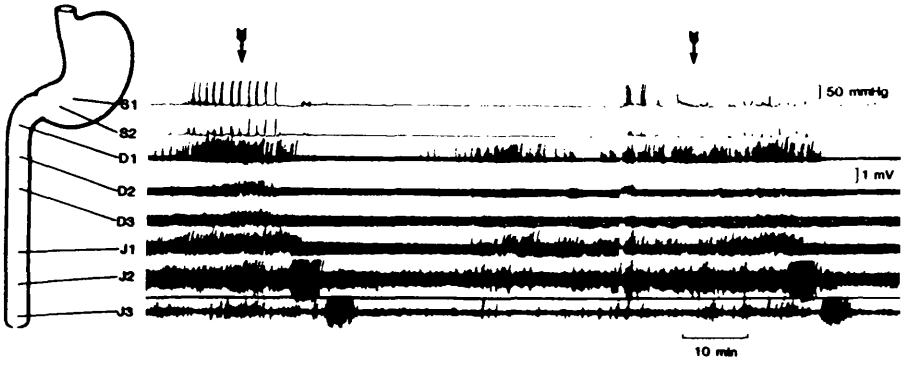
* Mean ± SEM, N=5 dogs.

** Different from the same region before autotransplantation; P<0.05

*** Different from stomach and duodenum after autotransplantation; P<0.05.

FIGURE 7-B-a.

MMC IN THE INTACT DOG DURING INFUSION OF SALINE

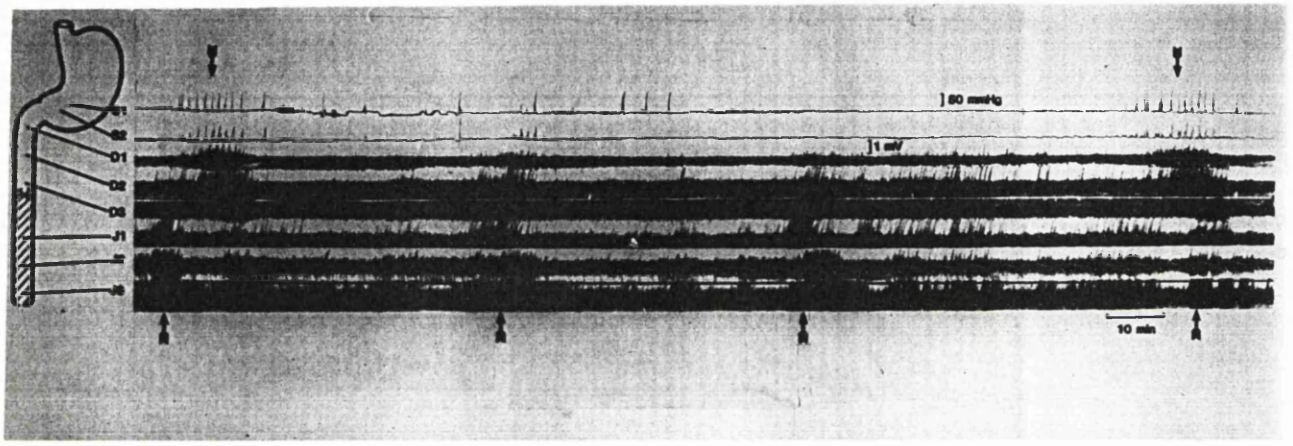


Characteristic interdigestive motor patterns in dog during jejunal infusion of 154 mM of NaCl.
Intact dog before jejunoileal autotransplantation.
Arrows depict onset of Phase III.

FIGURE 7-B-b.

MMC IN THE AUTOTRANSPLANTED DOG

DURING INFUSION OF SALINE



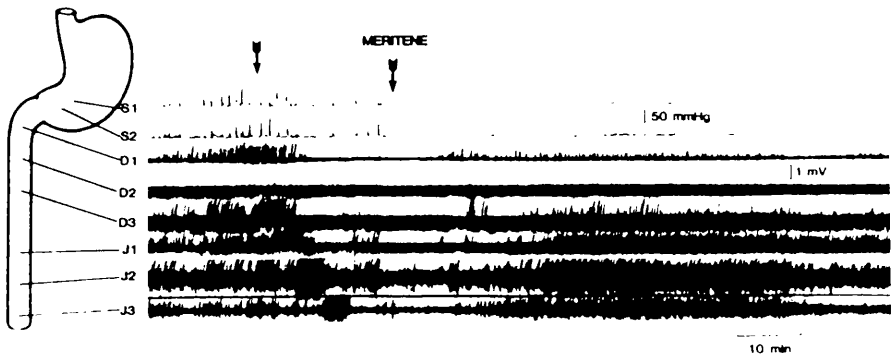
Characteristic interdigestive motor patterns in dog during jejunal infusion of 154 mM NaCl.
After jejunoileal autotransplantation. Note temporal dissociation of duodenal and jejunoileal MMCs. Upper arrows denote gastroduodenal phase III and lower arrows, jejunal phase III.

Nutrient infusion:

Infusion of the nutrient solution into the jejunum interrupted the MMC in the gastroduodenum and in the jejunum for the duration of the infusion (5 hours) in all dogs before (Figure 8-C-a) and after (Figure 8-C-b) jejunoileal transplantation. A noncyclic pattern of infrequent, low-amplitude contractions occurred in the stomach, while a noncyclic pattern of intermittent spike potentials (fed-like pattern) occurred in the duodenal and jejunal electrodes. This interruption of the MMC was established within 5±1min in the intact dogs and within 4±1min in the autotransplanted dogs.

FIGURE 7-C-a.

MMC IN THE INTACT DOG DURING INFUSION OF MERITENE



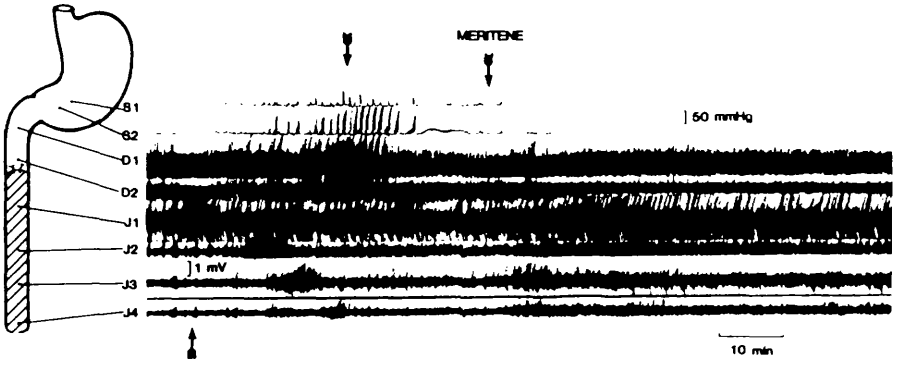
Motor patterns in dog after starting 5-hr jejunal infusion of isosmolar mixed nutrient solution (50% solution of Meritene).

Intact dog before jejunoileal autotransplantation. First arrow depicts onset of Phase III.

FIGURE 7-C-b.

MMC IN THE AUTOTRANSPLANTED DOG DURING

INFUSION OF MERITENE



After jejunoileal autotransplantation. Upper arrow shows gastroduodenal phase III and lower arrow, jejunoileal phase III.

c- SLOW-WAVE FREQUENCY:

The frequency (cycles/min) of the duodenal slow wave did not differ before (20.0±0.1) and after (19.0±0.5) jejunoileal transplantation. In contrast, the jejunal slow wave decreased from 17.0±0.5 before (Table 8-1-a) to 14.0 ±0.5 ($P<0.05$) after (Table 7-1-b) jejunoileal autotransplantation, as expected distal to an intestinal transection . Infusion of nutrients had no effects on slow-wave frequencies either in the duodenum (19.0±0.1) or in the jejunum (15.0±0.1).

4- DISCUSSION:

This study showed that the jejunoileum can regulate motor patterns of the stomach and duodenum. Infusion of nutrients into the intact jejunum and into the autotransplanted jejunum interrupted the MMC in the gastroduodenal region, as well as in the jejunoileum, and induced a fedlike pattern of intermittent contractile activity. This supports the hypothesis that one mechanism controlling postprandial inhibition of interdigestive motility (MMC) involves, at least in part, hormonal factors released from the jejunoileum in response to luminal nutrients and that this mechanism does not require

the maintenance of intrinsic or extrinsic neural continuity to or from the jejunoileum.

Considerable experimental evidence supports a complex interplay of hormonal factors, extrinsic innervation, intrinsic neural control, and local enteric or mechanical factors in the control of motor patterns. Probably the most well-studied mechanism involves a hormonal regulation. Infusion of putative postprandial regulatory peptides have been shown to inhibit the MMC and establish a fedlike pattern of motility (Sarna SK, 1985). In other studies, feeding the intact gut inhibited the MMC in an enterically isolated, autotransplanted fundic pouch (Thomas PA, 1979). Similarly, the contractile activity in an in vitro, isolated stomach perfused by the circulation of a donor dog was altered when the donor was fed (Pilot MA, 1982). The present study provides further support for an important regulation by the postprandial plasma hormonal profile because the autotransplanted jejunoileum lacked any neural continuity with the remainder of the gut. Thus the presence of jejunal nutrients released hormonal factors that altered gastric and duodenal motor patterns by inhibiting the MMC and inducing a fedlike pattern. The specific hormones involved remain unknown.

While hormonal control mechanisms undoubtedly exist, they may not be the only regulatory mechanisms. Support for a role of extrinsic innervation in control of postprandial motor activity comes both from studies of selective extrinsic peripheral denervation and from central neural stimulation. Early studies showed that after vagotomy (Marik F, 1975, Reverdin N, 1979), but not after gut sympathectomy (Marlett JA, 1979), conversion from a fasting to a fed motor pattern with feeding was impaired, suggesting a role for extrinsic vagal innervation. Additional support for neural factors was provided by demonstrating that feeding of small meals (50g and 100g of liver) failed to interrupt the MMC in the extrinsically denervated jejunoileum (Sarr MG, 1981, 1987, Heppell J, 1983); however, a larger meal (500 g of liver), which might be expected to be more effective in releasing postprandial regulatory hormones, did inhibit the MMC.

Central neural effects, induced by intracerebroventricular administration of putative neuroregulatory peptides such cholecystokinin and others (Bueno L, 1982, 1983a, 1983b, 1985, Fargeas MJ, 1985), alter upper gut motor patterns by turning

on or off the MMC; some of these specific effects act via vagal efferent pathways (Bueno L, 1983a, Bueno L, 1985). These studies support a role for central neural modulation of motor patterns via extrinsic innervation to the gut. However, Hashmonai and associates (1987), showed that after decentralisation of the upper gut (total sympathectomy and vagotomy), the motor response to feeding with inhibition of the MMC was unchanged compared to control dogs, suggesting that postprandial inhibition of the MMC may occur without central nervous input. The present study suggests that jejunal regulation of the upper gut postprandial motor patterns by luminal nutrients does not occur through activation of either afferent or efferent extrinsic nerves to the jejunoileum.

Intrinsic neural pathways within the wall of the bowel may also be important. Simple intestinal transection disrupts the coordination of fasting motor patterns across the site of transection (Sarna SK, 1983). Frantzides and colleagues (1987) have shown that long intestino-intestinal reflexes can inhibit the presence and migration of the MMC. Local intraarterial injection of neostigmine caused an increase in contractions locally and inhibited the MMC in progress both proximally and distally, this

effect was inhibited by intestinal transection.

The present study demonstrates that jejunoileal regulation of upper gut motility induced by the presence of luminal nutrients is not mediated by enteric intestino-intestinal inhibitory reflexes because it persists after jejunoileal autotransplantation, which severs all intrinsic neural continuity between the duodenum and the jejunum.

Local enteric control of intestinal motor patterns may also occur, either by mechanical effects or by the presence of luminal nutrients. Azpiroz and Malagelada (1984) have shown that proximal gastric distension with an intraluminal balloon abolished the MMC in the stomach and upper intestine, suggesting a role for mechanical factors in the stomach. Oral feeding failed to interrupt the MMC in an isolated (Thiry-Vella) jejunal loop; however, perfusion of the loop with postprandial duodenal chyme from another dog (Heppell J, 1983) or with nutrients (Eeckhout C, 1980) established a postprandial motor pattern in the loop, suggesting a local enteric control of motor activity.

The presence of postprandial chyme in the

lumen of that segment of gut, however, is not a prerequisite for induction of a fed pattern of motility. Although inhibition of the MMC in the jejunoileal segment in the present study may have been mediated by local effects of the nutrients within the lumen, the presence of luminal nutrients in the stomach and duodenum were not necessary for the inhibition of the gastric and duodenal MMC. One might question whether reflux of the nutrient infusion into the duodenum occurred; but no reflux could be demonstrated radiologically when radiocontrast agent was added to the infusate.

Finally, the present experiments showed that intrajejunal infusion of nutrients inhibited the MMC and induced a fed-like pattern of motility. Whether this fed-like pattern was indeed the characteristic postprandial pattern (Ehrlein HJ, 1987, Summers RW, 1981) is unknown. All that can be stated about the motility patterns during jejunal infusion of nutrients is that the MMC was inhibited and that a fedlike pattern was established for the duration of the nutrient infusion.

In a previous study (Spencer MP, 1990) the effect of extrinsic neural continuity to the stomach on the jejunal regulation of gastric motility

patterns was determined. Four dogs underwent transection of all extrinsic and intrinsic neural continuity to the stomach except for careful preservation of vagal innervation. Antral manometry catheters, antral electrodes, intestinal electrodes, and a jejunal infusion catheter were placed. After a 2-week recovery, studies of myoelectric and contractile activity of the stomach and the small bowel during fasting were recorded on four occasions during infusion of isosmolar solutions of either nonnutrient NaCl or mixed nutrients into the jejunum. Identical studies were repeated after completion of extrinsic denervation of the stomach by supradiaphragmatic vagotomy. Jejunal infusion of nutrients inhibited cyclic motility patterns in the stomach and small intestine, both before and after completion of extrinsic denervation. It was concluded that inhibition of interdigestive gastric motility patterns by jejunally infused nutrients is mediated by hormonal mechanisms and not by nonvagal or vagal extrinsic neural input to the stomach. These findings give indirect support to the results of the present study which lend support to a major role of hormonal factors in jejunoileal regulation of postprandial motility patterns, demonstrated in the canine model of jejunoileal autotransplantation. This information is important for the clinical

application of intestinal transplantation.

