Small bowel update. Part II

J LOVE, MD, FRCPC, ABR THOMSON, MD, PHD, FRCPC, FACP

J LOVE, ABR THOMSON. Small bowel update. Part II. Can J Gastroenterol 1992; 6(2):97-107.

Key Words: *Food allergy, Lipids, Motility, Permeability, Small bowel, Transplantation*

THE RECENT ADVANCES IN CLINICALLY important diseases of the small intestine have been reviewed; however, the basis for many of these clinical advances rests with important observations on alterations in the physiology of the small intestine, as well as mechanistic observations of alterations in small intestinal function in models of human disease. In this review, a summary of the past year's literature is presented which will draw attention to the considerable areas of progress in small bowel physiology soon to be translated into an improved understanding of the pathophysiology of a variety of intestinal disorders.

LIPIDS

The intestinal aspects of lipid absorption (1) and the effect of dietary fish oil on tissue lipid metabolism have been reviewed (2). Diets enriched in marine ('fish') oils decrease very low density lipoprotein (VLDL) synthesis and secretion, reduce plasma triacylglycerols and variably reduce plasma cholesterol levels. In the neonatal piglet, fish oil hydrolysis is initiated in the stomach and absorption proceeds adequately in the small intestine (3). Triacylglycerols of fish oils have an unusual fatty acid distribution pattern; docosahexaenoate (DHA, 22:6[n-3]) primarily are in the sn-2 position of glycerol, whereas a more random distribution of eicosapentaenoate (EPA, 20:5[n-3]) is found over all glycerol positions (4). The positional distribution of the acids in the lymph triacylglycerols is similar to that in fish oil which suggests that fish oil is absorbed from the rat intestine without substantial alteration in triacylglycerol's acyl chains.

Because MK-733 (simvastatin), a potent 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, also reduces enterocyte microsomal activity of acyl coenzyme A:cholesterol acyltransferase without affecting cholesterol esterase activities, the inhibitory effect of MK-733 on cholesterol absorption in cholesterol-fed rabbits may be via reduced acyl coenzyme A:cholesterol acyltransferase activity (5).

Bile acids are transported across the intestine by ionic and nonionic passive diffusion, and by active ileal brush border membrane (BBM) transport. Energy for the active process is derived from the sodium electrochemical gradient across the BBM arising from extrusion of sodium in exchange for potassium by Na^+/K^+-ATPase on the basolateral membrane. Using photoaffinity labelling techniques, a 54,000 molecular weight polypeptide has been identified in the ileum's basolateral membrane which may represent bile acid transporters different from those in the BBM (6). It is uncertain whether there are multiple independently regulated bile acid transporters.

Bile salt malabsorption may cause chronic diarrhea in several diverse clinical settings such as post cholecystectomy, post vagotomy and in patients with chronic 'functional' diarrhea. Both radiolabelled and endogenous bile acid excretion is abnormally high in most patients with chronic diarrhea compared with normal subjects even when equivoluminous diarrhea is in-

Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Alberta

Correspondence and reprints: Dr ABR Thomson, 519 Robert Newton Research Building, University of Alberta, Edmonton, Alberta T6G 2C2. Telephone (403) 492-6490, Fax (403) 492-7964

Received for publication August 26, 1991. Accepted January 28, 1992

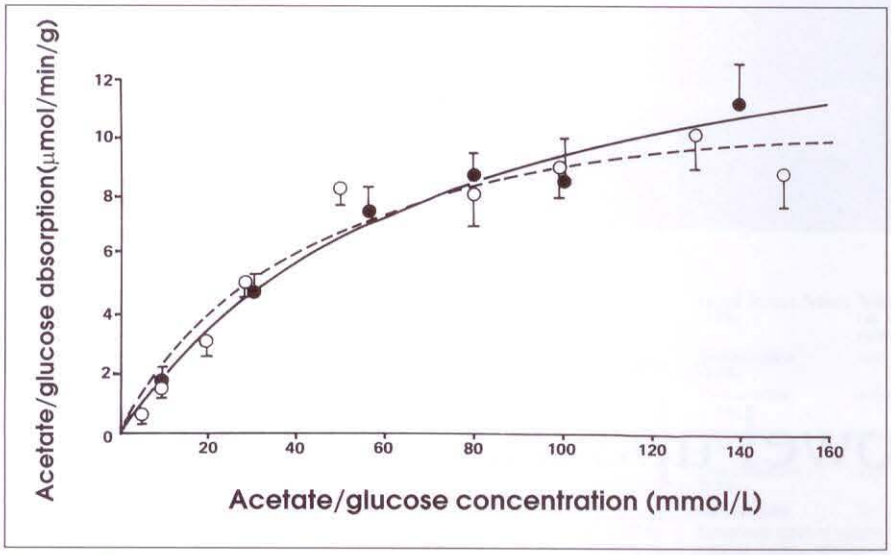

Figure 1) *Total acetate and glucose absorption in rat jejunum (Reproduced with permission from Watson et al. Gut 1990;31:170-4)*

duced in normal subjects by ingestion of osmotically active solutions (7). While there is a good correlation between radiolabelled and endogenous bile acid excretion, the results are not as abnormal as those in patients with ileal resection; no patient with diarrhea responded to treatment with cholestyramine, suggesting that bile acid malabsorption is not likely the primary cause of their diarrhea.

Pluronic L-81 is a potent inhibitor of chylomicrons' intestinal formation and transport. The digestion, uptake and re-esterification of absorbed monoacylglycerol and fatty acid to form triacylglycerols are unaffected by L-81 which also does not alter formation and transport of VLDL-sized particles by the small intestine (chylomicrons and VLDL may be packaged separately in the enterocytes) (8).

Severe malnutrition commonly is seen in patients with advanced liver disease and portal hypertension. In a rat model of portal hypertension and small bowel damage, there is increased villus tip denudation (9). Portal hypertension may alter the small intestinal mucosa and thereby increase its susceptibility to injury and the animal's susceptibility to malnutrition.

The short chain fatty acids (SCFAs) acetate, butyrate and proprionic acid are the major anions of colonic water and are formed in the colon by anaerobic bacterial fermentation of carbohydrate. High concentrations of SCFAs in the ileum suggests coloileal reflux and that these SCFAs stimulate motility in humans (10). Mortensen et al (11) studied SCFA concentration in intestinal output of 56 patients with various intestinal resections and found colectomized patients with short bowel syndrome have lower SCFA concentrations compared with healthy controls or patients with an ileostomy. Patients with a partial colectomy, small bowel bypass or short bowel syndrome with preserved colon had normal fecal SCFA concentrations and decreased SCFA production rates (11).

Acetate may be absorbed by nonionic diffusion or passage of ionized acetate through a paracellular pathway. Evidence for an acetate/bicarbonate exchange mechanism has been found in human ileal BBM vesicles. Acetate absorption quantitatively is similar to glucose in rat jejunum perfused in vivo (12) (Figure 1). Acetate absorption is diminished when the intestine is pretreated with cholera toxin; absorption may be reduced by solvent drag in the secreting intestine. Kinetics of acetate absorption may indicate the presence of a saturable step in the whole absorptive process, such as consumption of a finite supply of luminal hydrogen ions.

