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THE ASSESSMENT OF ISOTOPIC EXAMINATIONS FOR GASTROINTESTINAL PHYSIOLOGY AND METABOLISM

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Introduction

Our nation wide survey revealed approximately one fourth of in vivo nuclear medicine procedures performed in Japan is liver scintigraphy. However, there apparently is a trend that the liver scintigraphy is decreasing since the introduction of numbers of new modalities such as CT and US.

It is predictable that the nature and characteristics of tracer kinetics will be further emphasized in clinical nuclear medicine. The isotopic examinations for the assessment of gastrointestinal physiology and metabolism as listed in table 1 should become prevalent in near future, though these examinations have not been widely adopted in routine nuclear medicine practice in Japan. With that perception we have recently started the assessment of varieties of imaging procedures for the evaluation of gastro-intestinal function.

In the first part of my presentation I will quickly review some of those examinations introducing preliminary experience of ours and others.

In the second part I would like to emphasize the usefulness of breath tests using isotopes of carbon based on our more than 15 years experience.

Detection of Meckel's diverticulum

Detection of Meckel's diverticulum using ^{99m}Tc-pertechnatate can be regarded as a classical examination of the physiology of the gastric mucosa that excretes pertechnatate.

In normal subjects the stomach is started to be visualized within 10 min. after i.v. injection of ^{99m}Tc-pertechnatate (Fig. 1). No radioactivity is seen in the intestine in the early phase.

If ectopic mucosa is present in the Meckel's diverticulum, the diverticulum is clearly visualized (Fig. 2). The test is useful for the evaluation of patients with melena.

Esophageal and gastric transit

Gastric emptying have been studied using both solid and liquid foods labeled with a gamma emitting radionuclide.

The selection of an appropriate solid tracer is a souce of controversy. Malmud and Fisher

claims that chicken liver labeled with ^{99m}Tc-sulfar colloids while the animal is alive is the best solid tracer for this purpose.

We have been using ^{111}In DTPA disolved in water as a liquid tracer and ^{99m}Tc-pertechnatate injected into a "calorimate", mixed nutrient with known calories in the shape of biscuette as solid food.

The solid tracer remains longer in the stomach than the liquid tracer in a control subject (Fig. 3).

The quantitative analysis also revealed delayed clearance of the solid tracer from the stomach. This examination has been reported useful for the detection of pathologic conditions with delayed

Table 1. Isotopic Examinations for Assessment of Gastrointestinal Physiology and Metabolism

I. Imaging Procedures

1. Esophageal scintigraphy for measurement of esophageal transit.
2. Gastroesophageal scintigraphy for detection of gastroesophageal reflux.
3. Hepatobiliary scintigraphy for detection of bile reflux.
4. Gastric scintigraphy for measurement of gastric emptying.
5. Gastric mucosal scintigraphy for detection of Meckel's diverticulum.
6. Blood pool scan and radionuclide angiography for detection of G-I bleeding.
7. Tl-myocardial imaging for detection of porto-caval shunt.

II. Non-imaging in vivo procedures

1. Fat absorption test using ^{131}I-triorein and oreic acid.
2. Schilling test for pernicious anemia and malabsorption.
3. Gordon test for protein losing gastroenteropathy.
4. ^{14}C and ^{13}C breath tests.

III. In Vitro Tests

1. RIA of gastrointestinal hormones.
2. Radioassays of tumor markers.
3. RIA of Vit B_{12} and folic acid, trypsin and pancreatic secreting trypsin inhibitor (PSTI), etc.

Fig. 1. Anterior images of the abdomen in a normal subject after intravenous administration of ^{99m}Tc-pertechnetate.