The physiological changes in motility that occur with feeding, just as with gastric and pancreatic secretion, may very well involve cephalic, gastric, and intestinal (duodenal, jejunal, ileal) phases, each of which have their own interplay of hormonal, neural, and local control mechanisms.

CHAPTER VIII

HORMONAL INDUCTION OF THE MMC IN THE AUTOTRANSPLANTED JEJUNOILEUM

HORMONAL INDUCTION OF THE MMC IN THE AUTOTRANSPLANTED JEJUNOILEUM

1- INTRODUCTION

In the fasted interdigestive state, most nonruminants exhibit a characteristic cyclic pattern of gastrointestinal motility (Szurszewski JH, 1969) termed the interdigestive migrating motor complex (MMC). This cyclic motility pattern consists of four consecutive phases (Code CF, 1975). The most characteristic phase of the MMC is Phase III which consists of a burst of large-amplitude contractions lasting 4 to 8 minutes. Phase III activity originates in the lower oesophageal sphincter and stomach, from where it appears sequentially in the duodenum and migrates distally to the terminal ileum in an orderly fashion.

The factors governing the initiation of interdigestive motility patterns are not well understood. Several studies favour a primary neural control (Diamant NE, 1985), while others support the

concept of a primary hormonal control (Poitras P, 1984-a). Motilin, a putative regulatory peptide synthesised in the enterochromaffin cells of the duodenal mucosa and the proximal jejunum (Polak JM, 1975, Pearse AGE, 1974) has been suggested as the principal regulatory hormone.

The plasma concentration of motilin cycles in temporal association with the MMC in the duodenum reaching peak levels during Phase III (Sarr MG, 1981, Itoh Z, 1978, Lee KY, 1977, Vantrappen G, 1979). Exogenous motilin induces Phase III-like activity in the stomach and duodenum which migrates distally (Sarr MG, 1986a and 1986b, Vantrappen G, 1979, Bueno L, 1982, Wingate DL, 1977, Itoh Z, 1976, Thomas PA, 1979). Other studies suggest hormonal and humoral agents, such as morphine (Sarr MG, 1986, Sarna SK, 1982, 1984, 1986-b, Telford GL, 1982), serotonin (Ormsbee HS III, 1984), dopamine (Marzio L, 1986), insulin (Prasad KR, 1986), somatostatin (Thor P, 1978), and erythromycin (Itoh Z, 1985) can also initiate premature Phase III-like activity or increase the frequency of successive MMC cycles by decreasing their period.

While these humoral factors can initiate the MMC, the role played by extrinsic and intrinsic

enteric nerves in mediating hormonally-induced Phase III-like activity is not well understood. Previously, Sarr and associates (1981c) noticed that an infusion of motilin consistently failed to induce a premature MMC in the autotransplanted short segment of jejunum.

The present study was conducted to investigate the individual roles of extrinsic and intrinsic neural continuity in the initiation and migration of motilin-induced MMC activity in the duodenum and in the jejunoileum. In one group of dogs, the intrinsic nerves between the duodenum and the jejunum were divided by transecting the distal duodenum. Another group of dogs underwent autotransplantation of the jejunoileum, therefore all the extrinsic and intrinsic neural continuity to the entire jejunoileum was transected. The response to exogenous motilin was then determined.

2- MATERIALS AND METHODS

a- PREPARATION OF ANIMALS:

Three groups of healthy female mongrel dogs weighing 12 to 18 Kg were studied.

Group I- control (n=4) underwent a laparotomy and placement of nine monopolar Ag/AgCl electrodes on the serosa of intestine; four electrodes were spaced along the proximal to mid-duodenum and five were positioned at 20 cm intervals along the jejunum, starting 10 cm distal to the ligament of Treitz (Fig 8-A).

Group II- intrinsic transection (n=3) underwent identical placement of electrodes after transection and end-to-end reanastomosis of the duodenum 5 cm proximal to the ligament of Treitz (Fig 8-B).

Group III- intrinsic/extrinsic transection (n=4) underwent a jejunoileal autotransplantation whereby all neural, myogenic, lymphatic and connective tissue input to the jejunoileum was transected. Nine serosal monopolar Ag/AgCl electrodes were positioned a the same locations as in Groups I and II (Fig 8-C).

b- CONDUCT OF EXPERIMENTS:

All dogs were allowed two weeks to recover after each operation. All studies were performed in

fully conscious dogs resting comfortably in a Pavlov sling.

Dogs were fasted for at least 18 hours before each study. Myoelectric activity, recorded continuously using alternating current amplifiers and a time constant of one second, was displayed on Grass Model 7D polygraph recorder.

Studies were performed in each group on at least four occasions. Baseline studies of spontaneous myoelectric activity were obtained.

Administration of motilin (0.1 microg/kg IV over 15 to 30 seconds) was given 30 minutes after passage of Phase III through the duodenum. This dose, although leading to plasma concentrations three times greater than endogenous peak concentrations occuring during spontaneous Phase III, has been shown previously to reliably induce premature Phase III activity in neurally intact control dogs (Sarr MG, 1986b, 1988).

c- ANALYSIS OF DATA:

All myoelectric records were analysed by visual inspection. Phases of the MMC were recognised

according to the criteria set forth by Code and Marlett (Code CF, 1975). The records were evaluated for the induction of Phase III activity in the duodenum and jejunum after motilin. In each dog, the mean duration of Phase III activity and the mean latency to response was determined separately in the duodenum and jejunum. The presence or absence of aborally directed migration from one region to the other and within each region was assessed.

d- STATISTICAL ANALYSIS:

Summary values in the text are presented as mean values ± standard error of the mean (X±SEM) unless stated differently. Duodenal latencies were summarised as medians (range) in minutes to response (Table 8-1). The Kruskal-Wallis test was used to test for differences among the three groups for duodenal latency. The Wilcoxon Rank Sum statistic was used to test if Group I had a longer jejunal latency than did group II.

3- RESULTS:

a- General aspects

All dogs in all groups remained in a healthy state for the duration of the experiments.

In Group III (Autotransplants), all dogs developed a profuse, watery diarrhea within two days of operation, but they remained healthy with good appetites. The diarrhea lasted up to six weeks and was associated with loss of 9±1% of body weight.

b- MYOELECTRIC ACTIVITY AFTER EXOGENOUS MOTILIN

Group I- control:

Motilin induced a premature Phase III that began in the most proximal duodenal electrode and migrated sequentially along the distal electrodes in all dogs (Fig 8-D). The median latency between onset of Phase III in the proximal duodenal electrode and the proximal jejunal electrode was five minutes (Table 8-1). The characteristics of the Motilin-induced premature MMC were very similar in overall appearance and in the duration of Phase III activity when compared to the spontaneous MMC. The duration of duodenal and jejunal Phase III activity after motilin was 6±1 minutes and 5±1 minutes, respectively.

Group II- intrinsic transection:

The period of the jejunal MMC was shorter (78±13 minutes) than in the duodenum (126±30 minutes).($p<0.05$).

In each of the three dogs, administration of motilin induced premature Phase III of activity in both the duodenum and jejunum (Fig 8-E). The overall appearance and characteristics of motilin-induced Phase III were similar to those of spontaneously occuring Phase III's; spike potentials occured with each slow wave for a duration of 6.5±1 minutes in the duodenum and 7.5±1 in the jejunum (Table 8-1).

The motilin-induced Phase IIIs began simultaneously in the most proximal duodenal electrode and in the most proximal jejunal electrode, from where they migrated to the more distal (aboral) electrodes in each region. The median latency to onset of Phase III in the duodenum and in the jejunum were not different; two minutes vs two minutes, respectively. The latency to onset of duodenal Phase III was not statistically different from Group I- control, two minutes vs three minutes, respectively; $P>0.05$ (Table 8-1), but the latency in the jejunum was shorter than in the

controls; two minutes vs 10.5 minutes; P=0.028. The motilin-induced duodenal Phase IIIs did not migrate across the site of transection into the jejunum.

Group III- Autotransplantation of jejunoileum:

The administration of motilin resulted in a typical premature Phase III in the duodenum lasting 6±2.5 minutes and which migrated distally within the duodenal segment but was not propagated distally to the jejunal electrodes (Fig 8-F). The latency to onset of Phase III in the duodenum, one minute, was also not different than in Group I (Table 8-1). In contrast, in the extrinsically denervated jejunum, motilin induced a short burst of spike potentials which occured simultaneously in all jejunal electrodes (Fig 8-F). This spiking electrical activity occurred within one minute after administration of motilin, but did not migrate distally within the jejunum. In contrast to group II, no characteristic Phase III activity that began in proximal jejunum and migrated sequentially through the jejunal electrodes was ever evident.

TABLE 8-1.

Latency of Interdigestive Motility
After Exogenous Motilin (0.1 microg/kg IV)

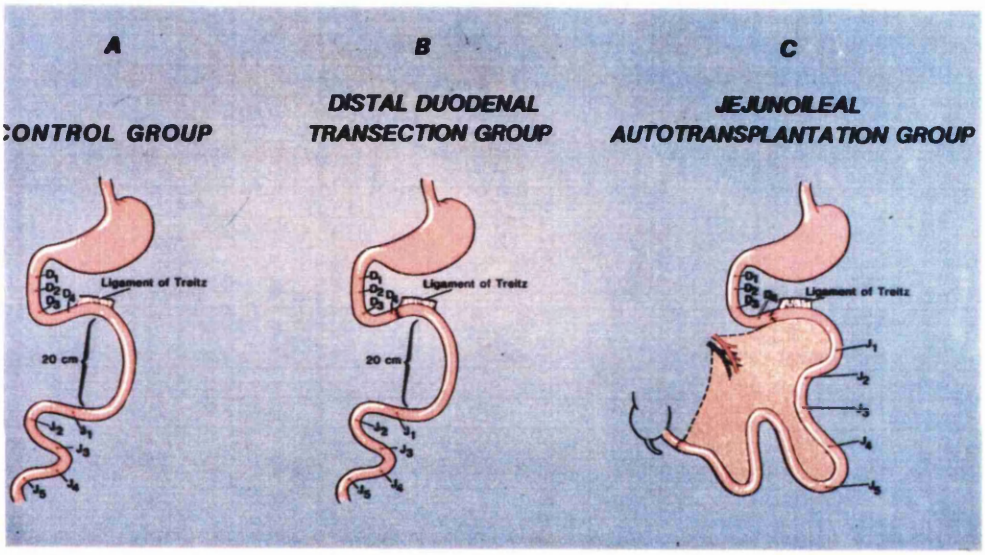
Characteristic	Group I Control n=4 dogs	Group II Intrinsic Transection n=3 dogs	Group III Intrinsic/ Extrinsic n=4 dogs
Latency to response			
Duodenum	3 (8)	2 (1)	1 (2)
Jejunum	10.5 (9)	2 (2)	---------

Minutes, median (range), n>4 experiments in each dog.
Shorter than Group I (controls), P=0.028.

FIGURE 8-A, 8-B, and 8-C.

JEJUNOILEAL PREPARATIONS

DISRUPTION OF NEURAL CONTINUITY



Preparations.

D1-4 and J1-5 serosal electrodes.

A) Group I- intact control

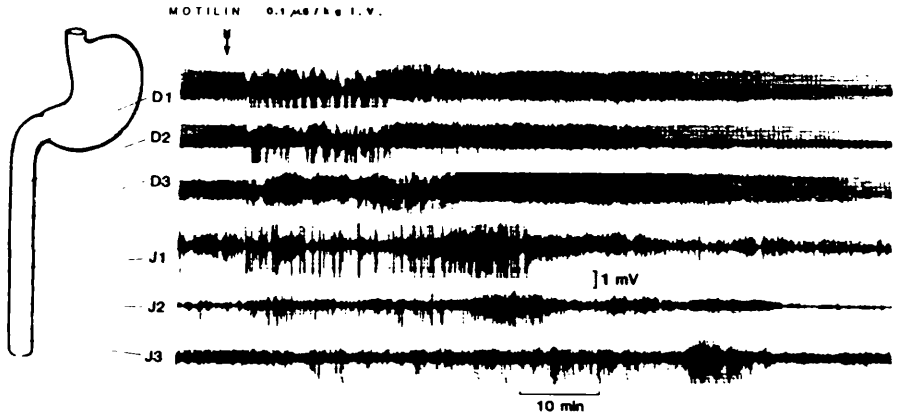
B) Group II- intrinsic transection with transection and reanastomosis of distal duodenum

C) Group III- Intrinsic/extrinsic transection with autotransplantation of the entire jejunoileum.

FIGURE 8-D.

MOTILIN-INDUCED MOTILITY PATTERNS

IN INTACT CONTROL DOG

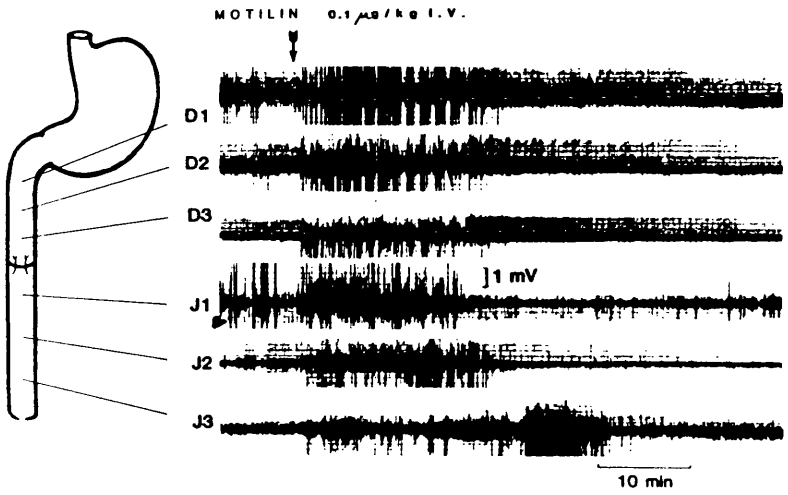


Induction of a premature Phase III activity (arrow) by exogenous motilin in Group I- Control.