Albumin enhances the flux of fatty acids across a lipid-water interface, possibly by more efficiently transporting fatty acids across the unstirred water layer adjacent to the interface (13). Long chain fatty acids' limited solubility in water may be overcome if the small flux of unbound fatty acid is augmented by a second flux (due to a more soluble bound form of fatty acid).

Infusion of triglyceride emulsions and complex carbohydrates into the ileum delays meal passage through the stomach and small intestine. When the 'ileal brake' is applied, the increase in small intestinal residence time in normal subjects is accompanied by enhanced absorption of a carbohydrate meal. In contrast, patients with terminal ileostomies produce more ileal effluent while taking a high, compared with a low, fat diet (14). A greater proportion of fat is absorbed during the high fat diet, with no change in carbohydrate output, increased protein output and no slowing of small bowel transit. These observations may be useful to formulate dietary recommendations for patients with ileostomy dysfunction.

Triglycerides containing medium chain fatty acids (MCTs) are useful in decreasing steatorrhea associated with lipid digestive disorders resulting from pancreatic exocrine insufficiency or cholestasis. Unlike long chain triglycerides, MCTs are absorbed intact as triglyceride molecules despite decreased intraluminal lipolysis or reduced micellar solubilization. MCTs comprise medium chain fatty acids (carbon chain length six to 12) esterified to glycerol and may vary in size and molecular weight from 420 to 639 kDa. Despite these differences, there is no significant variation in MCT absorption into the jejunum in rats assessed using a single pass marker perfusion technique (15).

CARBOHYDRATES, AMINO ACIDS AND NUCLEOSIDES

Carbohydrates usually are ingested as starch or sucrose and hydrolyzed to monosaccharides before absorption. Amylase and the BBM glucohydrolases – including sucrase, maltase, isomal-

tase and glucoamylase – are the major enzymes involved in carbohydrate hydrolysis. The glucohydrolase inhibitor acarbose decreases sucrase activity, inhibits glucose absorption and reduces the glycemic response to sucrose. Acarbose has been used in clinical trials in type II diabetes and has been shown to reduce blood glucose levels in patients with alcoholic cirrhosis following a meal containing 100 g carbohydrate (16).

Castanospermine, a potent glucohydrolase inhibitor, is an alkaloid with structural similarities to glucopyranose. In rats, castanospermine inhibits sucrase activity and dose-dependently reduces the glycemic response to sucrose with neither cumulative sucrase inhibition nor sucrase activity induction (17). Castanospermine remains to be tested clinically.

Membrane potentials and the mechanism(s) of intestinal sodium-dependent sugar transport has been reviewed (18). There is kinetic evidence of at least two distinct sodium-dependent glucose carriers in the jejunum of several animal species (including human fetuses [19]), but molecular biological methods have not yet allowed identification.

Intestinal BBM vesicles have been obtained from organ donor intestine and used to characterize nutrient absorption in the human intestine. For D-glucose and L-leucine the relative magnitude of transport is distal jejunum, proximal jejunum and then distal ileum (20). Eadie-Hofstee plot analysis demonstrates that L-leucine actively is transported by a single high-affinity transport system. The transport of D-glucose also occurs via a high-affinity system along the length of the intestine and via a low-affinity high-flux system limited to the proximal intestine. Both glucose transport systems are sodium-dependent and phlorizin-sensitive, confirming an earlier report by Harig et al (21).

Jejunal BBM vesicles may be prepared from conventional jejunal biopsies. When such techniques were applied to a patient with suspected glucose-galactose malabsorption, initial D-glucose uptake under sodium gradient conditions was only 10% of the control value (22). The ^{13}C breath test may also be used to detect impairment of glucose absorption occurring in children with congenital glucose-galactose malabsorption or severe villus atrophy (23).

The characterization of efflux pathways for D-glucose and L-amino acid has been reported in human jejunal basolateral membrane vesicles prepared from organ donor intestine (20). Glucose efflux from the enterocytes occurs by a carrier-mediated sodium-dependent transport mechanism inhibited by D-hexoses such as galactose, mannose, 2-deoxyglucose and 3-O-methylglucose. Transport of L-leucine and L-alanine across basolateral membranes is stimulated marginally by an inwardly-directed sodium gradient, contrasting to the 10-fold stimulation in BBM vesicles.

MOTILITY

Ileocolonic junction (24) and muscarinic receptor subtypes, (25) motility have been reviewed. The brain is the target site of action for several peptides altering gastrointestinal motor function (26). Peristalsis, initiated by intestinal wall distension, involves two reflexes, ascending contraction and descending relaxation; these move aborally and propel the intraluminal contents. The ascending enteric reflux involves cholinergic interneurons as well as cholinergic and noncholinergic transmission from motor neurons. Substance P and tachykinins may be transmitters of motor neurons while cholinergic interneurons and motor neurons constitute the main ascending enteric reflux pathway. There are likely multiple neural pathways with different transmitters and adaptive interactions after blockade of neurotransmitter systems (27).

Intestinal slow waves determine the frequency, velocity and duration of intestinal contractions, and decrease aborally along the small intestine (28). In the fasting state, the migrating motor complex occurs. This complex has been studied in detail, but much less information is available on postprandial motility. The ileum (but not the jejunum) in dogs has an unusual motor pattern accompanied by spike bursts of rhythmic frequency appearing 1 to 4 h after food ingestion when chyme reaches the ileum (29).

Prostaglandins are increased in the mucosa of some patients with inflammatory bowel disease. Dinoprostone causes contraction of intestinal longitudinal smooth muscle and relaxation of circular smooth muscle while dinoprost, in contrast, increases contractility of both circular and longitudinal muscle, increases contractile activity in the terminal ileum, proximal and distal colon, and increases spike potential frequency (30). The effect of prostaglandins on intestinal motility, therefore, depends on a balance between the different types of prostaglandins.

During signal-induced turnover of inositol phospholipids in the plasma membrane, diacylglycerol is produced transiently. Diacylglycerol activates protein kinase C, the calcium-activated phospholipid-dependent protein kinase. Phorbol esters are tumour-promoting agents structurally similar to diacylglycerol that activate protein kinase C and induce retrograde myoelectric activity in rabbit ileum in vivo (the effect may be in addition to protein kinase C activation [31]). This 'ileal brake' is due to altered antral, pyloric and duodenal motility (32), and induction of an irregular motility pattern in the jejunum (33). Ileal infusion of carbohydrate or fats also decreases pancreatic enzyme output (34), suggesting that the distal small intestine may participate in the late postprandial regulation of gastrointestinal function in humans.

Somatostatin exerts both excitatory and inhibitory effects on cholinergic neurons of the enteric nervous system by stimulating γ-aminobutyric neurons (35). Intestinal motility also is influenced by drugs affecting calcium ion influx across the smooth muscle cell membrane. The order of potency in calcium channel blockers inhibiting intestinal motility in vivo in the dog is nifedipine, verapamil then diltiazem (36). The spatial and temporal organization of contractions in the gastrointestinal tract is controlled by myogenic,

neural and chemical mechanisms manifested by electrical control activity.