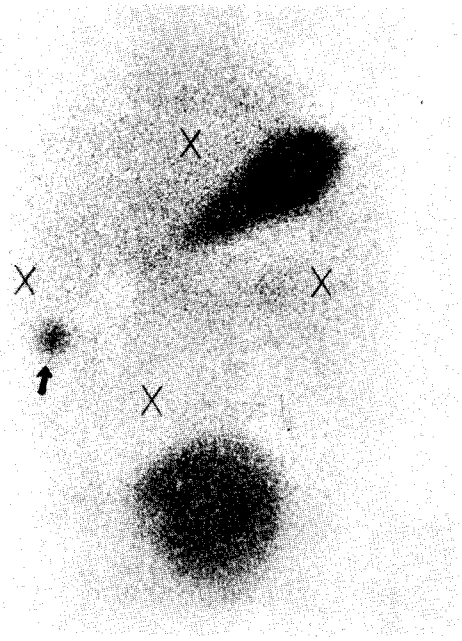


Fig. 2. A gastric mucosal scintigraphy visualizing Meckel's diverticulum with remnant gastric mucosa (arrow) in a child with melena.

Table 2. Breath Tests for Enterohepatic Diseases

Compounds used	Disease Conditons
^{14}C-trioctanoin	Steatorrhea
^{13}C-trioctanoin	
^{14}C-xylose	Malabsorption syndrome
^{14}C-tripalmitate	Fat malabsorption
^{14}C-lactose	Lactose intolerance
^{14}C-glucose	Protein-losing enteropathy
^{14}C-glycine-cholate	Bacterial overgrowth and
^{13}C-glycine-cholate	ileal dysfunction,
	Crohn's disease,
	Cystic fibrosis
^{14}C-manitol	Blind loop syndrome
^{14}C-aminopyrine	Liver diseases
^{13}C-aminopyrine	
^{14}C-galactose	Alcoholic Cirrhosis
^{13}C-galactose	
^{14}C-diazepam	Liver damage
^{14}C-methionine	Liver cirrhosis
^{14}C-valine	Liver cirrhosis
^{14}C-tryptophan	Liver cirrhosis

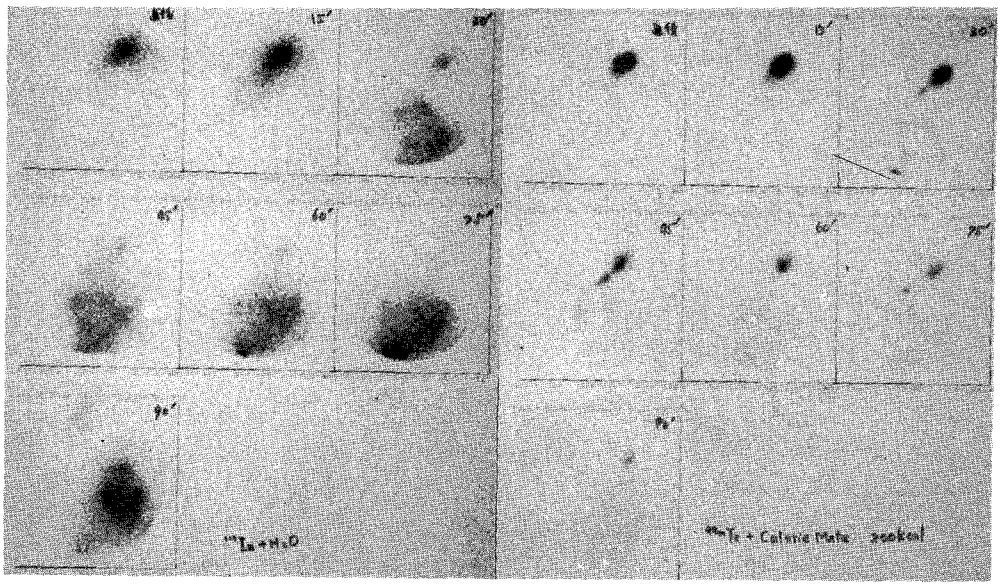


Fig. 3. Gastric Scintigraphies for measurement of gastric emptying in a normal control
a) gastric transit of a liquid food after oral administration of ^{111}In-DTPA with water.
b) gastric transit of simultaneously administered solid food, ^{99m}Tc-pertechnatate in "calorimate".

or accelerated gastric emptying. We have been using the method to compare with patterns of blood glucose in patients with diabetes and Graves' disease.

