Special Article

The Pathological Physiology of Small Intestine*

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It seems that the investigations, both basic and clinical, are underdeveloped in the field of small intestine, while the investigations in the field of stomach and liver have markedly developed. The author reported "mucosal metabolism and the clinical significance of digestive tract" as a special lecture at the 41st annual meeting of Japanese Society of Gastroenterology in 1955, and emphasized that the important role of small intestine is like that of liver. Since then, 18 years have passed. At the moment, I would like to speak about "the pathological physiology of the small intestine" at the 70th annual meeting of Japanese Society of Internal Medicine.

I. The Mechanisms of Digestion and Intestinal Absorption of Nutrients

The mechanisms of the digestion and absorption of lipids

The mechanisms of the digestion and absorption of lipids consist of the emulsion formation in the stomach, lipolysis, micelle formation, the passage across luminal surface, intramucosal triglyceride and phospholipid resynthesis, chylomicron formation as well as lymphatic transport in the form of the chylomicron which is the special form lipoprotein with very low density. In the process of the digestion and absorption of long chain triglycerides, intramucosal lipid resynthesis is considered to be the rate limiting step.

The mechanism of gastric emptying

From *in vivo* experiments with rats, a receptor seems to exist in the duodenal mucosa, to which fatty acid is more stimulative. In *in vitro* experiments, the mucosal uptake of fatty acid and monoglyceride from the micellar solution is made not by unit uptake but by simple diffusion of both lipids separately. It revealed that fatty acid was more rapidly absorbed than monoglyceride.

Chylomicron formation

Chylomicron formation was studied with rat everted sac method. It based upon the β -lipoprotein synthesis which was formed from resynthesized triglyceride and

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phospholipid together with newly synthesized protein. It was recognized that when larger amount of lipid existed such as fat intake, the chylomicron formation occurred.

The mechanism of digestion and absorption of medium chain triglyceride (MCT)

There was no difference between long chain triglyceride (LCT) and MCT in the *in vitro* lipolysis. However, MCT was more rapidly absorbed than LCT in the *in vivo* rat experiments. It was caused by the fact that the reesterification which is rate limiting step in the process of LCT absorption, is not necessary in the process of MCT absorption. Furthermore, it was also caused by the fact that transport by blood stream which is one hundred times faster than lymph stream was rate limiting step in the process of MCT absorption. A part from ^{14}C -labeled MCT appeared in thoracic duct lymph after intraluminal administration. The substances derived from MCT in the lymph was analysed and identified with LCT, in which medium chain fatty acid (MCFA) was incorporated at α -position. Therefore, it was verified that there were two pathways of postabsorptive intramucosal metabolism of MCT; the major pathway by which MCFA was transported via portal blood, and the minor pathway by which LC-MC-triglyceride was transported via lymph.

The mechanism of thiamine absorption

A discrepancy after intraluminal thiamine administration was noticed between disappearance from lumen and appearance in the blood. This was caused because the intestinal wall released thiamine very slowly for 6 hours after the administration.

The influence of aging upon digestion and absorption function

Clinically there was no influence of aging in the results of the fat digestion-absorption test up to 80ies of age. In the everted sac experiment obtained from aged rats, a retardation of LCT absorption was observed. This was caused by retardation of intramucosal resynthesis. This retardation was recovered by corticosteroid. MCT was not influenced by aging in the same experimental condition.

II. Present Status of the Diseases of the Small Intestine

A) Classification of the diseases of the small intestine

The diffuse changes of small intestine showing malabsorptive state were comprised in malabsorption syndrome. A new classification of malabsorption syndrome was proposed.

B) Statistics of the diseases of the small intestine

The cases having the diseases of the small intestine which appeared in Annual of the Pathological Autopsy Cases in Japan for 13 years from 1958 to 1970, were studied. There were 18,183 cases (8.17%) of the diseases of the small intestine among 222,293 cases autopsied for 13 years. In order of frequency, metastatic carcinoma, ulcer, enteritis, metastatic sarcoma, ileus, diverticulum etc. were found. Primary carcinoma was 3.4%, and primary sarcoma was 1.2%. When classified by localization, diffuse lesion was 41%, duodenum 37%, ileum 10%, ileocaecal region

4.7%, jejunum 4.6%. The frequency of the type of these diseases in every region was shown in Fig. 1. There was no definite change in the total number of carcinoma and sarcoma for 13 years. Tuberculosis of the small intestine showed a marked decrease in the middle-aged and a relative increase in the aged.