FIGURE 8-E.

MOTILIN-INDUCED MOTILITY PATTERNS

AFTER DISTAL DUODENAL TRANSECTION

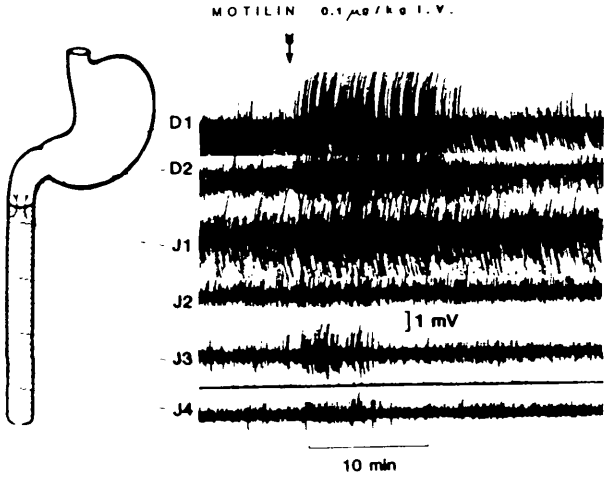


Induction of a premature Phase III activity in duodenum and jejunum by exogenous motilin in Group II- Intrinsic transection.

FIGURE 8-F.

MOTILIN-INDUCED MOTILITY PATTERNS

AFTER JEJUNOILEAL AUTOTRANSPLANTATION



Induction of a premature Phase III activity in duodenum and of spontaneous spike activity in denervated jejunum by exogenous motilin in Group III- intrinsic/extrinsic transection. Note lack of a characteristic Phase III activity in the jejunum.

4- DISCUSSION:

The peptide motilin is the most likely candidate hormone involved in the control of interdigestive motility patterns. Plasma motilin concentration fluctuates with the phases of the MMC, being greatest during Phase III in the stomach and duodenum (Sarr MG, 1981c, Itoh Z, 1978, Lee KY, 1977, Vantrappen G, 1979).

Exogenous motilin, when administered to neurally intact dogs, gives rise to premature Phase III activity which begins in the stomach and duodenum and migrates distally throughout the jejunoileum (Sarr MG, 1981c, 1986a, Vantrappen G, 1979, Bueno L, 1982, Wingate DL, 1977, Itoh Z, 1976, Thomas PA, 1979, Holloway RH, 1985). As confirmed in our present study, these motilin-induced MMCs closely resemble spontaneous MMCs in most characteristics, such as duration of premature Phase III activity and the velocity of migration (Sarr MG, 1986).

Administration of specific antimotilin serum, which immunoneutralises the circulating plasma motilin, inhibits the occurence of the MMC in the stomach and upper small intestine and converts

the motility pattern to one of intermittent, non-cyclic concentrations (Poitras P, 1984, Lee KY, 1983).

Tanaka and Sarr (Tanaka M, 1988) have shown that total duodenectomy, which removes the major source of endogenous motilin production, also abolishes the presence of gastric MMC activity. Feeding, which inhibits the cycling of the MMC, also leads to a decrease in plasma motilin concentration. (Itoh Z, 1978).

All these studies provide circumstantial and supportive evidence that plasma motilin concentration may play an important role in the initiation of the interdigestive MMC activity in the upper gut.

However, the importance of plasma motilin in the control of jejunal and ileal motility patterns is less well supported (Poitras P, 1980). The distal small intestine does not appear to be closely associated with cyclic release of endogenous motilin. Although immunoneutralisation (Poitras P, 1984, Lee KY, 1983) and duodenectomy (Tanaka M, 1988) abolished the MMC in the upper gut, distal jejunoileal MMCs persisted. Exogenous motilin

induces premature MMC activity in the proximal jejunum, but the sensitivity of response decreased in the distal small bowel and no response can be elicited in the ileum. (Matsumoto T, 1986).

Interest in this control stems from observations on motility patterns after selective denervations and specifically after jejunoileal transplantation. Sarr and colleagues (1989) have shown that after transection of intrinsic neural continuity between duodenum and jejunum, but with maintenance of extrinsic innervation, the MMCs in the duodenum and the jejunum remained, overall, temporally coordinated; however, the coordination was less exact than in control dogs. Indeed, the migration from duodenum to jejunum appeared to have been disrupted, but the initiation of MMCs in each region appeared, nevertheless, temporally associated. This might imply that the MMCs in each region were initiated separately, raising the question of separate but related hormonal induction of the MMC in each region. After autotransplantation of the entire jejunoileum, the jejunoileal MMC continues to cycle, but it cycles independently from the duodenal MMC and with a different period. (Sarr MG, 1981, 1987).

There was no association between plasma motilin concentration and the MMC in the autotransplanted jejunoileum; moreover, a continuous intravenous infusion of motilin did not shorten the period of the jejunal MMC (Sarr MG, 1981c). This suggested that extrinsic innervation may be involved in the induction of the MMC by the putative regulatory peptide motilin.

The present study appears to confirm this concept. In neurally intact control dogs, exogenous motilin induced a premature MMC that originated in the duodenum and migrated from there into the proximal jejunum few minutes later. This supports past observations suggesting that the duodenum suppresses the independent cycling of the jejunal MMC by a brake effect mediated via intrinsic neural continuity (Tanaka M, 1988). However, after disruption of intrinsic neural continuity, exogenous motilin induced a premature MMC simultaneously in the duodenum and in the jejunum. This observation suggests that when intrinsic neural continuity is disrupted, hormonal effects may act simultaneously on different regions (duodenum, jejunum) without the braking effect of the duodenum, similar to the findings of Matsumoto (1986).

In contrast, after disruption of both intrinsic and extrinsic neural continuity to the jejunoileum, in the autotransplantation model, exogenous motilin failed to induce premature MMC activity in the jejunoileum while still inducing an MMC in the duodenum. This is a strong evidence that extrinsic innervation may mediate the hormonal signal for induction of MMC activity, at least in the proximal jejunum.

Whether extrinsic innervation is necessary for humoral induction of the MMC in the duodenum is unknown and cannot be determined from the design of the experiments in this study. However, previous experiments (Sarr MG, 1986-b, 1988), suggest that motilin and morphine exert effects on the duodenum by stimulating a mechanism outside the wall of the duodenum; this mechanism may involve extrinsic innervation.

In the present study, motilin administered to the extrinsically denervated jejunum did trigger a burst of non-migrating spike potentials which occured simultaneously in all the jejunal electrodes. This is consistent with observations by Strunz et al (Strunz U, 1975) who found a direct motor effect of motilin on muscle strips of stomach

and upper small intestine from rabbit and man in vitro. The smooth muscle preparations contracted vigorously in response to nanomolar concentrations of motilin, and the response was not abolished after ganglion blockade by hexamethonium. In contrast, Fox and colleagues (1983, 1984) found a contractile response in the anaesthetised dog stomach and jejunum to close intraarterial administration of Motilin, but his response appeared to be a direct effect on intrinsic nerves and not on the small the smooth muscle cell. Although contradictory, these data suggest that motilin can act directly on the bowel wall, either the smooth muscle or the intrinsic nerves, to initiate contractions. The simultaneous, non-propagating spike activity seen in the group III dogs in this study may have been due to a direct effect of exogenous motilin on the smooth muscle itself. However, initiation of the MMC pattern of contractions, which may involve a more complex program in the bowel, requires extrinsic innervation.

In summary, these results support the hypothesis that extrinsic neural input to the jejunoileum plays a major role in mediating the initiation of Phase III activity in response to exogenous motilin. Intrinsic neural continuity with

the duodenum may suppress, by a brake effect, premature hormonal induction of motor patterns. Study of the autotransplanted jejunoileum allowed the investigation of the separate roles of intrinsic and extrinsic nerves when compared to the intrinsically denervated model.

CHAPTER IX

NET JEJUNAL ABSORPTION OF WATER, ELECTROLYTES, GLUCOSE, AND FOLATE IN THE AUTOTRANSPLANTED JEJUNOILEUM

NET JEJUNAL ABSORPTION OF WATER, ELECTROLYTES, GLUCOSE, AND FOLATE IN THE AUTOTRANSPLANTED JEJUNOILEUM

1- INTRODUCTION

While the immunobiology of intestinal transplantation has received considerable experimental attention, the effects of intestinal transplantation on the physiology of enteric function remain poorly understood. Many studies have utilised crude tests of absorption to predict the onset of immune rejection (Cohen WB, 1969, Kirkman RL, 1984, Hardy MA, 1970, Billiar TR, 1984), but detailed evaluations of the absorptive capability of the transplanted gut compared to the intact gut, especially in large animals, are notably lacking. This is an important subject because previous studies have shown that dogs lose weight and develop a profound but transient (up to four weeks) watery diarrhea early after autotransplantation (Lillehei RC, 1967, Williams JW, 1988). Moreover, the mucosa is allegedly blunted for up to three months (Ballinger WF II, 1962), and a complete, though

transient, lymphatic obstruction is established acutely secondary to operative disruption of all lymphatic drainage from the graft, as necessitated by the transplantation procedure. As seen in the first study there were changes in motility patterns in the autotransplanted jejunoileum. Also there is considerable experimental data implicating both extrinsic and intrinsic (enteric) nerves in the regulation of fluid and electrolytes transport across the small bowel mucosa (Cooke HJ, 1986). All these changes would be expected to have marked effects on the function of the gut.

The aim of this study was to determine the effects of jejunoileal autotransplantation on net absorption of water, glucose, electrolytes, and folate from the jejunum, using specifically an autotransplantation model to avoid confounding effects of pharmacologic immunosuppression or immune rejection. Moreover this model is ideally suited to examine changes that occur over time. The hypothesis, based on previous experimental work (Cooke HJ, 1986), was that the extrinsic denervation accompanying jejunoileal neural isolation would decrease net absorption of water and electrolytes from the jejunum but would have little effect on absorption of glucose or folate.

2- MATERIALS AND METHODS

a- PREPARATION OF ANIMALS

Two groups of six dogs each were prepared as follows.

Group A - Control dogs

Each dog underwent operative construction of an 80-cm modified Thiry-Vella loop of the proximal jejunum beginning 50 cm distal to the pylorus. Enteric neural continuity with the duodenum and proximal jejunum was maintained by preserving a bridge of tunica muscularis devoid of mucosa, 2 cm wide by 3 cm long , between the proximal jejunum and the enterically isolated jejunal loop, as described and validated previously (Sarr MG, 1980). This muscular bridge maintained a myoneural continuity with the proximal gut as evidenced by maintenance of normal myoelectric patterns in the enterically isolated loop. A metal perfusion cannula was inserted into the proximal end of the jejunal loop, the proximal end was oversewn, and the distal end was brought to the skin as an end-jejunostomy. Intestinal continuity was re-established by

end-to-end anastomosis of the jejunum proximal and distal to the loop. (Figure 9-A).

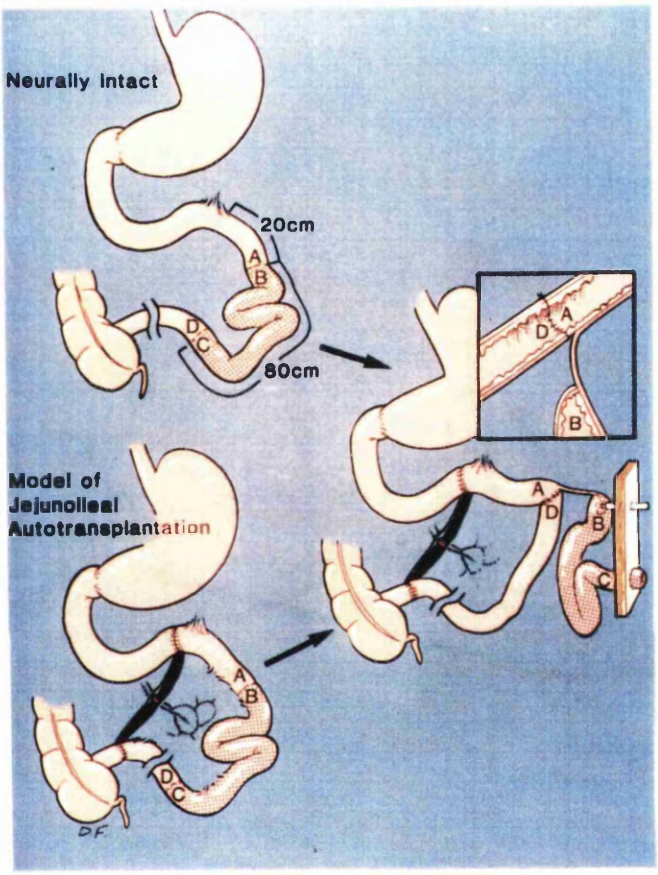
Group B - Jejunoileal autotransplantation

The dogs underwent operative construction of an identical jejunal loop after undergoing jejunoileal autotransplantation as described in Methodology (Chap VI). (Fig 9-A).

Figure 9-A.