The detection of gastro-esophageal reflux is important to determine the etiology of symptoms such as heartburn, pyrosis and regurgitation. Malmud and Fisher reported gastroesophageal scintigraphy, as the first test that permits the non-invasive detection of reflux with a high degree of sensitivity and quantitative ability.

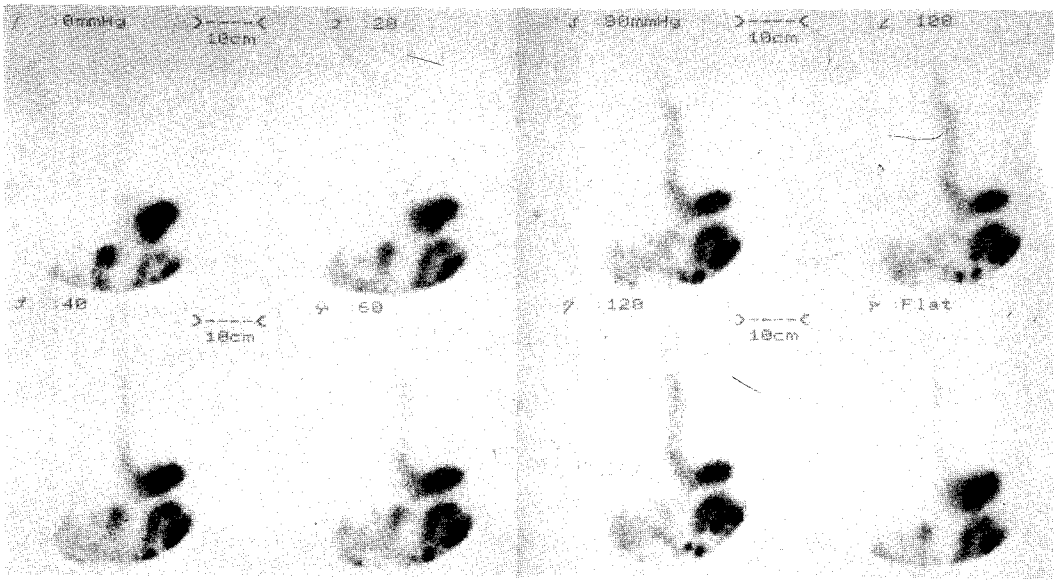


Fig. 4. Gastroesophageal scintigraphy demonstrating gastroesophageal reflux in a patient with heart burn and pyrosis (s.s. 56 y.o.m.)

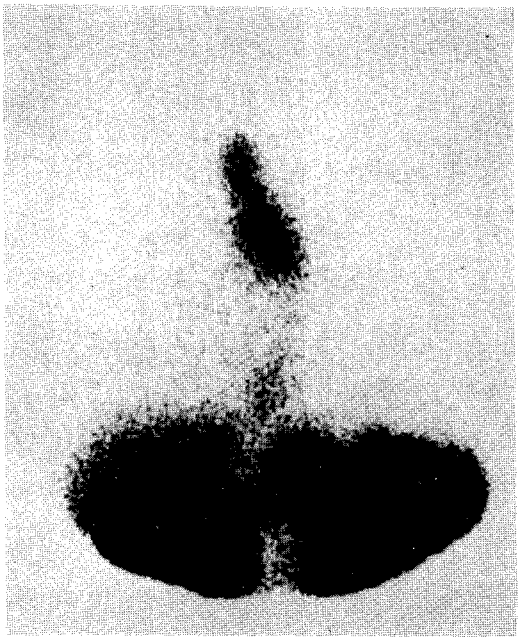


Fig. 5. Demonstration of bile reflux by hepatobiliary scintigraphy using ^{99m}Tc-diethyl IDA.