Small intestinal motility is influenced by clonidine, an action ascribed to inhibitory presynaptic α_2-adrenoceptors associated with motility pacemaker neurons on the enteric nervous system and localized to ileal enterocytes. The inhibitory effects of clonidine and morphine on intestinal motility are mediated through different receptors and the potent inhibition of small intestinal myoelectric activity by α_2-adrenoceptor agonists is executed mainly via peripheral mechanisms (37). Erythromycin stimulates gastrointestinal motility, possibly by acting as a motilin receptor agonist (38).

The migrating motor complex is an index of enteric neural circuitry integrity. Investigation of small intestinal motor patterns may help to diagnose gastrointestinal motor activity disorders. Perfused-tube manometry is the standard technique for recording intraluminal intestinal pressure in humans, but intraluminal strain gauges have been shown appropriate for recording ambulant small bowel motility (39).

In patients with irritable bowel syndrome (IBS), there are alterations in basal (fasting) motor activity in the small intestine and colon (compared with patterns observed in healthy subjects). Psychological or neurohumoral stimuli may provoke an exaggerated or dysrhythmic pattern. The duration of postprandial motor activity during the day is shorter in IBS patients than in controls, and diurnal migrating motor complex intervals are shorter in diarrhea-predominant than in constipation-predominant IBS patients (40). The differences in small intestinal motility between IBS patients and controls are confined to the waking state. Patients with IBS respond excessively to cholecystokinin octapeptide stimulation, a fatty meal or ileal distension (41) as these stimuli may cause intestinal dysmotility resulting in abdominal symptoms contributing to IBS diagnosis. Identification of food intolerances in 73 of 91 IBS patients treated by dietary exclusion suggests that a dietary factor may unmask intestinal dysmotility and give rise to abdominal symptoms in IBS patients (42). Foods most commonly incriminated are dairy products and grains.

Food intolerance is a common but controversial clinical problem. Most allergic reactions are due to a type I, immediate immunoglobulin E-dependent hypersensitivity. In a rat model of intestinal anaphylaxis, an immune-mediated reaction to food protein was associated with diarrhea and altered intestinal myoelectric and motor activity (43).

Orocecal transit time (measured using the breath hydrogen excretion test) is longer in geriatric females than in geriatric males or younger subjects (44). The gastrocecal transit time assessed with the hydrogen breath test is prolonged in patients with anorexia nervosa; both the altered gastric and small intestinal motility may contribute to gastrointestinal symptoms seen in these individuals (45).

The acute effects of abdominal radiation include nausea, vomiting, anorexia, diarrhea and pain. These may be due to intestinal structure or epithelial transport alterations (46). In dogs, fractionated doses of ionizing radiation alter the small intestinal motor activity and help develop giant migrating contractions and retrograde giant contractions (47), raising the possibility that some side effects of radiation may be related to these motor abnormalities.

INTESTINAL TRANSPLANTATION

Bowel transplant continues to represent a highly experimental but promising area of medicine (48). A review has been published which summarizes the progress in intestinal transplantation and highlights areas in which further research is required before this procedure becomes a practical therapeutic option (49). Twenty-two transplants of complete bowel or combined liver/bowel have been performed in humans worldwide, but none have been successful in the long term. After an initial flurry of activity in the mid 1970s, enthusiasm for intestinal transplantation waned because all patients died due to technical complications or rejection.

Rejection and sepsis continue to be major causes of graft loss. The discovery that cyclosporine had success in other applications in transplantation renewed interest in small intestinal transplantation. Several centres have been able to detect intestinal rejection and remove the graft before life-threatening complications occurred. Rejection remains the major obstacle to clinically successful intestinal transplantation. Because of lymphocytes in the intestinal graft and native class II antigen expression by intestinal epithelium, the gut provides strong stimuli for rejection. Many methods attempting to decrease the antigenicity of the graft are undergoing testing. These include irradiation, antithymocyte globulin, portal drainage, major histocompatibility complex matching and multivisceral transplants. Improved immunosuppressive protocols also need to be established. Early detection of intestinal rejection may be difficult since it is a patchy process, rendering biopsies alone inadequate, and noninvasive screening tests must be developed.

The small bowel contains a large amount of lymphatic tissue which complicates transplantation of this organ by potentially mediating a vigorous graft-versus-host disease (GVHD) reaction in addition to the expected rejection reaction. This appears to be an important problem in rats but not in humans. A rat model exists for investigating GVHD and rejection in isolation by crossing a Lewis and brown Norway rat. The resulting Fl generation will give a unidirectional GVHD reaction without rejection if the transplant from a parental strain is performed. In contrast, an Fl to parent transplant demonstrates only rejection. A transplant between parental strains, ie, brown Norway to Lewis or vice versa, will manifest both GVHD and rejection. The effects of pretreating donor animals with rabbit antirat lymphocyte serum as well as cyclosporine was performed using this model (50). This was an effective method of preventing both GVHD and rejection in the allogeneic rat small bowel transplant model.

Another group studied the effect of ex vivo allograft irradiation combined

with cyclosporine therapy in a pig intestinal transplant model (51); unfortunately, this did not improve survival.

A rat model using fully allogeneic orthotopic transplantation was used to assess two forms of pretreatment of the donor, namely irradiation and blood transfusions, with the aim of ameliorating GVHD (52). Pretreatment with donor-specific blood transfusions increased GVHD incidence and thus may induce immunosuppression as well as sensitization in the same rat. The irradiation group did not have any GVHD but did experience vigorous rejection. The hypothesis is that the absence of the immunosuppressive effect of GVHD in irradiated allotransplants may be responsible for the observed rejection. The authors postulate that a control GVHD may be useful to manipulate the severity of small bowel rejection.

The interrelationship between processes of GVHD and rejection are poorly understood, but they are dynamic phenomena involving complex traffic of lymphoid cells. A study using strain-specific monoclonal antibodies in a rat model to monitor the migration of infiltrating cells was able to distinguish lymphocytes of graft origin within the host reticuloendothelial system and to identify host cells responsible for rejection from the substantial lymphoid component of the graft bowel (53). There was simultaneous two-way migration of host and donor lymphocytes in both nonimmunosuppressed and cyclosporine-treated animals. The study also demonstrated that GVHD and rejection can coexist, and that a two-way traffic of lymphoid cells develops very quickly after grafting. Indeed, graft cells migrated to the gut lymphoid tissue of the host within 24 h of transplantation.

In the absence of immunosuppression, the vigorous host response destroys the lymphoid tissue of the graft. Therefore, after the first two or three days of initial migration, the source of graft lymphocytes (namely the Peyer's patches and mesenteric lymph nodes of the transplant) progressively are destroyed. The isolated graft lymphocytes are unable to proliferate within the host lymphoid tissue – their disappearance by day 6 suggests active destruction by host cells. With cyclosporine immunosuppression, the prolonged survival of the small bowel and its lymphoid tissue is able to fuel a much greater movement of lymphocytes to the host. This response peaks at day 14, with no graft cells visible in the host tissue at 21 to 28 days. The development of an indolent rejection process may be responsible for blocking the proliferation of graft lymphocytes within the host tissue and eventually causing their destruction. This model aims to provide the means of investigating immunosuppressive regimens and assessing the effect of these methods to reduce graft immunogenicity in small bowel transplantation.