MODEL OF JEJUNOILEAL AUTOTRANSPLANTATION

WITH ISOLATED JEJUNAL LOOP



Preparation of the isolated jejunal loop in intact dogs (top) and in dogs after jejunoileal autotransplantation (bottom) in which all connections to the entire jejunoileum are transected at the base of mesentery except for the superior mesenteric artery and vein. Insert shows muscular bridge to jejunal loop to maintain intrinsic (enteric) myoneural continuity.

b- CONDUCT OF EXPERIMENTS

The measurements of intestinal absorption were conducted after an overnight fast in fully conscious dogs resting comfortably in a Pavlov sling for the duration of the experiment. The jejunal segment was perfused at 2.8 ml/min for three hours with a prewarmed (39 C) isosmolar balanced salt solution containing NaCl (120mM), NaHCO3 (20 mM), KCl (5 mM), glucose (5.6 mM), 3H-Folate (pteroylmonoglutamic acid) (10 microCi/ml), unlabelled folate 1.5 microgram/ml and 5 g/l of PEG labelled with 14C-PEG (5 microCi/l). Each dog was given a loading dose of 15 mg of unlabelled sodium folate (Lypho Med, Rosement, Illinois) intramuscularly the day before. Pteroylmonoglutamate was used, in preference to the naturally occurring dietary folates (which contain multiple glutamic units bound in peptide linkage) to avoid the need for hydrolysis by a mucosal hydrolase prior to absorption (Halsted, 1975). Similarly, glucose was used to avoid the need for brush border hydrolysis as with maltose or sucrose. 14C-PEG was incorporated to determine steady state conditions. After reaching a steady state, all effluent was collected from the jejunostomy in 15-minute intervals to assess net absorption. Transit times ($T_{\frac{1}{2}}$) through the loop were

assessed at one and two hours by bolus injection of 0.5 ml of PSP, 300 microg/ml, with collection of effluent in 3-minute intervals thereafter from the stoma for 15 minutes.

Between experiments, the jejunal loops were not perfused with any solutions.

Design. Experiments were conducted at two weeks, four weeks, and eight weeks after construction of the loop. At each time point, the dogs were studied on three separate days during fasting and on three separate days after feeding a meal of 500g of porcine liver. The order of studies was randomised. A mucosal biopsy was performed at the site of the isolated loop at each time point for histologic review.

c- LABORATORY TESTS

Radionuclide (3H, 14C) activities in the effluent were determined using a standard, dual-counting liquid scintillation technique.

In the loop effluent, sodium and potassium concentrations were measured by a flame photometry (Beckman Klina Flame), chloride was measured by a

chloride electrode (Corning Chloride Meter 920m), glucose concentration was assayed with an enzymatic spectrophotometric technique (Sigma Diagnostics Glucose HK Kit), and PSP concentration was measured with a modification of a colorimetric analysis. (McLeod GM, 1968).

d- ANALYSIS OF DATA

Steady state conditions were confirmed by analysing 15-minute intervals for recovery of the nonabsorbable 14C-PEG marker. Net recovery per 15-minute interval was determined in each dog for each separate experiment . A steady state for each dog was determined when the mean net recovery of marker in the effluent reached at least 95% of the total marker infused for the 15-minute interval. A steady state was typically achieved in 30 minutes. (Figure 9-B).

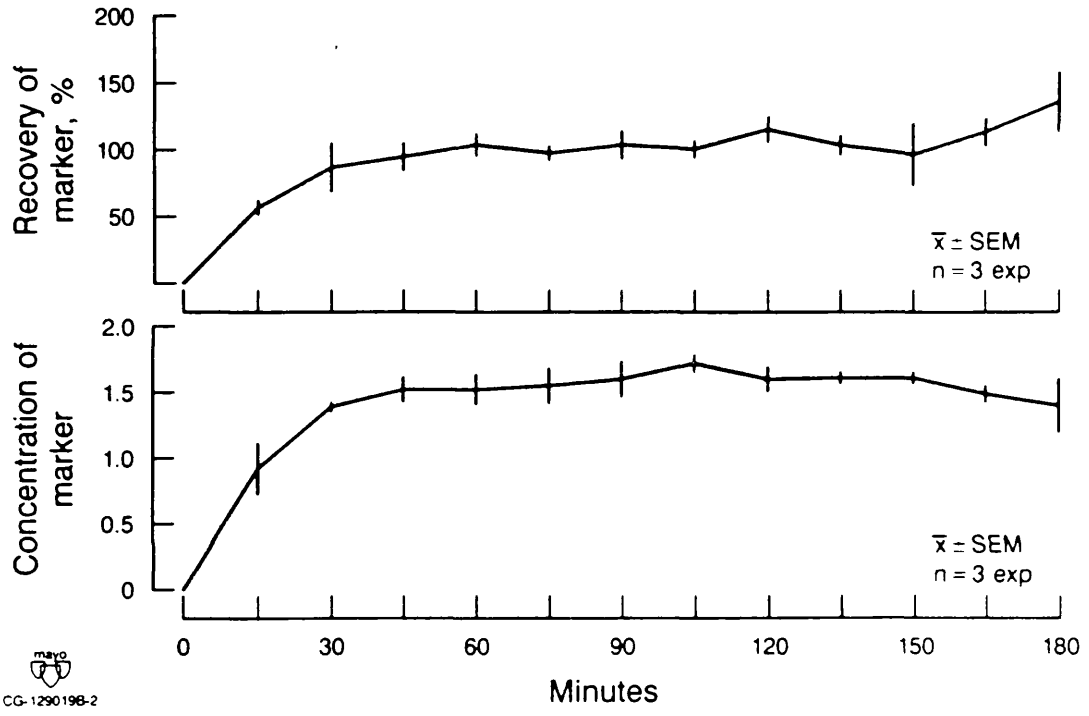
Recoveries of water, electrolytes, glucose, and folate were calculated for each 15-minute period by multiplying volume of effluent recovered by the concentration of substance in the effluent. Net absorption was calculated as the difference between the amount infused and amount recovered for the intervals after steady-state was reached. A steady

state rate of absorption over the three-hour experiment was confirmed by showing that the concentration of marker did not change over the three-hour experiment after a steady state delivery was reached.

Transit time ($T_{\frac{1}{2}}$) was expressed as the mean time needed for 50% of the corrected PSP to traverse the perfused loop. Transit times ($T_{\frac{1}{2}}$) at one and two hours were similar and were thus combined.

Figure 9-B.

STEADY STATE DYNAMICS



Steady state dynamics during three-hour perfusion of the neurally isolated jejunal loop. Top: Marker recovery. Bottom: Concentration of marker.

e- STATISTICAL ANALYSIS

Net absorption and transit during fasting and after feeding at two weeks, four weeks, and eight weeks following surgery were compared between groups A and B using Student's t test. Fasting versus fed net absorption and transit were compared within groups using the same test for paired data. Changes over time (2,4 and 8 weeks) were analysed using a multivariate analysis of variance of the differences (week 4-week 2, week 8-week 4), which were approximately normally distributed.

3- RESULTS

a- GENERAL ASPECTS

All dogs in both groups remained in a healthy state for the duration of the experiments with good appetites. In group B, all dogs developed a profuse, watery diarrhea that began within two days of operation; diarrhea lasted at least six weeks and was associated with loss of 15±8% body weight. In group A, dogs had normal formed stools. Histologic comparisons of mucosal biopsies showed no gross differences in villus height, crypt depth, or epithelial cells between groups at any time point.

b- ABSORPTION AND TRANSIT TIME

Water and electrolytes:

Differences in the values for net absorption of water during fasting were not detected between groups when compared separately at two, four, or eight weeks after construction of the jejunal loop. Similarly, the values for net absorption of water at each time point after feeding were also not different. Median volumes of loop effluent per 15-minute interval during fasting in Group A vs Group B dogs at two weeks were 31.2 ml vs 34.8 ml, respectively ($p>0.05$) (Table 9-13) and after feeding were 25.2 ml vs 31.4 ml, respectively ($p>0.05$). Similarly, median values for volume of loop effluent at four and eight weeks and for sodium, potassium, and chloride recovery in loop effluent at the three time points were also not statistically different during fasting or after feeding.

Glucose and folate:

Net absorption of glucose and folate, as determined by recovery of each in the loop effluent, were similar between groups at all time points.

Transit time ($T_{\frac{1}{2}}$):

There were no differences in mean transit times between groups during fasting and after feeding at any time point.

Fasting vs fed states:

When net absorption of water was compared within group B during fasting versus after feeding at each time point, statistically significant differences were not detected ($p>0.05$), although the tendency in group B was to absorb more infusate after feeding as indicated by median values. For example, the median volumes of effluent during fasting and after feeding for Group A were 31.2 ml and 25.2 ml, respectively, and for Group B were 34.8 ml and 31.4ml, respectively. Similar results were found with sodium, potassium, chloride, glucose and folate. Transit times ($T_{\frac{1}{2}}$) were not different in the fasted and fed states in either group.

Changes in net loop absorption over time:

When values for net absorption during fasting were compared within groups (week 4 vs week

2, week 8 vs week 4), no significant changes in absorption were detected over the eight-week period. Similarly, values during feeding did not change significantly over the three time points.

Tables 1-6 summarise the absorption at 2, 4, and 8 weeks, in control intact dogs, comparing the fasting and fed states.

Tables 7-12 summarise the absorption at each time point, in the autotransplanted dogs, comparing the fasting and fed states.

Tables 13-18 summarise the absorption in the fasting state, comparing control and autotransplanted dogs.

Tables 19-24 summarise the absorption in the fed state, comparing control and autotransplanted dogs.

Table 19-25 gives the Transit time ($T_{\frac{1}{2}}$) in the control and transplant dogs.

Table 9-1.

Group A Control dogs

Volume effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	31.2	25.2	35	26.1	34.3	31.6
SD	3.8	3.0	6.0	8.1	6.6	4.2
SEM	1.6	1.2	2.5	3.3	2.9	1.9
n	6	6	6	6	5	5
p	0.01*		0.044*		0.15	

% Absorption of H20

X	25.7	40.0	16.7	37.9	18.3	29.8
SD	9.0	7.1	14.3	19.3	15.7	10.0
SEM	3.8	2.8	5.9	7.9	6.9	4.5
n	6	6	6	6	5	5

Table 9-2.

Group A Control dogs

Sodium effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	4144	3550	4642	3680	4680	4070
SD	700	400	780	1110	1070	1010
SEM	290	160	320	450	480	450
n	6	6	6	6	5	5
p	0.10		0.037*		0.03*	

% Absorption of Sodium

X	29.5	39.6	21.5	37.4	20.3	30.8
SD	11.9	6.8	13.2	18.9	18.1	17.2
SEM	4.8	2.7	5.4	7.7	8.0	7.7
n	6	6	6	6	5	5

Table 9-3.

Group A Control dogs

Chloride effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	4150	3650	4790	3780	4670	3900
SD	680	380	820	1000	1080	1020
SEM	280	160	330	410	480	450
n	6	6	6	6	5	5
p	0.11		0.039*		0.05*	

% Absorption of Chloride

X	20.9	30.4	8.8	28.0	11.0	25.7
SD	12.9	7.3	15.5	19.0	20.4	19.3
SEM	5.3	3.0	6.3	7.8	9.1	8.6
n	6	6	6	6	5	5

Table 9-4.

Group A Control dogs

Potassium Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	176	160	196	165	204	181
SD	11	23	15	39.7	37	41
SEM	4	9	6	16	17	18
n	6	6	6	6	5	5
p	0.23		0.12		0.07	

% Absorption of Potassium

X	16.2	23.8	6.7	21.4	2.9	13.8
SD	5.2	11.0	7.1	18.9	17.6	19.2
SEM	1.9	4.3	2.9	7.6	8.1	8.6
n	6	6	6	6	5	5

Table 9-5.

Group A Control Dogs

Glucose Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	3.7	1.5	3.7	0.5	4.3	2.4
SD	3.6	1.3	3.1	0.2	2.8	1.2
SEM	1.5	0.5	1.2	0.1	1.3	1.06
n	6	6	6	6	5	5
p	0.08		0.042*		0.23	

% Absorption of Glucose

X	91.2	96.6	91.2	98.7	89.8	94.4
SD	8.6	3.2	7.2	0.7	6.7	3.0
SEM	3.5	1.5	2.9	0.3	3.0	2.5
n	6	6	6	6	5	5

Table 9-6.

Group A Control dogs

Folate absorbed

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	45.6	56.4	40.7	42.6	46.1	51.7
SD	22.6	24.9	24.3	24.3	27.8	19.5
SEM	9.2	10.2	9.9	10.2	12.4	8.7
n	6	6	6	6	5	5
p	0.015*		0.59		0.30	

% Absorption of Folate

X	59.2	72.1	54.7	56.2	56.6	58.7
SD	8.7	5.4	11.9	14.7	10.6	11.6
SEM	4.3	2.9	6.0	7.4	5.3	5.8
n	6	6	6	6	5	5

Table 9-7.

Group B Autotransplant

Volume Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	34.8	31.4	32.6	31.4	37.5	33.8
SD	5.9	8.2	7.4	9.5	5.0	8.2
SEM	2.4	3.3	3.3	4.6	2.0	3.3
n	6	6	5	4	6	6
p	0.16		0.63		0.07	

% Absorption of H2O

X	17.1	25.2	22.4	25.2	10.7	24.8
SD	14.0	19.5	17.6	22.6	11.9	19.5
SEM	5.0	6.0	7.9	11.0	4.8	7.9
n	6	6	5	4	6	6

Table 9-8.

Group B Autotransplant

Sodium Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	4680	4080	4200	4240	5070	4300
SD	830	1120	1100	1393	960	1448
SEM	340	460	490	700	390	590
n	6	6	5	4	6	6
p	0.11		0.92		0.03*	

% Absorption of Sodium

X	20.3	30.6	28.5	27.9	13.8	26.9
SD	14.2	19.0	18.6	23.7	16.3	24.6
SEM	5.3	7.0	8.3	11.9	6.6	10.3
n	6	6	5	4	6	6

Table 9-9.