In this symptomatic patient evidence of esophageal reflux was demonstrated after the stepwise increase of abdominal pressure up to 120mmHg (Fig. 4). The quantitative analysis showed a elevated esophageal curve that indicates gastroesophageal reflux.

Esophagitis due to bile reflux can be diagnosed by hepatobiliary scintigraphy. Regurgitation of radioactivity up to the esophagus is clearly seen at 90 min. after i.v. injection of ^{99m}Tc-diethyl IDA in this patient (Fig. 5).

Detection of porto-caval shunt

The early detection of the presence of porto-caval shunt is requested in patients with hapatosplenic diseases. Several isotopic methods have been reported. Use of ^{201}Tl for this purpose was reported by Tonami of Kanazawa University.

In control subjects most radioactivity is demonstrated in the liver after infusion of ^{201}TlCl into the rectum. Radioactivity in the left ventricle remains very low with small myocardium/liver count ratio (Fig. 6).

The left ventricular myocardium is clearly seen when portocaval shunt is present. The count rates on the region of the heart is almost identical with that on the liver in this case (Fig. 7).

Ikegami of Kanto Teishin Hospital demonstrated the markedly increased myocardium/liver ratio in patients with liver cirrhosis and hepatocellular carcinoma. He further correlated the M/L ratio with the presence of hepatic encephalopathy. Among 19 patients with M/L ratio over 80, 14 had encephalopathy. Whereas in 18 patients with M/L ratio less than 80, 14 did not have encephalopathy.

Fat absorption test

Among non-imaging procedures fat absorption tests using ^{131}I-triorein and oreic acid have been widely used. These tests require collection of the stool and measurement of radioactivity in it. Which are not comfortable for both patients and examiners. In addition these tracers are no more available in the market.

Carbon dioxide in expired air on the other hand is a readily available and product of body metabolism that may be repeatedly sampled from patients with ease and comfort. The labelling of organic compounds with isotopes of carbon provides convenient tracers to be oxidized and excreted into the breath as labeled carbon dioxide.

For example, when ^{14}C-tripalmitate is given orally, $^{14}CO_2$ excretion in the breath increases to reach a peak at 3 to 4 hours followed by gradual decline in normal subjects.

In contrast in patients with malabsorption syndrome and steatorrhea excretion of $^{14}CO_2$ is very small and flat $^{14}CO_2$ curves are observed. The study was performed by Kaihara and Wagner.

Breath tests with isotopes of carbon

In 1966, Abt and von Schuching reported a simple breath collecting apparatus which allowed trapping of a mixed amount of respired carbon dioxide in alkaline.

The radioactivity of $^{14}CO_2$ was measured in a liquid scintillation counter to be expressed as specific activity. This apparatus symbolized the "extremely simple breath tests" which have been