The early detection of small bowel transplant rejection is necessary to allow for reversal of the rejection process as well as for protection of the patient. Two new in vitro methods for detecting rejection in rat small bowel transplant were published recently (54,55). The first measured gastrointestinal peptide tissue levels following intestinal transplantation in rats. Serial tissue samples of transplanted intestine were obtained from vascularized syngeneic and allogeneic jejunal transplants in rats. Baseline levels of peptides were determined in nontransplanted jejunum of the same animals. Tissue levels of somatostatin, vasoactive intestinal peptide and substance P showed that normal gut peptide levels in syngeneic bowel were maintained up to one year after transplantation. Allogeneic bowel showed a progressive decline in peptide concentrations simultaneously with or preceding histological evidence of rejection.

The second study correlated transluminal leakage of low molecular weight polyethylene glycol (PEG) with the development of allograft rejection (55). Again, vascularized allogeneic and syngeneic jejunal transplants were performed in rats without immunosuppression, with histological correlation performed. Two days following transplantation, urinary PEG levels were elevated in both allogeneic and syngeneic groups. However, four days after the transplant, syngeneic urine PEG levels decreased and were not significantly different from controls. The allogeneic group continued to show significantly higher levels from day 4 until the end of the experiment. These elevated levels most likely represent the development of rejection preceding the first significant histological signs of rejection which were found six days post transplant. Further study is required to refine these techniques, but detection of transluminal leakage of low molecular weight PEGs and/or gastrointestinal monitoring of peptide tissue levels may prove to be useful adjuncts to monitoring possible development of small bowel transplant rejection.

Based on successful studies that showed high dose intravenous cyclosporine followed by oral cyclosporine reliably would prevent intestinal rejection in outbred piglets, a clinical program was started in London, Ontario. The first successful small bowel/liver grafting occurred in November of 1988 in a patient with short bowel syndrome (56). The patient suffered thrombosis of the superior mesenteric artery leading to small intestinal infarction. Small bowel/liver transplantation offered the hope of oral feeding, obviating the requirement for chronic venous access and correcting the hypercoagulable state associated with antithrombin III deficiency. The donor was pretreated preoperatively with 10 mg OKT3 (Ortho-McNeil) intravenously, Minnesota antilymphocyte globulin 30 mg/kg intravenously over 12 h and methylprednisolone 1 mg/kg intravenously. The patient was able to return to an enteral diet eight weeks post transplantation. Measures taken to avoid the complications of rejection, GVHD and sepsis included: postoperative treatment with continuous high dose intravenous cyclosporine, donor pretreatment with OKT3 and antilymphocyte globulin to reduce the number of lymphoreticular cells in the graft, donor red blood cell transfusion and enteral feeding to maintain a normal intestinal barrier function.

Liver transplantation has been

shown to induce donor-specific tolerance in pigs and rats, so simultaneous liver grafting also may have helped. The patient did experience one episode of rejection, but this was detected early by monitoring intestinal permeability changes with ^{51}Cr-labelled EDTA. The patient also had a mild episode of GVHD manifested by donor lymphocytes appearing in peripheral blood samples 11 days post transplant concurrent with GVHD's characteristic rash.

Ten patients with primary malignant tumours of the biliary tract, duodenum or stomach and with secondary involvement of the liver underwent removal of most or all of the stomach, liver, pancreas, spleen, duodenum, proximal jejunum, terminal ileum and ascending and transverse colon. An organ cluster graft was placed in the cavity, consisting of liver, pancreas, duodenum and variable segments of proximal jejunum. Eight of 10 patients are alive after three to nine months, all with good liver and pancreas function and most with satisfactory gastrointestinal tract function. Recurrent tumour has not yet been proven in any of the survivors (57). This same group, however, has reported on transplantation of multiple abdominal viscera in the pediatric age group (58). In that operation, evisceration and transplantation en bloc of the stomach, small intestine, colon, pancreas and liver were done to treat two children with short gut syndrome and secondary liver failure. The first patient died perioperatively, but the second survived for six months, eventually dying of an Epstein-Barr virus-associated lymphoproliferative disorder.

Another group has reported a similar operation in two infants with short bowel syndrome and liver failure associated with the necessary use of parenteral nutrition. The infants received en bloc composite allografts of liver, stomach, duodenum, pancreas, jejunum and ileum (59). The first patient died of early complications while the second patient developed near-normal liver and small intestinal function until a monoclonal, malignant, B cell lymphoproliferative disorder occurred.

RADIOLOGICAL AND ENDOSCOPIC DIAGNOSTIC TECHNIQUES

The topic of interventional radiology in the abdomen has been reviewed (60). Plain abdominal radiographs do not always distinguish obstruction from ileus, and enteroclysis may be useful for this purpose in the early postoperative period (61). The overall yield of enteroclysis in the evaluation of suspected small intestinal bleeding is low (10%), but important lesions may be found (62). Small bowel enteroscopy may gain wider acceptance for the evaluation of patients with obscure gastrointestinal bleeding (63).

FOOD ALLERGY

Food hypersensitivity or food allergy is perceived by the public as a major health problem. While it decreases in incidence with age, it may be as common as 1 to 3% in infants (64). The etiological mechanisms have not been completely defined, but the current hypothesis is that increased gastrointestinal absorption of intact antigen leads to systemic immunization, and subsequent immunological damage to the gastrointestinal tract develops when the same food is ingested again; it has been shown that there is increased absorption of newly introduced food antigens in infants.

A prospective study in infants with suspected food protein enterocolitis was performed. Those not responding to food challenge were assumed not to have an allergic mechanism and were used as controls. Serum ovalbumin and serum anti-ovalbumin antibody were measured in blood and urine after the ingestion of egg white. All infants studied absorbed some ovalbumin and there was no correlation between serum ovalbumin levels and age, and no significant difference between serum ovalbumin concentrations in infants who subsequently had positive oral food challenges and the matched group of negative responders. These data, therefore, do not support the hypothesis of antigen absorption as the major etiological factor in the development of food sensitivity. As well, because there was no correlation with age, the idea of intestinal 'closure' or antigen exclusion which develops as the gut matures (at least in rats) may not be operative (65).

The diagnosis of food hypersensitivity still depends upon double-blind food challenge. However, the quest for reliable diagnostic laboratory tests continues. Intradermal tests of aqueous material have not proved reliable and are only 10% accurate when positive. Newer laboratory tests for food allergy are expensive and highly sophisticated. The radioallergosorbent test (RAST) is capable of identifying only type I reactions. Patch tests have been used for over 10 years with data in 400 patients tested indicating it is a safe and sensitive procedure. After first identifying patients with possible food allergy (using elimination diet and food challenge), patch tests demonstrated a 74% sensitivity. Patch tests also detected all four types of allergic reactions to food antigens. The authors questioned whether the other 26% of patients not detected by this test were actually of immune etiology. Of the type I reactions, the patch test picked up only 36% of all those that RAST testing detected, indicating that RAST testing should be employed to identify immediate or type I food allergens and that the patch test should be used to detect types II, III and IV. The diagnostic accuracy of skin prick (SPT) and RAST tests proved comparable for peanuts, hazelnuts and peas, whereas the pin prick test proved more sensitive in confirming history with apples, oranges, tomatoes, carrots, cherries, celery and peaches (66).