Group B Autotransplant

Chloride Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	4770	4120	4170	4150	4880	3870
SD	800	1230	1000	1369	670	1107
SEM	330	500	450	680	270	450
n	6	6	5	4	6	6
p	0.10		0.90		0.03*	

% Absorption of Chloride

X	9.2	21.5	20.5	20.9	7.0	26.3
SD	15.3	23	19.1	26.0	12.7	21.1
SEM	5	7	9.1	13.0	5.2	8.6
n	6	6	5	4	6	6

Table 9-10.

Group B Autotransplant

Potassium Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	212	183	190	190	217	186
SD	18	48	33	56.1	26	54.2
SEM	7	20	15	28	11	22
n	6	6	5	4	6	6
p	0.13		0.96		0.9	

% Absorption of Potassium

X	0	12.9	9.5	9.5	0.3	11.4
SD	8.6	22.9	15.7	26.7	12.4	25.8
SEM	4.0	7.0	7.1	13.3	5.2	10.5
n	6	6	5	4	6	6

Table 9-11.

Group B Autotransplant

Glucose Effluent

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	7.4	2.8	7.4	2.0	10.2	3.4
SD	3.6	2.8	6.0	2.7	10.5	3.5
SEM	1.6	1.1	2.7	1.4	4.3	1.4
n	6	6	5	4	6	6
p	0.02*		0.05*		0.07	

% Absorption of Glucose

X	82.5	93.2	82.5	95.1	75.7	92.0
SD	8.5	6.1	14.5	6.6	25.0	8.5
SEM	3.0	2.5	6.5	3.3	10.2	3.5
n	6	6	5	4	6	6

Table 9-12.

Group B Autotransplant

Folate Absorbed

	2 weeks		4 weeks		8 weeks	
	Fast	Fed	Fast	Fed	Fast	Fed
X	33.5	40.2	42.6	43.7	42.5	41.2
SD	32.4	41.3	31.4	46.3	29.3	36.1
SEM	13.2	16.9	14.0	23.2	12.0	14.7
n	6	6	5	4	6	6
p	0.28		0.64		0.79	

% Absorption of Folate

X	52.7	62.9	56.2	66.4	60.7	62.4
SD	1.7	11.0	7.7	8.1	5.2	9.0
SEM	0.5	4.0	3.9	4.8	4.6	4.5
n	6	6	5	4	6	6

Table 9-13.

Fasting

Volume Effluent (42 ml infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	31.2	34.8	35.0	32.6	34.3	37.5
SD	3.8	5.9	6.0	7.4	6.6	5.0
SEM	1.6	2.4	2.5	3.3	2.9	2.0
n	6	6	6	5	5	6
p	0.24		0.58		0.40	

Fasting

% Absorption of H2O

X	25.7	17.1	16.7	22.4	18.3	10.7
SD	9.0	14.0	14.3	17.6	15.7	11.9
SEM	3.8	5.7	5.9	7.9	6.9	4.8
n	6	6	6	5	5	6

Table 9-14.

Fasting

Sodium Effluent (5880 mEq infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	4144	4682	4642	4204	4684	5070
SD	699	834	779	1097	1066	957
SEM	285	340	318	490	475	390
n	6	6	6	5	5	6
p	0.25		0.48		0.54	

% Absorption of Sodium

X	29.5	20.3	21.5	28.5	20.3	13.8
SD	11.9	14.2	13.2	18.6	18.1	16.2
SEM	4.8	5.8	5.4	8.3	8.0	6.6
n	6	6	6	5	5	6

Table 9-15.

Fasting

Chloride Effluent (5250 mEq infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	4150	4770	4790	4170	4670	4880
SD	680	800	820	1000	1080	670
SEM	280	330	330	450	480	270
n	6	6	6	5	5	6
p	0.18		0.29		0.71	

% Absorption of Chloride

X	20.9	9.2	8.8	20.5	11.0	7.0
SD	12.9	15.3	15.5	19.1	20.4	12.7
SEM	5.3	6.2	6.3	9.1	9.1	5.2
n	6	6	6	5	5	6

Table 9-16.

Fasting

Potassium Effluent (210 mEq infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	176	212	196	190	204	217
SD	11	18	15	33	37	26
SEM	4	7	6	15	17	11
n	6	6	6	5	5	6
p	0.002*		0.7		0.49	

% Absorption of Potassium

X	16.2	0.0	6.7	9.5	2.9	0.3
SD	5.2	8.6	7.1	15.7	17.6	12.4
SEM	1.9	3.3	2.9	7.1	8.1	5.2
n	6	6	6	5	5	6

Table 9-17.

Fasting

Glucose Effluent (42 mg infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	3.7	7.4	3.7	7.4	4.3	10.2
SD	3.6	3.6	3.0	6.1	2.8	10.5
SEM	1.48	1.6	1.2	2.7	1.3	4.3
n	6	6	6	5	5	6
p	0.11		0.22		0.24	

% Absorption of Glucose

X	91.2	82.5	91.2	82.5	89.8	75.7
SD	8.6	8.5	7.2	14.5	6.7	25.0
SEM	3.0	3.5	2.9	6.5	3.0	10.2
n	6	6	6	5	5	6

Table 9-18.

Fasting

% Folate Absorbed

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	45.6	33.5	40.7	42.6	46.1	42.5
SD	22.6	32.4	24.3	31.4	27.8	29.3
SEM	9.2	13.2	9.9	14.0	12.4	12.0
n	6	6	6	5	5	6
p	0.47		0.91		0.83	

% Absorption Folate

X	59.2	52.7	54.7	56.2	56.6	60.7
SD	8.7	1.7	11.9	7.7	10.6	5.2
SEM	4.3	0.9	6.0	3.9	5.3	4.6
n	4	4	4	4	4	4

Table 9-19.

Fed

Volume Effluent (42 ml infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	25.2	31.4	26.1	31.4	31.6	33.8
SD	3.0	8.2	8.1	9.5	4.2	8.2
SEM	1.2	3.3	3.3	4.6	1.9	3.3
n	6	6	6	4	5	6
p	0.11		0.37		0.58	

% Absorption of H2O

X	40.0	25.2	37.9	25.2	29.8	24.8
SD	7.1	19.5	19.3	22.6	10.0	19.5
SEM	2.8	7.9	7.9	11.0	4.5	7.9
n	6	6	6	4	5	6

Table 9-20.

Fed

Sodium Effluent (5880 mEq infusion)

	2 weeks		4 weeks		8weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	3550	4080	3680	4240	4070	4300
SD	400	1120	1110	1393	1010	1448
SEM	160	460	450	700	450	590
n	6	6	6	4	5	6
p	0.32		0.49		0.76	

% Absorption of Sodium

X	39.6	30.6	37.4	27.9	30.8	26.9
SD	6.8	19.0	18.9	23.7	17.2	24.6
SEM	2.5	6.8	7.7	11.9	7.7	10.3
n	6	6	6	4	5	6

Table 9-21.

Fed

Chloride Effluent (5250 mEq infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	3650	4120	3780	4150	3900	3870
SD	380	1230	1000	1369	1016	1107
SEM	160	500	410	680	450	450
n	6	6	6	4	5	6
p	0.43		0.62		0.95	

% Absorption of Chloride

X	30.4	21.5	28.0	20.9	25.7	26.3
SD	7.2	23.4	19.0	26.0	19.3	21.1
SEM	3.0	9.5	7.8	13.0	8.6	8.6
n	6	6	6	4	5	6

Table 9-22.

Fed

Potassium Effluent (210 mEq infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	160	183	165	190	181	186
SD	23	48	39.7	56.1	40.4	54.2
SEM	9	20	16	28	18	22
n	6	6	6	4	5	6
p	0.31		0.42		0.89	

% Absorption of Potassium

X	23.8	13.0	21.4	9.5	13.8	11.4
SD	11.0	19.0	18.9	26.7	19.2	25.8
SEM	5.0	8.0	7.6	13.3	8.6	10.5
n	6	6	6	4	5	6

Table 9-23.

Fed

Glucose Effluent (42 mg infused)

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	1.4	2.8	0.5	2.0	2.3	3.3
SD	1.3	2.7	0.3	2.7	1.2	3.5
SEM	0.54	1.13	0.12	1.3	1.0	1.4
n	6	6	6	4	5	6
p	0.29		0.20		0.26	

% Absorption of Glucose

X	96.6	92.3	98.7	95.0	94.4	92.0
SD	3.2	3.0	2.7	3.0	3.0	8.5
SEM	1.0	1.0	0.3	0.5	2.5	3.5
n	6	6	6	4	5	6

Table 9-24.

Fed

Folate Absorbed

	2 weeks		4 weeks		8 weeks	
	Control	AutoTx	Control	AutoTx	Control	AutoTx
X	56.4	40.2	42.6	43.7	51.7	41.2
SD	24.9	41.3	24.9	46.3	19.5	36.1
SEM	10.2	16.9	10.2	23.2	8.7	6.0
n	6	6	6	4	5	6
p	0.43		0.96		0.87	

% Absorption of Folate

X	72.1	62.3	56.2	66.8	58.7	62.4
SD	5.4		14.7		11.6	9.0
SEM	2.5		7.4		5.8	4.5
n	4	4	4	4	4	4

Table 9-25.

Transit time ($T\frac{1}{2}$)=min

Control intact dogs (n=6)

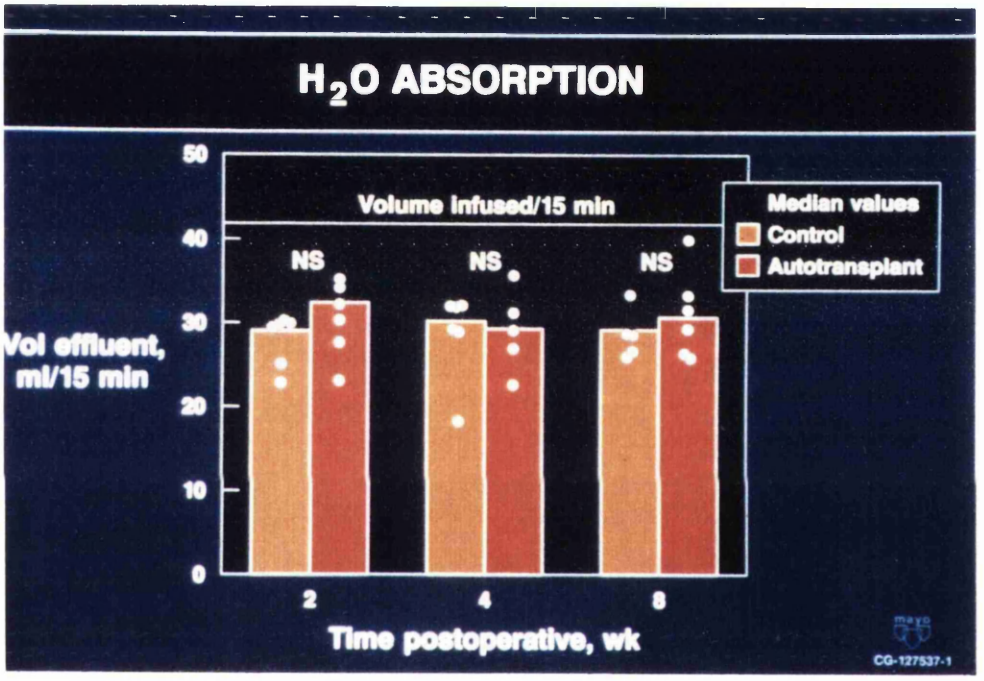
	Fasting			Fed		
	2 weeks	4 weeks	8 weeks	2 weeks	4 weeks	8 weeks
X	5.6	5.7	5.9	7.0	6.7	8.1
SEM	1.1	1.3	1.2	0.8	1.0	2.2

Autotransplanted dogs (n=6)

X	6.4	6.1	7.3	5.4	5.9	6.1
SEM	1.0	1.0	1.2	0.3	0.9	1.1

Figure 9-C.

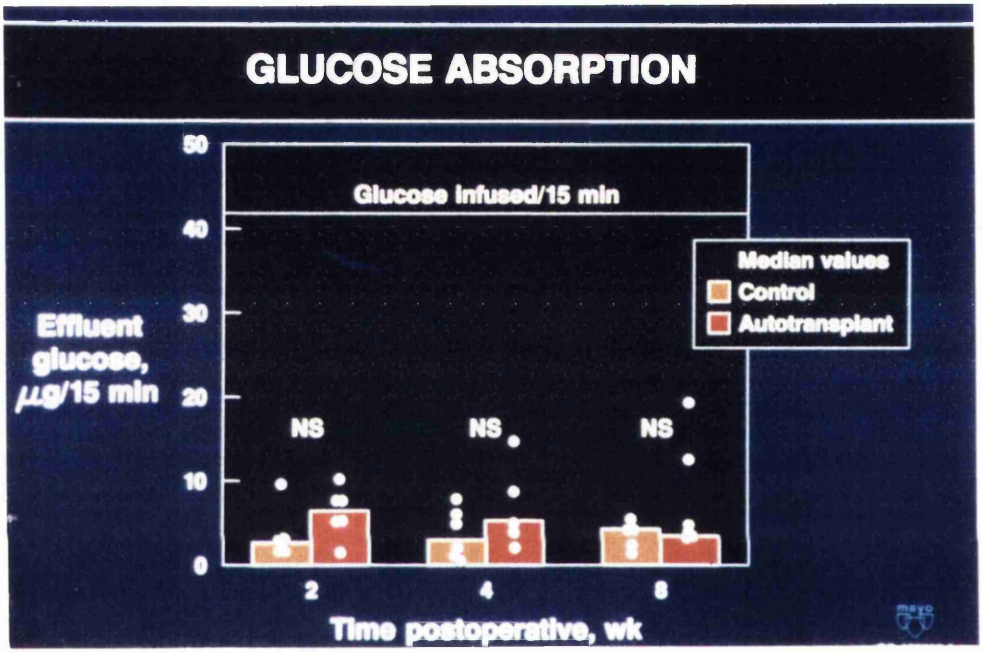
VOLUME OF LOOP EFFLUENT



Net absorption of water during perfusion of control and autotransplanted dogs. No difference in the values were detected between groups.