Fig. 1. The frequency (%) of various types of the disease of the small intestine, in every region.

III. Recent Advances in the Diagnosis of the Diseases of the Small Intestine

A) Digestion-absorption test

The fecal excretion method of radioisotopic (RI) digestion-absorption test is equal to RI labeled balance study. The advantages of RI digestion-absorption test are time-saving and no need of special facilities such as metabolic ward. Therefore, digestion-absorption test is most adequate for diagnosing the grade of digestion-absorption disturbance. Usually, ^{131}I -triolein digestion-absorption test is employed most often, because the disturbance of fat digestion-absorption is found most often and severe. The test meal, the procedure, and the calculation formula are shown in Table 1. The normal range was settled as follows: normal range, below 2.0%; border range, 2.1-4.0%; abnormal, over 4.1%. Reconfirmation by the percentages of false diagnosis, revealed that this settlement was right, when 1.0 ml/kg body weight of cold meal was administered.

Table 1. Test Meal and Procedure of ^{131}I -Triolein Test

Test meal

cold meal	peanut oil	200 ml	1.0 ml/kg body weight
	water	200 ml	
	tween 80	15 ml	
hot meal	^{131}I -triolein 25-50 μCi		

Procedure

Pretreatment: thyroid blockade with iodine soln. for 3 days

Administration of test meal on the 3rd day

Collection of feces for 3 days (at least 3 times when constipated) after the administration

$$\text{Fecal Excretion Ratio} = \frac{\text{Radioactivity of 3 days feces}}{\text{Radioactivity of the test meal}} \times 100 (\%)$$

A good correlation was found between fecal excretion ratio of labeled fat and fecal fat amount chemically determined, while there was no correlation between blood RI level and fecal fat amount. There was not very good correlation between fecal excretion ratio of labeled fat and blood RI level. This concludes that the blood RI level is less reliable than fecal excretion ratio.

The amount of RI is enough at a detectable minimum. Because RI labeled digestion-absorption test itself is a type of tracer experiment, the cold meal should be chemically the same as the RI nutrient. The dosage of the cold meal should be around the upper limit (0.5 ml of peanut oil/kg b. wt.) of the physiological range of the food intake. In the author's method, an aliquot of emulsion, consisting of 0.5 ml/kg b. wt. of peanut oil, the same amount of water and a little of emulsifying agents, was employed. The digestion-absorption disturbances were well evaluated in various types of secondary malabsorption syndrome, when 1.0 ml/kg b. wt. of cold meal was administered.

A combination of ^{131}I -triolein fat digestion-absorption test and ^{131}I -oleic acid absorption test seemed to be useful for differentiating maldigestion and malabsorption, but recent advances in the knowledge of the mechanism of lipid digestion-absorption revealed inadequacy of this method. A combination of ^{131}I -triolein test and the repeated ^{131}I -triolein test with sufficient amount of digestive enzyme preparation gives the pancreatic lipase activity. Basic experiment of ^{131}I -triolein test and ^{131}I -oleic acid test was done in rat experiments. Since there was a criticism that the diagnosis of malabsorption syndrome should not be made by the results of the digestion-absorption test of a single nutrient, ^{131}I -RISA test for protein digestion-absorption function was performed as the second test for malabsorptive state. The normal range was settled likely as ^{131}I -triolein test. Basic experiment of ^{131}I -RISA test was done in rat experiments. The combination of ^{131}I -triolein test and ^{131}I -RISA test gives more accurate diagnosis, but it will take more than two weeks to perform both tests successively. The author originated the simultaneous fat and protein

digestion-absorption test using ^{131}I -triolein and ^{125}I -RISA as the hot meal and loading peanut oil-gelatin mixture as the cold meal.

Advantages of simultaneous fat and protein digestion-absorption test are: 1) it is time-saving; digestion-absorption functions of both fat and protein can be determined by a single test. 2) emulsifying agent (tween 80) is unnecessary. 3) the cold meal is quite similar to the normal meal, in terms of the composition and volume. The simultaneous digestion-absorption tests were performed in malabsorption syndrome. In most cases, fat digestion-absorption was affected more often and more severely than protein. But in some cases, protein was more markedly affected than fat. Basic experiments of the simultaneous digestion-absorption test was done in rat experiments, using pancreatic duct ligated, bile duct ligated and both pancreatic and bile duct ligated rats.