A study was performed to clarify the immunopathogenesis, diagnosis and value of immunological testing in children with cow's milk allergy (67). Children reacting to a cow's milk challenge test were studied with serum levels of immunoglobulins G, A, M and E, complement fractions 3 and 4, class specific cow's milk antibodies, and different lymphocyte subsets. Responses of lymphocytes in whole blood to stimulation by phytohemaglutinin, concanavalin A and beta-lactoglobulin were also noted. No single laboratory method was sufficient to discriminate between the children who reacted

clinically to cow's milk and those who did not. The best combination of tests was the measurement of cow's milk-specific immunoglobin E and the index of lymphocyte stimulation with beta-lactoglobulin. This combination had a sensitivity of 80% and a specificity of 67% for predicting a clinical reaction. Thus, because of the heterogeneity of the immunopathogenesis of cow's milk allergy, no single laboratory method is valid for diagnosing cow's milk allergy.

The problems with in vitro analysis of food allergy are well documented (68-70). Since food challenge remains the only accepted method for diagnosis, a study was performed to evaluate the prevalence in children with atopic dermatitis of immediate and late reactions following challenge tests. The sensitivity, specificity and positive and negative predictive values of SPT and RAST in both immediate and late reactions and the prevalence of late reactions not preceded by immediate symptoms after challenge tests was also studied (71). The authors concluded six major points: immediate reactions following food challenge tests are frequent even in children who never experienced them previously; history usually is unreliable because reactions can occur despite a negative history; since immediate reactions can be severe, appropriate emergency equipment and personnel should be present during testing; SPT only rarely can predict severe reactions whereas RAST is useful in excluding them due to their high negative predictive value; sensitivity and specificity of RAST are low with regard to immediate and late reactions – the positive and negative predictive values are lower than those of SPT which easily and quickly are performed and have a lower cost; and the challenge test appears to be the only way to diagnose food allergy.

A novel approach has been developed for in vitro diagnosis of food allergy: studying antigen-induced histamine release from intestinal biopsy specimens (72). Duodenal mucosal biopsies were obtained during endoscopic examination and incubated with different foods. The authors concluded that the measurement of histamine release from biopsy specimens is a feasible technique and may be a reliable tool for gastrointestinal food allergy diagnosis.

Just as the diagnosis of food allergy is limited mainly to food challenge, treatment is limited mainly to avoidance of the allergen. A review article has been published on the pharmacotherapy of food allergy (73). Recently, ketotifen has been shown effective in patients sensitized to different foods and suffering from various cutaneous, nasal, conjunctival, respiratory and gastrointestinal disorders after food ingestion. Ketotifen is an oral tricyclic benzochloheptathiophene agent. Its principal pharmacological effect is to block the release of chemical mediators from human leukocytes, but it also has an antihistamine effect and some calcium antagonism. One of the novel modes of ketotifen action is the inhibition of eosinophil degranulation, as observed in patients with cow's milk allergy manifesting as bronchial asthma. Preliminary results obtained with this drug in patients with atopic dermatitis and food allergy problems have been reported (74). Thus, ketotifen administered in a dose of 1 mg twice daily over a long period may produce significant protection in patients with atopic dermatitis and food allergy symptoms. The drug was well-tolerated and did not register any side effects except for drowsiness in 10 to 15% of adult patients during the first week of use (the drowsiness subsequently resolved).

Sensitization to food protein and appearance of immunoglobulin E antibodies to food antigens occur early during infancy, even in infants exclusively fed breast milk. Mothers who had a diet free from eggs, cow's milk and fish during the first three months post partum were compared to mothers who consumed an ordinary diet. The diet of the infants was similar in both groups (that is, cow's milk was not supplied until six months of age and fish was not taken until nine months of age). The incidence of atopic dermatitis was significantly lower in the maternal special diet group during the first six months post partum (11 versus 28%, respectively); no difference was noted at later periods. Other allergic manifestations did not differ, and the number of positive SPTs to egg white, cow's milk or fish at age nine months was similar in both groups. The authors concluded that a maternal diet devoid of eggs, cow's milk and fish during the first three months of breast feeding decreased the severity of atopic dermatitis for the first six months of life in infants prone to atopy.

Rheumatic disease has been considered a food allergy manifestation for some patients. A study performed to assess the prevalence of food-related rheumatic symptoms and to identify clinical and serological features of these patients showed that probably not more than 5% of rheumatic disease patients have immunological sensitivity to foods. However, in patients with joint manifestations of food allergy identified by controlled challenge studies, arthritis seems to be seronegative, palindromic and nonerosive (75).

Finally, it is uncommon for peanut-sensitive patients to lose their clinical reactivity and, although there is some cross-reactivity between peanuts and other legumes such as soybeans and peas, none of these patients cross-reacted to nonlegume nuts (76).

DIAGNOSTIC TESTS

During a two-year period, 200 consecutive, unselected patients presenting with diarrhea had a three-day fecal collection. Forty-seven of the patients were screened to detect the ingestion of anthraquinones, bisacodyl, phenolphthalein and magnesium salts; seven patients had positive tests (77). The yield may appear to be low (about 15%), but tests for laxatives are inexpensive and are cost effective compared with extensive investigations for rare disorders. The use of a comprehensive and early laxative screening program thus may be recommended in patients with diarrhea of uncertain origin.

Near infrared analysis of fecal fat agrees closely with values obtained using the traditional titrimetric and gravimetric methods (78). The results may be obtained quickly from small quantities of unprocessed feces. Measurement of the fecal fat concentration does not permit distinction between

steatorrhea due to pancreatic disease or that produced by celiac disease or gastric resection, and this measurement, therefore, does not differentiate between pancreatic and intestinal steatorrhea (79).

INTESTINAL PERMEABILITY

The epithelial lining of the small intestine acts as a barrier restricting a variety of solutes from reaching the systemic circulation. The topic of intestinal barriers to bacteria and their toxins has been reviewed (80). The rapid resealing of the epithelial barrier after exposure to noxious luminal compounds is important as a primary defence mechanism. The epithelium of the small intestine undergoes 'restitution' after denudation of the villus tip by the structural formation of a continuous epithelial monolayer, and functionally by return of transepithelial resistance and solute flux towards normal. This restitution is aided by the energy-dependent neurally-mediated shortening of the villi which minimizes the denuded surface area to be re-epithelialized (81). Basement membrane components actively promote fetal intestinal epithelial cell differentiation (82), and the subepithelial network of myofibroblasts may be responsible for this process of villus contraction occurring after injury.

The greater susceptibility of the jejunum to acid-induced increases in permeability to EDTA may be due partly to its lower capacity to neutralize hydrochloric acid (83). Fasting maintains the increased intestinal permeability to lactulose and mannitol seen in children with acute gastroenteritis whereas early feeding may promote reduction of permeability and hasten recovery (84).