Figure 9-D.

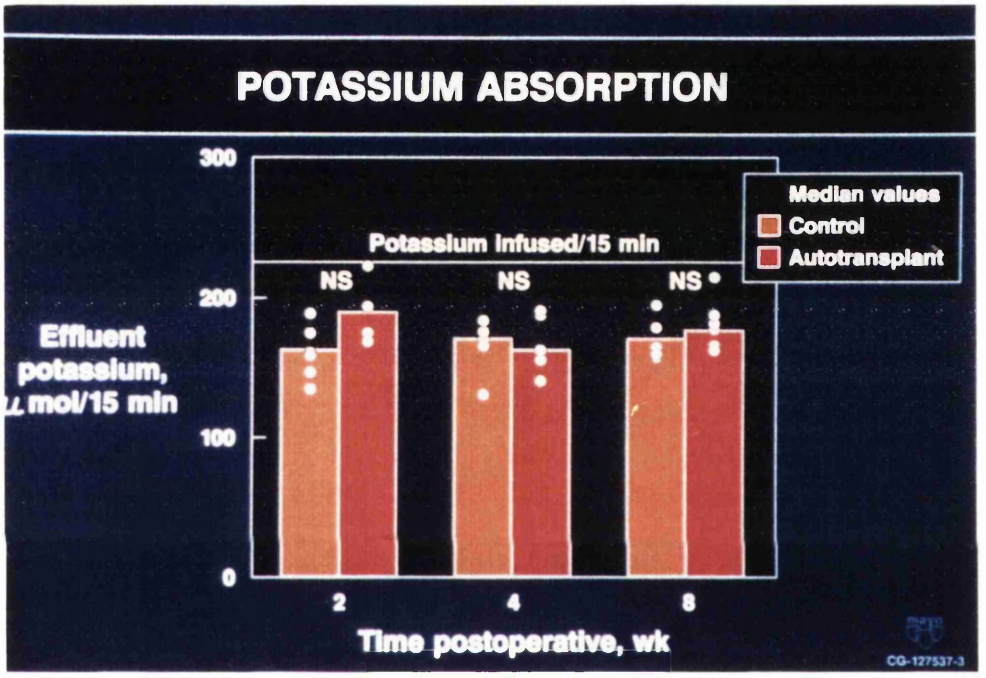
GLUCOSE ABSORPTION



Net absorption of glucose was similar between groups at all time points.

Figure 9-E.

POTASSIUM ABSORPTION



Potassium absorption was not statistically different between groups at all time points.

4- DISCUSSION

This study was designed to determine if intestinal transplantation would alter jejunal transport of water and electrolytes from a simple crystalloid solution. Net jejunal absorption of water and electrolytes under baseline conditions of crystalloid jejunal perfusion was not affected when assessed two, four, and eight weeks after neural isolation. Also, normal absorption of glucose and folate were preserved at these time points. These findings suggest that jejunal transport of water, electrolytes, and simple sugars might be expected to be little affected at least two to eight weeks after transplantation.

Because the long-term effect of intestinal denervation and intestinal transplantation on intestinal absorptive function is not well understood, the aim of the study was to determine any temporal effects of extrinsic denervation on net absorption of a simple crystalloid solution.

Previous work investigating the effects of intestinal transplantation or extrinsic denervation on transport of water and electrolytes has yielded

conflincting results. Using a rat model of intestinal transplantation, Watson (1988) and Lear (1988) reported a decrease in net absorption, while Kimura and colleagues (1989) reported no significant change compared to neurally intact controls. Dennison (1987), found that in the autotransplanted canine ileal loops the absorption of water, electrolytes, carbohydrate and aminoacids was normal at 8 days post-transplantation and that the absorption of fat started to recover at 4 weeks.

Previous studies of surgical sympathectomy (Cooke HJ, 1986, Sjovall H, 1985) and various forms of pharmacologic chemical sympathectomy (Hubel KA, 1976), have shown that sympathetic denervation of the gut decreases net absorption by increasing the unidirectional secretory flux. However, these studies examined the acute effects of sympathectomy. This study was designed to determine the effects of extrinsic denervation in a large animal model at different times after transplantation in an attempt to determine if any changes or adaptation would take place over time. It is known that lymphatic regeneration after intestinal transplantation is complete at the end of four weeks (Kocandrle V, 1966), while sprouting of enteric nerves across intestinal anastomoses, and presumably restoration

of enteric neural continuity, also occurs early after surgery in the first six weeks (Galligan JJ, 1989). Reinnervation of the gut wall by extrinsic nerves would take a much longer time and probably would be incomplete after the model used in this study. Based on previous literature (Cooke HJ, 1986, Watson AJM, 1988), it was surprising to find no effect of autotransplantation on net absorption in the jejunum at two weeks, when the dogs were still experiencing considerable diarrhea. Also, there was no major differences over time compared to control dogs despite the weight loss that occured in the neurally isolated group. Whether net absorption was affected within the two weeks after surgery is unknown.

The effects of feeding the in-continuity gut on net absorption from the jejunal loop were also studied. Previous work (Sarr MG, 1980, 1981-b) has suggested that feeding increases net absorption from an enterically isolated jejunal loop. In this study the tendency in both groups of dogs was to increase net absorption of water and electrolytes after feeding the in-continuity gut to a similar degree as in previous studies (Sarr 1981-b).

In conjunction with previous studies in this

dog model (Sarr MG, 1981a, 1987, 1989b), these findings are of potential clinical significance. They suggest that transport of water and electrolytes and absorption of simple sugars from the transplanted jejunum is maintained at least from two weeks onward after surgery. The aetiology of the diarrhea is as yet unexplained but may possibly be related to ileal or colonic effects on transport of water and electrolytes.

The conclusions drawn from this study must be made with caution because of the experimental design employed. An enterically isolated loop was chosen in order to completely control the conditions of fluid entering the loop and to allow the collection of all effluent. This preparation is subject to the changes involved in an enterically isolated, defunctionalised gut segment devoid of inflow of chyme and enteric content (Williamson RCN, 1978, Altman GG, 1971) the integrity of small bowel mucosa demands the physical presence of food in the gut; this may alter the enteric function and the full response to feeding the insitu gut. Also, the use of a constant perfusion of a simple crystalloid solution may alter the hydrodynamics of intestinal flow and thereby after absorption. Similarly, a simple crystalloid solution devoid of the proximal

inflow of intestinal and pancreatobiliary content and nutrient chyme may affect overall mucosal transport of water and electrolytes. Indeed pancreatic secretion play a major role in the villus-enlarging influence which reach the intestine (Rijke RP, 1977). Nevertheless, this study clearly demonstrates that the extrinsic denervation that accompanies the procedure of intestinal transplantation does not lead to significant or prolonged depression of jejunal absorptive function. Other factors, including immunosuppression, rejection and ischaemia could be accountable for the alterations seen in other studies.

CHAPTER X

GENERAL DISCUSSION AND CONCLUSIONS

GENERAL DISCUSSION AND CONCLUSIONS

After autotransplantation of the jejunoileum characteristic jejunal patterns of fasting motility persist but cycle independently from the duodenal MMC, suggesting that the coordination of the jejunal MMCs is controlled by the intrinsic and/or extrinsic nervous system of the gut. However these observations demonstrate that cyclic interdigestive motility patterns occur in the absence of direct neural input and strongly implicate hormonal factors in this control.

Studies utilising selective extrinsic denervation of intestinal segments with maintenance of intrinsic myoneural continuity have shown little or no effect on migration of the MMC (Heppell J, 1983) while intrinsic denervation (duodenal transection and reanastomosis) disrupted the orderly migration of the MMC along the bowel. Autotransplantation of the jejunoileum led to complete disruption of temporal coordination of

motility patterns between the gastroduodenum and the autotransplanted segment.

The infusion of nutrients into the autotransplanted jejunoileum interrupted the MMC in both the gastroduodenum and jejunum for the duration of the infusion. Because inhibition of the gastroduodenal and jejunoileal MMC continued to occur during infusion of nutrients into the transplanted jejunum, it is concluded that jejunoileal regulation of postprandial inhibition of the MMC in the stomach and duodenum is mediated by hormonal factors and does not require intrinsic neural continuity.

There is a definite role for hormonal factors in coordinating motility. Plasma motilin concentration cycles in temporal association with the gastric and duodenal MMC. The results of this study confirm that exogenous motilin initiates a premature Phase III in the intact gut, and also in the jejunum distal to an intestinal transection. However experimental evidence suggests that motilin may act via a mechanism located outside the wall of the duodenum. (Sarr MG, 1987). The observations in this work support this concept as motilin was unable to initiate Phase III activity after

autotransplantation of the jejunoileum where extrinsic innervation to the jejunum had ben transected.

The relative maintenance of temporal coordination of jejunal Phase III activity with duodenal Phase III after intrinsic transection may be related to the peaking of plasma motilin concentration which then acts to initiate Phase III in the jejunum via extrinsic nerves. Extrinsic neural pathways appear to mediate motilin-induced MMC activity in the jejunum.

After Autotransplantation of the jejunoileum, the lack of intrinsic or extrinsic neural continuity with the jejunum prevents a neural mechanism from coordinating motor patterns. Morover, the loss of extrinsic innervation prevents the cycling of plasma motilin from initiating Phase III activity in the jejunum at or near the time of initiation of Phase III in the duodenum.. Thus the continued independent cycling of the MMC in the jejunum virtually eliminates the possibility of a hormonal coordination and implicates the intrinsic nerves of the jejunum as possessing the ability to generate the MMC.

Control of the jejunal MMC appears to arise within the intrinsic nervous system of the gut. Other factors, such as extrinsic innervation and hormonal factors may modulate the cycling of the MMC and thereby coordinate patterns between regions, but the underlying control mechanism lies within the intrinsic nerves.

In a previous study aiming to determine the role of intrinsic myoneural and luminal continuity in the coordination of gastric and duodenal motility patterns, Tanaka and colleagues (1990) chose to compare motility patterns in three groups of dogs. A control group with an intact gastrointestinal tract. A pyloric transection group where dogs had transection and reanastomosis of the duodenum 0.5 cm distal to the pylorus, and a group who had identical proximal duodenal transection, but with oversewing of duodenum and pylorojejunostomy to a Roux-en-Y limb. The gastric MMCs were similar in appearance, and the latency of appearance of duodenal MMC was not statistically different in the three groups. Feeding inhibited the gastric and duodenal MMCs in all groups, but the duodenal MMC returned earlier in the Roux-en-Y group. It was concluded that intrinsic myoneural continuity was not necessarily important in regulating temporal coordination of gastric and

duodenal motor patterns. Those findings suggest that unlike in the small intestine, intrinsic myoneural continuity is not necessary for temporal coordination of the gastric and duodenal MMC and that the gastric MMC does not migrate or propagate across the pylorus and into the duodenum.

The interpretation of the findings of the motility study is that continuity of the intrinsic nerves controls the orderly migration of the MMC along the small bowel wall. Extrinsic nerves serve as another mechanism to coordinate temporally the patterns of motility between regions of the upper small intestine. Extrinsic innervation is necessary for motilin to induce Phase III activity in the jejunum. Jejunoileal regulation of the postprandial gastroduodenal motility is mediated by hormonal factors. Overall, an interplay of neural, hormonal, and enteric mechanisms is probably involved in the gastroduodenal and intestinal motility and its regulation.

Jejunal absorptive studies in the autotransplanted jejunoileum have shown that there was no significant impairment of the absorptive capacity and it is therefore concluded that jejunal transport of water, electrolytes, and simple

sugars might be expected to be little affected by the obligatory extrinsic and intrinsic denervation and interruption of lymphatic continuity that would be necessitated by the intestinal transplantation procedure.

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APPENDIX 1

PUBLISHED WORKS RELATED TO THIS THESIS

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Hakim NS, Sarr MG: Humoral induction of migrating motor complexes (MMC): Role of extrinsic innervation. Gastroenterology 94:A166, 1988.

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APPENDIX 2

RAW DATA

RAW DATA

In view of the large number of experiments (>80 in the first study, >44 in the second study, >216 in the third study), it was decided to give the detailed results of one set of experiments in one dog in each study. The complete results being available upon request.

REGULATION OF GASTRODUODENAL MOTILITY (CHAPTER VII)

Manometry/Myoelectric activity in a control dog
during the perfusion of saline
Dog Number U 588
date: 17-7-87

Manometry/Myoelectric Activity

	Duration (min)				Period of MMC		
	Phase 3	Phase 4	Phase 1	Phase 2	Stomach	Duoden.	Jejunum
1st MMC							
Stomach	9	2	40	41	92		
Duoden.	5	5	35	46		91	
SW = 20 c/min							
Jejunum	7	2	32	52			91
SW = 18 c/min							
2nd MMC							
Stomach	3	3	23	71	99		
Duoden.	4	2	22	72		100	
SW = 20 c/min							
Jejunum	10	2	2	12	78		102
SW = 18 c/min							

3rd MMC

Stomach	10	5	32	117	164		
Duoden.	13	1	27	124		165	
SW = 20 c/min							
Jejunum	5	1	27	132			175
SW = 18c/min							

There was no interruption of the MMC by the Jejunal perfusion with Normal saline.

Regulation of gastroduodenal motility

Manometry/Myoelectric activity in a control dog
during the perfusion of Meritene
Dog number U 588
date: 27-7-87

Manometry/Myoelectric Activity

	Duration (min)				Period of MMC		
	Phase 3	Phase 4	Phase 1	Phase 2	Stomach	Duoden.	Jejunum
1st MMC							
Stomach	17	3	17	55	92		
Duoden.	8	11	15	58		92	
SW = 20 c/min							
Jejunum	4	11	13	62			98
SW = 17 c/min							

The infusion of Meritene interrupted the MMC. No further migrating motor complexes appeared for the duration of the perfusion (5 hours).