D-xylose absorption test is useful for evaluating absorption function without influence of digestion. D-xylose absorption test mostly remained normal, even in the cases of digestion-absorption disturbance of fat. It becomes abnormal in the types of reduced absorptive surface.

B) Biopsy of small intestinal mucosa

Two types of biopsy apparatus: Tohoku University type originating from Crosby and Nippon University type originating from Shiner were manufactured so far in Japan. The number of mucosal pieces biopsied was limited to 1-2 by those apparatuses. The author has been using multi-retrieving hydraulic biopsy apparatus of University of Michigan, which has been employed for the multipurpose small intestinal mucosal biopsy; such as routine histology, histochemistry, enzyme-histochemistry, scanning electron microscopy, electron microscopy, fluorescent antibody study as well as mucosal lipid analysis. The form of the normal small intestinal villi was seen as finger-like shaped under light-microscope but it was observed as leaf-, tongue-, or roof-shaped under scanning electron microscope. With the aid of the multi-retrieving biopsy capsule, the mucosal specimen may be obtained from the saline stream circulating within the capsule, so that it may instantly undergo the fixing for electron microscopic observation. Cut section of microvilli showed filamentous or microtubular core in its central part. Outside of microvilli was covered with fuzzy coat. In the crypt, there observed the goblet cells which secreted mucus by apocrine type. Goblet cell does not only package mucus but the synthesis of mucus is also taken place there. A typical endocrine cell containing fine, dense granules was observed in the part next to basal lamina. The endocrine cells of small intestine are classified in type I to V according to Forsmann.

C) Fluoroscopic examination of the small intestine

For the fluoroscopic examination of small intestine, various techniques such as fractional administration of barium meals, barium administration through intestinal tube and fractional filling of intestinal loop, have been devised. A localized lesion of the small intestine can be clearly expressed by the double contrast technique. However, adequate technique for the fluoroscopic examination of malabsorption

syndrome, which is mainly functional changes, is the sequential observation of gastrointestinal tract after single dose administration of barium meal. In the diseases of malabsorption syndrome, besides the inflammatory changes and the mechanical, morphological changes particularly to each disease, a common figure i.e. sprue pattern was observed. Almost every patient with sprue exhibits in varying degrees the small intestinal changes of dilatation, segmentation, fragmentation, scattering of the barium column, and hypersecretion. Dilatation of the lumen of the small intestine is one of the most important and constant findings in sprue.

D) The endoscopic examination of the small intestine

In 1965, the authors have investigated transmural endoscopic technique for the diagnosis of small intestine. As non surgical per oral fiberscopy, push type, rope-way type and sound type have been devised so far. The small intestinal fiberscopes, either per oral or per anal, have been employed, but experiences to be reached to the distal jejunum, were not so many. A case of leiomyoma of ileum was confirmed with the aid of small intestinal fiberscopy. There will be two possibilities in the future of small intestinal endoscopy; to develop the endoscopy with biopsy and to develop the fiberscope by which entire small intestine can be easily observed.

IV. Immunological Aspects for the Mechanism of Establishment of Intestinal Disorders

Agammaglobulinemia had been known as one of the causes of secondary malabsorption syndrome, but the mechanism by which malabsorptive state occurred remained unknown.

In a case of secondary malabsorption syndrome with the chief complaint of unendurable heavy diarrhea lasting over 5 years, the decrease in serum IgA level and the decrease in the IgA production and the amount of secretory IgA and secretory IgE in the biopsied jejunal mucosa were observed attractively using fluorescent antibody technique. Moving trophozoites of giardia lamblia and cysts of isospora belli were found in watery stool as well as in duodenal juice. Both protozoas were also found in the biopsied jejunal mucosa. Quinacrine administration was effective for giardia and sulfisomezole was tentatively effective for isospora, which was the main cause of the watery stool in the view point of the therapeutic effect. Isospora disappeared completely by the administration of piromidic acid, with the improvement of the symptoms and the normalization of serum IgA level. Lymphocytosis with atypical binucleated lymphocyte found in the patient's peripheral blood was also diminished after the treatment.

The relationship among low level of serum IgA, decrease in IgA production, secretory IgA and secretory IgE, concomitant infestation of isospora and giardia, and the establishment of secondary malabsorption syndrome was considered and showed schematically in Fig. 2.

In general, abnormal local immunity in the mucosa of the small intestine would

Fig. 2. Immunological aspects for the mechanism of establishment of intestinal disorders.

play a role in the establishment of intestinal disorders, repeating such a vicious circle.