Intestinal permeability measured with ^{51}Cr-labelled EDTA is increased in patients with Crohn's disease but not in their healthy relatives (85), contrasting an earlier study using PEG 400. Increased intestinal permeability to an oral dose of EDTA (86) may reflect active Crohn's disease assessed with [^{111}In] leukocyte scanning and acute phase reactive proteins (86). PEG 400 is a hydrophilic molecular probe (not a lipophilic probe as was originally thought) which is useful to measure intestinal permeability (87). PEG 400 permeation in rats is mediated by passive diffusion and by solvent drag, suggesting that PEG 400 uses aqueous pathways for its permeation across intestinal epithelium (88). Endogenous or exogenous prostanoids may play a role in the regulation of PEG 400 permeation. The effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on PEG 400 permeation may be via changes in solvent drag (89). Intestinal permeability to PEG 400 is increased in patients with Crohn's disease, rheumatoid arthritis, celiac sprue and those taking NSAIDs. Children with acute rotavirus infection excrete less PEG of all sizes than do children with shigella, salmonella or enteropathogenic *Escherichia coli* infection, suggesting that a more severe mucosal lesion is caused by rotavirus (90). In children with severe malnutrition, PEG absorption is also impaired. Unfortunately, both the PEG permeability test and D-xylose test predict the presence of an abnormal small bowel biopsy in infants with severe diarrhea in only about two-thirds of patients. Although the two tests did not differ significantly in their ability to predict an abnormal small bowel biopsy, neither test is a reliable indicator of small intestinal mucosal damage (91).

Methotrexate (MTX) inhibits the de novo synthesis of purines and pyrimidines, leading to reduced DNA synthesis and increased cell death. MTX is used to treat acute lymphocyte leukemia in children and may decrease intestinal glucose-dependent sodium transport. MTX administration may also increase transmucosal passage of PEG, suggesting an increase in intestinal permeability (92). It would be of interest to determine if measurement of PEG permeability might be a useful clinical test of MTX damage to the intestine.

The urinary cellobiose:mannitol ratio also is increased in children with iron deficiency anemia, small intestinal Crohn's disease, and in patients with villus atrophy (93). Although urinary mannitol:lactulose excretion ratios show a high specificity and sensitivity for severe villous atrophy in children, the sensitivity declines rapidly with decreasing mucosal damage, indicating that this test would not be appropriate as a screening procedure for patients with mildly or moderately abnormal small intestinal mucosa (94).

Intestinal permeability in the rat to fluorescein isothiocyanate-dextran is enhanced after parenteral but not after enteral nutrition. Enhanced leakiness of the intestinal barrier may contribute to development of gut bacteria translocation and endotoxins, resulting in sepsis in patients receiving total parenteral nutrition (95). Permeation of the intestine to latex particles of different sizes occurred in M cells of Peyer's patches (96). The use of technetium-99m-diethylenetriamine tetraacetate is increased in patients with Crohn's disease and reflects the magnitude of the disease's activity index (97). Thus, there continues to be interest to develop an ideal permeability marker of intestinal function and dysfunction, a marker sensitive and specific for diseases such as celiac or Crohn's and which would be safe, economical and reliable to point out which patient with intestinal symptoms needs further investigation.

REFERENCES

1. Thomson ABR, Keelan M, Garg ML, Clandinin MT. Intestinal aspects of lipid absorption: In review. Can J Physiol Pharmacol 1989;67:179-91.
2. Garg ML, Thomson ABR, Clandinin MT. Effect of dietary fish oil on tissue lipid metabolism. In: Chandra RK, ed. Health Effects of Fish and Fish Oils. ARTS Biomedical Publishers, St John's, 1989:53-79.
3. Chiang S-H, Pettigrew JE, Clarke SD, Cornelius SG. Digestion and absorption of fish oil by neonatal piglets. J Nutr 1989;119:1741-3.
4. Chernenko GA, Barrowman JA, Kean KT, Herzberg GR, Keough KMW. Intestinal absorption and lymphatic transport of fish oil (MaxEPA) in the rat. Biochim Biophys Acta 1989;1004:95-102.
5. Ishida F, Sato A, Iizuka Y, Kitani K, Sawasaki Y, Kamei T. Effects of MK-733 (simvastatin), an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, on intestinal acylcoenzyme A:cholesterol acyltransferase activity in rabbits. Biochim Biophys Acta 1989;1004:117-23.