Regulation of gastroduodenal motility

Manometry/Myoelectric activity in the autotransplanted dog during the perfusion of saline

Dog Number U 588

date: 28-9-87

Manometric/Myoelectric activity

	Duration (min)				Period of MMC		
	Phase 3	Phase 4	Phase 1	Phase 2	Stomach	Duoden.	Jejunum
1st MMC							
Stomach	29	1	38	21	90		
Duoden.	12	1	35	19		67	
SW = 17 c/min							
Jejunum	7	-	-	-			108
SW = 13 c/min							
2nd MMC							
Stomach	8	0	36	168	212		
Duoden.	15	1	27	171		214	
SW = 18 c/min							
Jejunum	6						136
SW = 13 c/min							

The infusion of saline did not interrupt the MMC in the autotransplanted jejunoileum.

Regulation of gastroduodenal motility

Manometry/Myoelectric activity
in the autotransplanted dog
during the perfusion of Meritene
Dog Number U 588
date: 20-9-87

Manometry/Myoelectric activity

	Duration (min)				Period of MMC		
	Phase 3	Phase 4	Phase 1	Phase 2	Stomach	Duoden.	Jejunum
1st MMC							
Stomach	7	1	39	36	83		
Duoden.	6	1	31	45		87	
SW = 20 c/min							
Jejunum	12	1	37	49			99
SW = 16 c/min							

The jejunal infusion of Meritene interrupted the MMC both in the gastroduodenum and in the autotransplanted jejunum.

HORMONAL INDUCTION OF THE MMC (CHAPTER VIII)

Induction of the MMC

in the

autotransplanted jejunoileum

by Exogenous Motilin (0.1 microgram/Kg IV)

Dog Number U 967

Date: 9-11-87

Time	Phase 1	Phase 2	Phase 3	Phase 4	Phase 1	Phase 2	Phase 3
Stomach							
S1							8:30
S2							8:30
Duodenum							
D1							8:35
D2							88:42
Jejunum							
J1			6:49	6:56	6:57	7:20	8:27
J2			6:53	7:03	7:04	7:23	8:35
J3			6:58	7:06	7:07	7:25	8:39
J4			7:04	7:13	7:14	7:26	8:45

Motilin given at 9:14*

	Phase 4	Phase 1	Phase 2	Phase 3	Phase 4	Phase 1	Phase 2
Stomach				*			
S1	8:53			9:14	9:25		
S2	8:53			9:14	9:26		
Duodenum							
D1	8:42			9:14	9:20		
D2	8:52			9:14	9:21		
Jejunum							
J1	8:34			9:14	9:19		
J2	8:42			9:14	9:20		
J3	8:48			9:14	9:20		
J4	8:54			9:14	9:20		

	Phase 3	Phase 4	Phase 1	Phase 2	Phase 3	Phase 4	Phase 1
Stomach							
S1					15:00	15:20	
S2					15:00	15:20	
Duodenum							
D1					15:01	15:07	
D2					15:10	15:17	
Jejunum							
J1	12:23	12:30			14:55	15:05	
J2	12:28	12:38			15:00	15:07	
J3	12:35	12:43			15:06	15:13	
J4	12:35	12:43			15:12	15:20	

Almost immediate induction of a premature phase 3 activity in the gastroduodenum and of spontaneous spike activity in the autotransplanted jejunum by exogenous motilin. There was lack of a characteristic phase 3 activity in the jejunum. There was a complete temporal discoordination between the phase 3s in the gastroduodenum and the transplanted jejunoileum.

Induction of the MMC in a control dog
by Exogenous Motilin (0.1 microgram/Kg IV)

Dog Number P 163

Duration

	Phase 3	Phase 4	Phase 1	Phase 2
1st injection	4	2	77	13
2nd Injection	4	2	78	21

Induction of a premature phase 3 activity by exogenous motilin in a control dog.

ABSORPTION VALUES IN CONTROL DOGS (CHAP IX)

Study 1 Date 3-21 Number of weeks Postoperative 2 Control Jejunal Loop X
Dog # 867 Fast X Fed 500 g Liver Transplanted Jejunoileum and Jejunal Loop

			Perfusate Content		123 mg/l	5.5 mg/l	125 mg/l	16638	5514	102.8 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values		Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 7.9
			30		120	5.7	120	7883	4969	7.3	
1	15′	42 C	46								
			30		123	6.1	120	9372	7539	11.0	
2	30′	C	30								
			24		124	2.6	122	9663	7791	10.6	
3	45′	C	29.7								
			35		132	6.0	132	9307	7646	10.6	
4	60′	C	30								
				3′	Volume = 9			PSP Concentration		= 58.4	
				6′	= 7					= 34.5	
5	1.15′		PSP*	9′	= 9					= 13.8	at 1 Hr 50.9
				12′	= 3					= 6.4	
			31		125	5.9	125	8525	5690	14.2	
		C	31								
			29		135	6.3	138	8236	9363	8.9	
6	1.30′	C	25								
			24		94	9.6	100	7900	9035	5.7	
7	1.45′	C	25.6								
			26		97	4.7	104	7548	9423	4.5	
8	2.00′	C	25								
				3′	Volume = 12			PSP Concentration		= 59.4	
				6′	= 4					= 24.4	
9	2.15′		PSP*	9′	= 4					= 36.8	at 2 Hrs 137
				12′	= 7					= 3.7	
			31		104	4.9	110	6040	6215	11.8	
		C	31								
			18		108	5.2	111	8398	8534	7.3	
10	2.30′	C	27								
			35		136	6.3	137	8014	8107	14.6	
11	2.45′	C	28.5								
			41		103	5.0	107	8061	8225	9.3	
12	3.00′	C	28.15								

280 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 55	at 18 Hr = 450
Urine	3H Folate	3435	6566

* Bolus PSP 300 mg/l - 2ml
Correction factor 541.2 mg/l

Study 7 Date 4-4 Number of weeks Postoperative 4 Control Jejunal Loop X
Dog # 867 Fast X Fed 500 g Liver Transplanted Jejunoileum and Jejunal Loop

				Na	K	Cl	H3 Folate	C14 PEG	Glucose	
			Perfusate Content	123 mg/l	5.3 mg/l	123 mg/l	11530	9927	101.6 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 22
			34	101	4.9	104	3265	6475	2.4	
1	15′	42 C	64							
			33	86	4	91	4365	12023	10.6	
2	30′	C	34.67							
			28	125	5.7	125	4831	11329	19.2	
3	45′	C	36.8							
			25	121	5.1	127	5705	11848	25.7	
4	60′	C	35							
				3′ Volume = 18				PSP Concentration	= 20.2	
				6′ = 5					= 29.9	
5	1.15′		PSP*	9′ = 5					= 23.5	at 1 Hr 46
				12′ = 9					= 21.2	
			32	134	5.5	143	3708	12197	10.6	
		C	34.18							
			37	117	5.0	123	3494	12839	11.0	
6	1.30′	C	32.47							
			34	130	5.7	137	3090	11336	9.4	
7	1.45′	C	36.78							
			35	---	---	---	3382	12768	---	
8	2.00′	C	32.65							
				3′ Volume = 5				PSP Concentration	= 30.8	
				6′ = 9					= 33.1	
9	2.15′		PSP*	9′ = 5					= 10.6	at 2 Hrs 75
				12′ = 5					= 15.2	
			30	136	5.8	140	2445	12801	3.3	
		C	32.57							
			39	111	4.8	121	4010	13376	10.2	
10	2.30′	C	31.17							
			34	100	4.5	104	4454	13378	15.1	
11	2.45′	C	31.16							
			44	135	5.9	136	6394	12540	31.0	
12	3.00′	C	33.25							

336 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 130	at 18 Hr = 1000
Urine	3H Folate	4108	1780

* Bolus PSP 300 mg/l - 2ml
Correction factor 421.8 mg/l

Study 13 Date 4-25 Number of weeks Postoperative 8 Control Jejunal Loop X
Dog # 867 Fast X Fed 500 g Liver Transplanted Jejunoileum and Jejunal Loop

				Na	K	Cl	H3 Folate	C14 PEG	Glucose	
			Perfusate Content	125 mg/l	5.2 mg/l	120 mg/l	11371	4337	111.0 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 46
			20	115	5.2	129	3002	3549	0.8	
1	15′	42 C	51							
			30	134	5.7	139	5518	6889	9.3	
2	30′	C	26.4							
			29	90	4	96	7410	5491	9.3	
3	45′	C	33.1							
			20	127	5.4	130	8591	6036	15.2	
4	60′	C	30							
				3′ Volume = 5			PSP Concentration		= 13.1	
				6′ = 5					= 17.3	
5	1.15′		PSP*	9′ = 4					= 24.1	at 1 Hr 265
				12′ = 4					= 25.4	
			25	118	4.9	127	4422	5337	13.1	
		C	34							
			45	118	5.1	124	9466	5109	10.1	
6	1.30′	C	35							
			35	126	5.8	133	4143	5632	10.1	
7	1.45′	C	32							
			26	129	5.7	136	4186	5303	7.2	
8	2.00′	C	34							
				3′ Volume = 12			PSP Concentration		= 44.8	
				6′ = 11					= 15.6	
9	2.15′		PSP*	9′ = 5					= 8.5	at 2 Hrs 90
				12′ = 9					= 5.1	
			40	129	5.7	134	6139	6135	17.7	
		C	29							
			31	130	5.6	134	7677	5495	32.5	
10	2.30′	C	33							
			19	112	5.2	120	6772	6003	17.3	
11	2.45′	C	30.3							
			23	120	5.5	128	5319	6742	4.6	
12	3.00′	C	27.15							

292 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 65	at 18 Hr = 455
Urine	3H Folate	1922	2036

* Bolus PSP 300 mg/l - 2ml
Correction factor 348 mg/l

Study 5 Date 3-25 Number of weeks Postoperative 2 Control Jejunal Loop X
Dog # 867 Fast Fed 500 g Liver X Transplanted Jejunoileum and Jejunal Loop

			Perfusate Content		122 mg/l	6 mg/l	126 mg/l	15663	5218	106.4 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values		Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 24
				30	108	6	107	5228	3895	5.4	
1	15′	42 C		46							
				30	129	7	130	6455	6751	3.3	
2	30′	C		30							
				24	136	7	141	5622	7226	8.7	
3	45′	C		29.7							
				35	134	6	146	5061	7703	4.5	
4	60′	C		30							
				3′	Volume = 12			PSP Concentration		= 22.2	
				6′	= 6					= 29	
5	1.15′		PSP*	9′	= 6					= 15.4	at 1 Hr 146
				12′	= 6					= 5.9	
				31	139	5.9	142	3818	6791	4.1	
		C		31							
				29	139	7	149	4254	8102	2.5	
6	1.30′	C		25							
				24	138	7	145	3913	7886	1.7	
7	1.45′	C		25.6							
				26	139	7	151	4524	7627	4.5	
8	2.00′	C		25							
				3′	Volume = 5			PSP Concentration		= 23.1	
				6′	= 5					= 12.2	
9	2.15′		PSP*	9′	= 5					= 5	at 2 Hrs 180
				12′	= 4					= 1.4	
				31	135	7	143	4120	8115	2.9	
		C		31							
				18	138	6	148	4775	7383	3.7	
10	2.30′	C		27							
				35	138	6	152	4300	7455	2.9	
11	2.45′	C		28.5							
				41	141	7	146	5058	7612	3.3	
12	3.00′	C		28.15							

289 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 80	at 18 Hr = 375
Urine	3H Folate	17608	5118

* Bolus PSP 300 mg/l - 2ml
Correction factor 313.1 mg/l

Study 10 Date 4-7 Number of weeks Postoperative 4 Control Jejunal Loop X
Dog # 867 Fast Fed 500 g Liver X Transplanted Jejunoileum and Jejunal Loop

				Na	K	Cl	H3 Folate	C14 PEG	Glucose	
			Perfusate Content	114 mg/l	4.9 mg/l	121 mg/l	14129	4736	101.2 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 40
			26	97	4.4	101	5032	3381	6.9	
1	15′	42 C	58							
			20	115	5.1	124	4976	6364	2.9	
2	30′	C	31							
			24	121	5.2	128	3577	7294	1.2	
3	45′	C	27.2							
			28	129	5.7	141	3301	7686	0.4	
4	60′	C	25.8							
				3′ Volume = 15			PSP Concentration		= 59	
				6′ = 8					= 45	
5	1.15′		PSP*	9′ = 3					= 47	at 1 Hr 184
				12′ = 3					= 25.2	
			27	136	5.2	152	2975	8018	0.0	
		C	24.81							
			33	79	3.5	93	2757	7415	0.4	
6	1.30′	C	26.82							
			30	90	4	101	4253	7550	0.0	
7	1.45′	C	26.3							
			24	129	5.4	141	4897	6832	2.9	
8	2.00′	C	29.11							
				3′ Volume = 12			PSP Concentration		= 22.5	
				6′ = 22					= 33.9	
9	2.15′		PSP*	9′ = 5					= 21.9	at 2 Hrs 148
				12′ = 5					= 29.0	
			40	130	5.4	144	3800	6845	0.8	
		C	29							
			32	56	2.5	62	4489	7177	1.6	
10	2.30′	C	27							
			34	133	5.8	145	5286	7200	4.1	
11	2.45′	C	27							
			15	82	3.6	93	5140	7084	4.9	
12	3.00′	C	28							

272 volume recovered in 3 Hrs

	Volume	at 3 Hr = 60	at 18 Hr = 400
Urine	3H Folate	13686	11154

* Bolus PSP 300 mg/l - 2ml
Correction factor 865 mg/l

Study 16 date 4-26 Number of weeks Postoperative 8 Control Jejunal Loop X
Dog # 867 Fast Fed 500 g Liver X Transplanted Jejunoileum and Jejunal Loop