6. Lin MC, Weinberg SL, Kramer W, Burckhardt G, Wilson FA. Identification and comparison of bile acid-binding polypeptides in ileal basolateral membrane. J Memb Biol 1988;106:1-11.
7. Schiller LR, Bilhartz LE, Santa Ana CA, Fordtran JS. Comparison of endogenous and radiolabeled bile acid excretion in patients with idiopathic chronic diarrhea. Gastroenterology 1990;98:1036-43.
8. Nutting D, Hall J, Barrowman JA, Tso P. Further studies on the mechanism of inhibition of intestinal chylomicron transport by Pluronic L-81. Biochim Biophys Acta 1989;1004:357-62.
9. Jonas G, Erickson RA, Morgan T. Effect of portal hypertension on in vivo bile acid-mediated small intestinal mucosal injury in the rat. Dig Dis Sci 1990;35:743-8.
10. Kamath PS, Phillips SF, Zinsmeister AR. Short-chain fatty acids stimulate ileal motility in humans. Gastroenterology 1988;95:1496-502.
11. Mortensen PB, Hegnhoj J, Rannem T, Rasmussen HS, Holtug K. Short-chain fatty acids in bowel contents after intestinal surgery. Gastroenterology 1989;97:1090-6.
12. Watson AJM, Elliott EJ, Rolston DDK, Borodo MM, Farthing MJG, Fairclough PD. Acetate absorption in the normal and secreting rat jejunum. Gut 1990;31:170-4.
13. Weisiger RA, Pond SM, Bass L. Albumin enhances unidirectional fluxes of fatty acid across a lipid-water interface: Theory and experiments. Am J Physiol 1989;257:G904-16.
14. Higham SE, Read NW. Effect of ingestion of fat on ileostomy effluent. Gut 1990;31:435-8.
15. Chow BPC, Shaffer EA, Parsons HG. Absorption of triglycerides in the absence of lipase. Can J Physiol Pharmacol 1990;68:519-23.
16. Zillikens MC, Swart GR, van den Berg JWO, Wilson JHP. Effects of the glycosidase inhibitor acarbose in patients with liver cirrhosis. Aliment Pharmacol Therap 1989;3:453-9.
17. Robinson KM, Heineke EW, Begovic ME. Quantitative relationship between intestinal sucrase inhibition and reduction of the glycemic response to sucrose in rats. J Nutr 1990;120:105-11.
18. Kimmich GA. Membrane potentials and the mechanism of intestinal Na^+-dependent sugar transport. J Membrane Biol 1990;114:1-27.
19. Malo C. Separation of two distinct Na^+-D-glucose cotransport systems in the human fetal jejunum by means of their differential specificity for 3-0-methylglucose. Biochim Biophys Acta 1990;1022:8-16.
20. Harig JM, Soergel KH, Barry JA, Ramaswamy K. Brush border membrane vesicles formed from human duodenal biopsies exhibit Na^+-dependent concentrative L-leucine and D-glucose uptake. Biochem Biophys Res Commun 1988;156:164-70.
21. Harig JM, Barry JA, Rajendran VM, Soergel KH, Ramaswamy K. D-glucose and L-leucine transport by human intestinal brush border membrane vesicles. Am J Physiol 1989;256:G618-23.
22. Booth IW, Patel PB, Sule D, Brown GA, Buick R, Beyreiss K. Glucose-galactose malabsorption: Demonstration of specific jejunal brush border membrane defect. Gut 1988;29:1661-5.
23. Lifschitz CH, Boutton TW, Carrazza F, et al. A carbon-13 breath test to characterize glucose absorption and utilization in children. J Pediatr Gastroenterol Nutr 1988;7:842-7.
24. Phillips SF, Quigley EMM, Kumar D, Kamath PS. Motility of the ileocolonic junction. Gut 1988;29:390-406.
25. Goyal RK. Muscarinic receptor subtypes. Physiology and clinical implications. New Engl J Med 1989;321:1022-9.
26. Taché Y, Garrick T, Raybould H. Central nervous system action of peptides to influence gastrointestinal motor function. Gastroenterology 1990;98:517-28.
27. Holzer P. Ascending enteric reflex: Multiple neurotransmitter systems and interactions. 1989;256:G540-5.
28. Siegle M-L, Bühner, Schemann M, et al. Propagation velocities and frequencies of contractions along canine small intestine. Am J Physiol 1990;258:G738-44.
29. Fich A, Phillips SF, Hanson RB, Zinsmeister AR. Rapid frequency rhythmic postprandial motility in the canine ileum. Am J Physiol 1989;257:G766-72.
30. Burakoff R, Nastos E, Won S. Effects of $PGF_2\alpha$ and of indomethacin on rabbit small and large intestinal motility in vivo. Am J Physiol 1990;258:G231-7.
31. Davis RH, Mathias JR. Phorbol esters induce retrograde myoelectric activity in rabbit ileum in vivo. Am J Physiol 1989;257:G578-83.
32. Fone DR, Horowitz M, Read NW, et al. The effect of terminal ileal triglyceride infusion on gastroduodenal motility and the intragastric distribution of a solid meal. Gastroenterology 1990;98:568-75.
33. Welch I McL, Davison PA, Worlding J, Read NW. Effect of ileal infusion of lipid on jejunal motor pattems after a nutrient and nonnutrient meal. Am J Physiol 1988;256:G800-6.
34. Layer P, Peschel S, Schlesinger T, Goebell H. Human pancreatic secretion and intestinal motility: Effects of ileal nutrient perfusion. Am J Physiol 1990;258:G196-201.
35. Takeda T, Taniyama K, Baba S, Tanaka C. Putative mechanisms involved in excitatory and inhibitory effects of somatostatin on intestinal motility. Am J Physiol 1989;257:G532-8.
36. DePonti F, D'Angelo L, Frigo GM, Crema A. Inhibitory effects of calcium channel blockers on intestinal motility in the dog. Eur J Pharmacol 1989;168:133-44.
37. Thollander M, Hellström PM, Svensson TH. Suppression of small intestinal motility and morphine withdrawal diarrhoea by clonidine: Peripheral site of action. Acta Physiol Scand 1989;137:385-92.
38. Peeters T, Matthijs G, Depoortere I, et al. Erythromycin is a motilin receptor agonist. Am J Physiol 1989;257:G470-4.
39. Gill RC, Kellow JE, Browning C, Wingate DL. The use of intraluminal strain gauges for recording ambulant small bowel motility. Am J Physiol 1990;258:G610-5.
40. Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. Gastroenterology 1990;98:1208-18.
41. Kellow JE, Philips SF, Miller LJ, Zinsmeister AR. Dysmotility of the small intestine in irritable bowel syndrome. Gut 1988;29:1236-43.
42. Nanda R, James R, Smith H, et al. Food intolerance and the irritable bowel syndrome. Gut 1989;30:1099-104.
43. Scott RB, Diamant SC, Gall DG. Motility effects of intestinal anaphylaxis in the rat. Am J Physiol 1988;255:G505-11.
44. Piccione PR, Holt PR, Culpepper-Morgan JA, et al. Intestinal dysmotility syndromes in the elderly: Measurement of orocecal transit time. Am J Gastroenterol 1990;85:161-4.
45. Hirakawa M, Okada T, Iida M, et al. Small bowel transit time measured by hydrogen breath test in patients with anorexia nervosa. Dig Dis Sci 1990;35:733-6.
46. Churnratanakul SC, Wirzba B, Lam T, Walker K, Fedorak R, Thomson ABR. Radiation and the small intestine: Future perspectives for preventive therapy. Dig Dis 1990;8:45-60.

47. Otterson MF, Sarna SK, Moulder JE. Effects of fractioned doses of ionizing radiation on small intestinal motor activity. Gastroenterology 1988;95:1249-57.
48. Grant D. Intestinal transplantation: Current status. Transplant Proc 1989;21:2869-71.
49. Watson AJM, Lear PA. Current status of intestinal transplantation. Gut 1989;30:1771-82.
50. Diflo T, Shaffer D, Maki T, Monaco AP. The effects of antilymphocyte serum and cyclosporine on orthotopic small bowel allografts in the rat. Transplant Proc 1988;XX (Suppl 1):200-2.
51. Grant D, Duff J, Zhong R, Mimeault R, Inch R, Stiller S. Effect of ex vivo allograft irradiation combined with cyclosporine therapy in a pig intestinal transplant model. Transplant Proc 1989;21:2879-80.
52. Saat RE, de Bruin RWF, Heineman E, Marquet RL, Jeekel J. Orthotopic small bowel transplantation in rats: Pretreatment of the donor with the aim of ameliorating graft-versus-host disease. Transplant Proc 1989;21:2892-3.
53. Lear PA, Cunningham AJ, Crane PW, Wood RFM. Lymphocyte migration patterns in small bowel transplants. Transplant Proc 1989;21:2881-2.
54. Teitelbaum DE, O'Dorisio TM, Qualman SJ, Sonnino RE, Dunaway DJ, Harmel RP Jr. Alteration in gastrointestinal peptide tissue levels in rejecting small bowel transplants. J Pediatr Surg 1989;24:629-33.
55. Teitelbaum DH, Dunaway DJ, Sonnino RE, Stellin G, Berend ME, Harmel RP Jr. Leakage of intraluminal low molecular weight polyethylene glycol as a marker of small bowel transplant rejection. J Pediatr Surg 1989;24:64-9.
56. Grant D, Wall W, Mimeault R, et al. Successful small bowel/liver transplantation. Lancet 1990;335:181-84.
57. Starzl TE, Todo S, Tzakis A, et al. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 1989;210:374-86.
58. Starzl TE, Rowe MI, Todo S, et al. Transplantation of multiple abdominal viscera. JAMA 1989;1261:1449-57.
59. Williams JW, Sankary HN, Foster PF, Lowe J, Goldman GM. Splanchnic transplantation. An approach to the infant dependent on parenteral nutrition who develops irreversible liver disease. JAMA 1989;261:1458-62.
60. Mueller PR, van Sonnenberg E. Interventional radiology in the chest and abdomen. New Engl J Med 1990;322:1364-74.
61. Dehn TCB, Nolan DJ. Enteroclysis in the diagnosis of intestinal obstruction in the early postoperative period. Gastrointest Radiol 1989;14:15-21.
62. Rex DK, Lappas JC, Maglinte DDT, et al. Enteroclysis in the evaluation of suspected small intestinal bleeding. Gastroenterology 1989;97:58-60.
63. Lewis BS, Waye JD. Small bowel enteroscopy in 1988; pros and cons. Am J Gastroenterol 1988;83:799-802.
64. Schreiber RA, Walker WA. Food allergy: Facts and fiction. Mayo Clin Proc 1989;64:1381-91.
65. Powell GK, McDonald PJ, van Sickle GJ, Goldblum RM. Absorption of food protein antigen in infants with food protein-induced enterocolitis. Dig Dis Sci 1989;34:781-8.
66. Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. J Allergy Clin Immunol 1989;83:683-90.
67. Tainio V-M, Savilahti E. Value of immunologic tests in cow milk allergy. Allergy 1990;45:189-96.
68. Pearson DJ. Clinical diagnosis in food allergy. Clin Exper Allergy 1989;19:83-5.
69. Trevino RJ, Rapoport AS. Problems with in-vitro diagnosis of food allergy. Ear Nose Throat J 1990;69:42-6.
70. Pastorello E, Stocchi L, Bigi A, et al. Value and limits of diagnostic tests in food hypersensitivity. Allergy 1989;44:151-8.
71. Meglio P, Giampietro PG, Farinella F, Cantani A, Businco L. Personal experience in the diagnostic procedures in children with atopic dermatitis and food allergy. Allergy 1989;44:165-73.
72. Baenkler HW, Lux G. Antigen-induced histamine release from duodenal biopsy in gastrointestinal food allergy. Ann Allergy 1989;62:449-52.
73. Podleski WK. Pharmacotherapy of food allergy – a neglected option. Int J Immunopharmacol 1989;11:311-26.
74. Molkhous P, Dupont C. Ketotifen treatment of atopic dermatitis and other food allergy diseases. Allergy 1989;44:117-23.
75. Panush RS. Food induced ('allergic') arthritis: Clinical and serologic studies. J Rheumatol 1990;17:291-4.
76. Bock SA, Atkins FM. The natural history of peanut allergy. J Allergy Clin Immunol 1989;83:900-4.
77. Bytzer P, Stokholm M, Andersen I, Klitgaard NA, Schaffalitzky OB, Muckadell DE. Prevalence of surreptitious laxative abuse in patients with diarrhoea of uncertain origin: A cost benefit analysis of a screening procedure. Gut 1989;30:1379-84.
78. Benini L, Caliari S, Guidi GC, et al. Near infrared spectrometry for faecal fat measurement: Comparison with conventional gravimetric and titrimetric methods. Gut 1989;30:1344-7.
79. Bai JC, Andrush A, Matelo G, et al. Fecal fat concentration in the differential diagnosis of steatorrhea. Am J Gastroenterol 1989;84:27.
80. Walker RI, Owen RL. Intestinal barriers to bacteria and their toxins. Annu Rev Med 1990;41:393-400.
81. Moore R, Carlson S, Madara JL. Villus contraction aids repair of intestinal epithelium after injury. Am J Physiol 1989;257:G274-83.
82. Hahn U, Stallmach A, Hahn EG, Riecken EO. Basement membrane components are potent promoters of rat intestinal epithelial cell differentiation in vitro. Gastroenterology 1990;98:322-35.
83. Nylander O, Kvietys P, Granger DN. Effects of hydrochloric acid on duodenal and jejunal mucosal permeability in the rat. Am J Physiol 1989;257:G653-60.
84. Isolauri E, Juntunen M, Wiren S, et al. Intestinal permeability changes in acute gastroenteritis: Effects of clinical factors and nutritional management. J Pediatr Gastroenterol Nutr 1989;8:466-73.
85. Ainsworth M, Eriksen J, Rasmussen JW, Schaffalitzky OB, Muckadell DE. Intestinal permeability of ^{51}Cr-labelled ethylenediaminetetraacetic acid in patients with Crohn's disease and their healthy relatives. Scand J Gastroenterol 1989;24:993-8.
86. Pironi L, Miglioli M, Ruggeri E, et al. Relationship between intestinal permeability to (^{51}Cr)EDTA and inflammatory activity in asymptomatic patients with Crohn's disease. Dig Dis Sci 1990;35:582-8.
87. Ma TY, Hollander D, Krugliak P, Katz K. PEG 400, a hydrophilic molecular probe for measuring intestinal permeability. Gastroenterology 1990;98:39-46.
88. Krugliak P, Hollander D, Ma TY, et al. Mechanisms of polyethylene glycol 400 permeability of perfused rat intestine. Gastroenterology 1989;97:1164-70.
89. Krugliak P, Hollander D, Le K, et al. Regulation of polyethylene glycol 400 intestinal permeability by endogenous and exogenous prostanoids. Influence

of non-steroidal anti-inflammatory drugs. Gut 1990;31:417-21.
90. Johansen K, Stintzing G, Magnusson KE, et al. Intestinal permeability assessed with polyethylene glycols in children with diarrhea due to rotavirus and common bacterial pathogens in a developing community. J Pediatric Gastroenterol Nutr 1989;9:307-13.
91. Lifschitz CH, Shulman RJ, Langston C, Gopalakrishna GS. Comparison of the D-xylose and polyethylene glycol absorption tests as indicators of mucosal damage in infants with chronic diarrhea. J Pediatric Gastroenterol Nutr 1989;8:47-50.
92. Lifschitz CH, Mahoney DH. Low-dose methotrexate-induced changes in intestinal permeability determined by polyethylene glycol polymers. J Pediatric Gastroenterol Nutr 1989;9:301-6.
93. Hodges S, Ashmore SP, Patel HR, Tanner MS. Cellobiose: Mannitol differential permeability in small bowel disease. Arch Dis Childhood 1989;64:853-74.
94. Nathavitharana KA, Lloyd DR, Raafat F, et al. Urinary mannitol: Lactulose excretion ratios and jejunal mucosal structure. Arch Dis Child 1988;63:1054-9.
95. Purandare S, Offenbartl K, Weström B, Bengmark S. Increased gut permeability to fluorescein isothiocyanate-dextran after total parenteral nutrition in the rat. Scand J Gastroenterol 1989;24:678-82.
96. Sass W, Dreyer H-P, Seifert J. Rapid insorption of small particles in the gut. Am J Gastroenterol 1990;85:255-60.
97. Resnick RH, Royal H, Marshall W, et al. Intestinal permeability in gastrointestinal disorders. Use of oral [^{99m}Tc] DTPA. Dig Dis Sci 1990;35:205-11.