			Perfusate Content		130 mg/l	5.3 mg/l	129 mg/l	15982	5800	114.4 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values		Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 56
			27		74	3.5	148	2914	1908	8.0	
1	15′	42 C	27								
			30		133	5.9	136	6096	6009	8.4	
2	30′	C	40.5								
			30		144	6.2	135	5174	7927	5.9	
3	45′	C	30.72								
			26		133	5.8	115	6175	8354	3.8	
4	60′	C	29.15								
				3′	Volume = 9			PSP Concentration		= 64.7	
				6′	= 7					= 38.9	
5	1.15′		PSP*	9′	= 5					= 13.9	at 1 Hr 113
				12′	= 2					= 8.5	
			25		139	6.1	132	4448	6342	3.0	
		C	38								
			32		137	6.2	133	5240	7840	6.8	
6	1.30′	C	31								
			26		139	6.2	147	6522	7151	8.0	
7	1.45′	C	34								
			28		102	4.6	111	6815	8220	8.9	
8	2.00′	C	29.6								
				3′	Volume = 8			PSP Concentration		= 50.3	
				6′	= 4					= 54.1	
9	2.15′		PSP*	9′	= 5					= 22	at 2 Hrs 107
				12′	= 5					= 7.6	
			25		126	5.7	127	5947	8602	12.7	
		C	28.31								
			26		134	6.1	139	6722	7959	12.7	
10	2.30′	C	30								
			26		133	6.1	136	6474	8241	10.6	
11	2.45′	C	29.5								
			25		130	5.8	134	4065	4885	14.4	
12	3.00′	C	25								

306 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 30	at 18 Hr = 500
Urine	3H Folate	4576	1450

* Bolus PSP 300 mg/l - 2ml
Correction factor 319 mg/l

ABSORPTION VALUES IN TRANSPLANTED DOGS (CHAP IX)

Study 3 Date 2-24 Number of weeks Postoperative 2 Control Jejunal Loop
Dog # 330 Fast X Fed 500 g Liver Transplanted Jejunoileum and Jejunal Loop X

			Perfusate Content	119 mg/l	7.7 mg/l	127 mg/l	25417	4239	94.3 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 42
			20	131	7.5	139	9496	4818	0.8	
1	15′	42 C	37							
			25	141	7.7	136	11987	6687	2.3	
2	30′	C	26.6							
			21	139	8.1	134	9351	9156	2.3	
3	45′	C	19.5							
			17	137	7.5	129	9363	7305	3.1	
4	60′	C	24							
				3′ Volume = 7			PSP Concentration		= 52.4	
				6′ = 5					= 31.9	
5	1.15′		PSP*	9′ = 5					= 44.6	at 1 Hr 66
				12′ = 3					= 30	
			21	145	8.2	136	9738	8721	3.1	
		C	20.41							
			26	146	7.7	128	13336	6648	2.7	
6	1.30′	C	26.7							
			26	141	7.8	145	11958	8549	3.5	
7	1.45′	C	20.8							
			26	143	8.1	104	12625	8117	3.1	
8	2.00′	C	22							
				3′ Volume = 8			PSP Concentration		= 0	
				6′ = 6					= 46.9	
9	2.15′		PSP*	9′ = 6					= 45	at 2 Hrs 204
				12′ = 3					= 10.8	
			27	143	8.1	139	14397	6450	7.0	
		C	27.6							
			26	145	8.6	142	13963	7711	3.5	
10	2.30′	C	23.08							
			33	148	9.1	133	15964	8357	3.1	
11	2.45′	C	22							
			23	154	9.1	157	19296	8047	3.9	
12	3.00′	C	22							

280 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 41	at 18 Hr = 325
Urine	3H Folate	28870	12695

* Bolus PSP 300 mg/l - 2ml
Correction factor 370 mg/l

Study 7 Date 3- 7 Number of weeks Postoperative 4 Control Jejunal Loop
Dog # 330 Fast X Fed 500 g Liver Transplanted Jejunoileum
and Jejunal Loop X

			Perfusate Content	116 mg/l	4.7 mg/l	116 mg/l	13042	3305	112.5 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 44
			31	110	5.4	106	6100	2182	3.5	
1	15′	42 C	63							
			27	135	5.9	130	8462	5337	5.8	
2	30′	C	26							
			26	137	6.2	135	9348	5421	11.2	
3	45′	C	25.6							
			23	125	5.6	126	9224	5911	12.8	
4	60′	C	23.5							
				3′ Volume = 6				PSP Concentration	= 19.4	
				6′ = 5					= 18.9	
5	1.15′		PSP*	9′ = 5					= 18.4	at 1 Hr 84
				12′ = 4					= 17.5	
			25	134	6.2	137	9869	8405	6.6	
		C	16.5							
			16	134	6.2	137	8015	6815	16.2	
6	1.30′	C	20.37							
			22	131	6.1	141	7357	7056	8.5	
7	1.45′	C	19.7							
			22	139	6.5	132	7993	6775	7.3	
8	2.00′	C	20.5							
				3′ Volume = 5				PSP Concentration	= 11.3	
				6′ = 5					= 33.5	
9	2.15′		PSP*	9′ = 4					= 10.9	at 2 Hrs 129
				12′ = 5					= 17.0	
			25	136	6.6	139	13593	12402	5.4	
		C	11.2							
			11	137	6.9	138	8493	6886	5.8	
10	2.30′	C	20.16							
			21	136	6.4	137	8007	7097	10.4	
11	2.45′	C	19.56							
			32	138	6.6	136	8734	6693	13.5	
12	3.00′	C	20.75							

197 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 38	at 18 Hr = 200
Urine	3H Folate	6505	5570

* Bolus PSP 300 mg/l - 2ml
Correction factor 261.6 mg/l

Study 13 Date 4-4 Number of weeks Postoperative 8 Control Jejunal Loop
Dog # 330 Fast X Fed 500 g Liver Transplanted Jejunoileum
and Jejunal Loop X

# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 3
		Perfusate Content		124 mg/l	5.4 mg/l	122 mg/l	11930	10344	90.6 mg/100ml	
			33	119	7.2	122	2800	3537	0	
1	15′	42 C	122							
			19	129	6.6	133	4259	7252	3.3	
2	30′	C	59.9							
			20	136	6.5	140	3396	11858	0	
3	45′	C	36.6							
			37	105	4.7	112	4906	12413	13.1	
4	60′	C	35							
				3′ Volume = 1			PSP Concentration		= 0.9	
				6′ = 15					= 2.8	
5	1.15′		PSP*	9′ = 5					= 3.7	at 1 Hr 38
				12′ = 2					= 2.8	
			25	142	6.5	150	3040	17470	0	
		C	25							
			35	193	8.9	145	3420	13900	10.2	
6	1.30′	C	35							
			15	157	7.1	121	4409	16088	8.2	
7	1.45′	C	27							
			28	137	6.3	124	3264	16840	4.3	
8	2.00′	C	25.8							
				3′ Volume = 6			PSP Concentration		= 0	
				6′ = 5					= 3.7	
9	2.15′		PSP*	9′ = 14					= 12.9	at 2 Hrs 72
				12′ = 24					= 11.5	
			44	138	6.8	141	3718	12773	3.7	
		C	34							
			24	140	7	123	5314	8267	18.4	
10	2.30′	C	52							
			17	143	6.4	140	4368	13986	7.3	
11	2.45′	C	31							
			38	145	6.4	145	3183	16736	2.9	
12	3.00′	C	26							

327 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 130	at 18 Hr = 1500
Urine	3H Folate	2420	878

* Bolus PSP 300 mg/l - 2ml
Correction factor 453 mg/l

Study 4 Date 2-25 Number of weeks Postoperative 2 Control Jejunal Loop
Dog # 330 Fast Fed 500 g Liver X Transplanted Jejunoileum
and Jejunal Loop X

		Perfusate Content		125 mg/l	5.5 mg/l	125 mg/l	29175	4522	99.3 mg/100ml	
# Sample	Time	500 ml Vol	Aspirate Content Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 46
			30	132	6.6	131	14682	4416	7.3	
1	15′	42 C	46							
			30	137	6.4	130	14952	5834	11.0	
2	30′	C	30							
			24	140	7.1	102	14485	7252	10.6	
3	45′	C	29.7							
			35	141	7.0	133	15698	7131	10.6	
4	60′	C	30							
				3′ Volume = 10			PSP Concentration		= 15.5	
				6′ = 7					= 53.9	
5	1.15′		PSP*	9′ = 5					= 27.7	at 1 Hr 79
				12′ = 5					= 11.7	
			31	140	6.9	130	14516	7594	1.9	
		C	31							
			29	145	7	131	18421	5186	3.9	
6	1.30′	C	25							
			24	148	6.4	129	19472	5695	3.9	
7	1.45′	C	25.6							
			26	144	6.7	133	22490	5307	2.3	
8	2.00′	C	25							
				3′ Volume = 5			PSP Concentration		= 5.2	
				6′ = 8					= 57.7	
9	2.15′		PSP*	9′ = 6					= 44.1	at 2 Hrs 215
				12′ = 5					= 20	
			31	143	6.7	138	18871	6432	2.7	
		C	31							
			18	142	7.2	132	20338	9058	2.7	
10	2.30′	C	27							
			35	142	7.3	137	20937	8625	4.3	
11	2.45′	C	28.5							
			41	145	7.2	140	22880	8019	2.3	
12	3.00′	C	28.15							

280 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 65	at 18 Hr = 355
Urine	3H Folate	22910	14200

* Bolus PSP 300 mg/l - 2ml
Correction factor 393.2 mg/l

Study 12 Date 3-14 Number of weeks Postoperative 4 Control Jejunal Loop
Dog # 330 Fast Fed 500 g Liver X Transplanted Jejunoileum and Jejunal Loop X

# Sample	Time	500 ml Vol	Aspirate Content / Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 42
		Perfusate Content		122 mg/l	5.2 mg/l	123 mg/l	14192	4742	93.9 mg/100ml	
			39	81	5.1	110	1769	817	25.2	
1	15′	42 C	24.3							
			15	151	6.8	121	8478	6725	0	
2	30′	C	29.6							
			30	149	6.9	131	7790	7505	0.8	
3	45′	C	26.53							
			15	151	7.8	138	9264	9129	1.2	
4	60′	C	21.8							
				3′ Volume = 5			PSP Concentration		= 41.1	
				6′ = 5					= 16.4	
5	1.15′		PSP*	9′ = 6					= 9.3	at 1 Hr 10
				12′ = 6					= 2.8	
			30	149	6.5	138	8890	5574	0	
		C	35.7							
			39	153	7.4	138	9003	5264	0	
6	1.30′	C	37.83							
			13	133	5.9	122	7559	8402	0	
7	1.45′	C	23.7							
			16	102	5.2	101	7318	9453	0	
8	2.00′	C	21							
				3′ Volume = 4			PSP Concentration		= 6.1	
				6′ = 5					= 9.4	
9	2.15′		PSP*	9′ = 7					= 31.8	at 2 Hrs 93
				12′ = 5					= 18.7	
			30	82	4.4	77	7395	9900	0.4	
		C	20.1							
			17	148	7.3	134	9244	8824	0	
10	2.30′	C	22.5							
			37	153	7.4	138	10227	6241	0	
11	2.45′	C	31.9							
			27	154	7.2	128	10788	5665	0	
12	3.00′	C	35.16							

276 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 40	at 18 Hr = 375
Urine	3H Folate	12862	1941

* Bolus PSP 300 mg/l - 2ml
Correction factor 348.6 mg/l

Study 17 Date 4-8 Number of weeks Postoperative 8 Control Jejunal Loop
Dog # 330 Fast Fed 500 g Liver X Transplanted Jejunoileum
and Jejunal Loop X

# Sample	Time	500 ml Vol	Aspirate Content Corrected Values	Na	K	Cl	H3 Folate	C14 PEG	Glucose	Blood H3 Folate at 0 Hrs 45
		Perfusate Content		75 mg/l	3 mg/l	78 mg/l	13648	5704	69.4 mg/100ml	
			25	94	4.5	138	4187	2592	0.8	
1	15′	42 C	92							
			38	20	0.8	38	7959	7246	0.4	
2	30′	C	33							
			32	83	3.4	122	7302	7567	1.2	
3	45′	C	31.6							
			30	63	2.8	63	6208	7920	0.4	
4	60′	C	30.25							
				3′ Volume = 15			PSP Concentration		= 15.3	
				6′ = 3					= 41.4	
5	1.15′		PSP*	9′ = 4					= 39.3	at 1 Hr 75
				12′ = 12					= 13.7	
			26	133	5.5	139	6274	7756	0	
		C	30.8							
			37	146	6.5	130	9683	4518	0	
6	1.30′	C	37							
			13	148	5.8	129	8242	6815	0	
7	1.45′	C	35							
			34	39	1.6	40	7173	8599	0	
8	2.00′	C	27.8							
				3′ Volume = 11			PSP Concentration		= 5.4	
				6′ = 3					= 21.1	
9	2.15′		PSP*	9′ = 18					= 24	at 2 Hrs 150
				12′ = 12					= 11.6	
			40	72	3.4	156	7950	7098	0.4	
		C	33.95							
			29	92	3.7	87	10295	6361	0	
10	2.30′	C	37.6							
			32	39	1.7	37	7513	9040	0	
11	2.45′	C	26.5							
			28	77	3.4	78	9471	7610	0.8	
12	3.00′	C	31.5							

321 Volume recovered in 3 Hrs

	Volume	at 3 Hr = 60	at 18 Hr = 750
Urine	3H Folate	10406	2956

* Bolus PSP 300 mg/l - 2ml
Correction factor 265.7 mg/l

APPENDIX 3

INDEX OF AUTHORS

APPENDIX 4

GENERAL INDEX