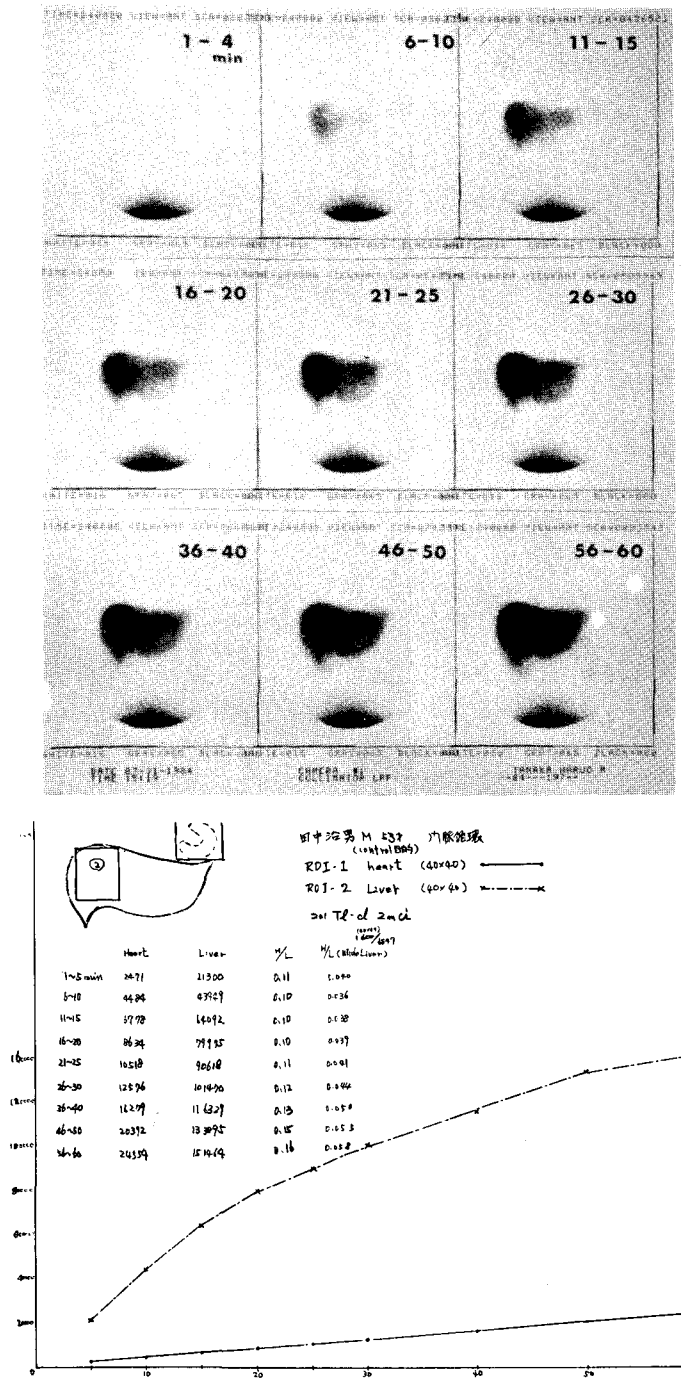
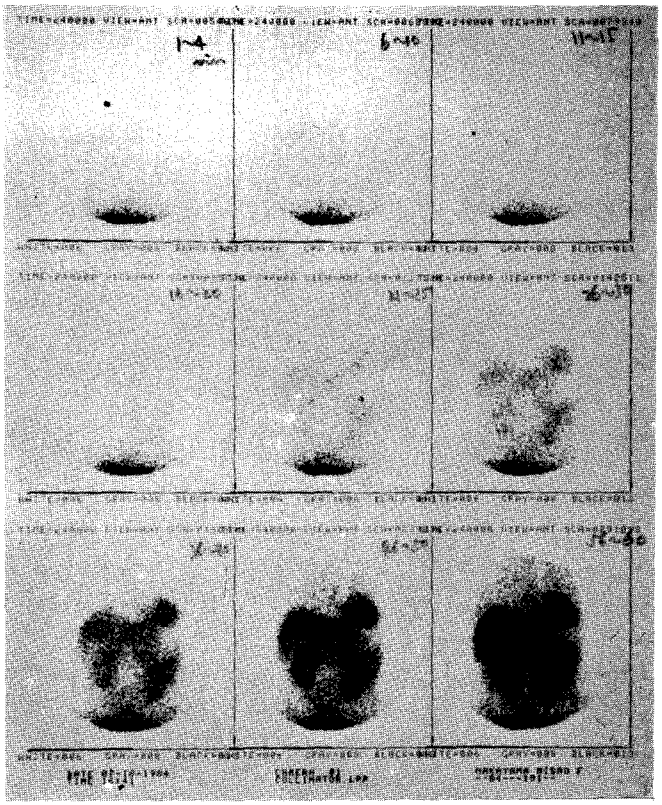


Fig. 6. Serial chest-abdominal images after infusion of ^{201}TlCl into the rectum in a patient without portocaval shunt. Little radioactivity is seen in the left ventricular myocardium.



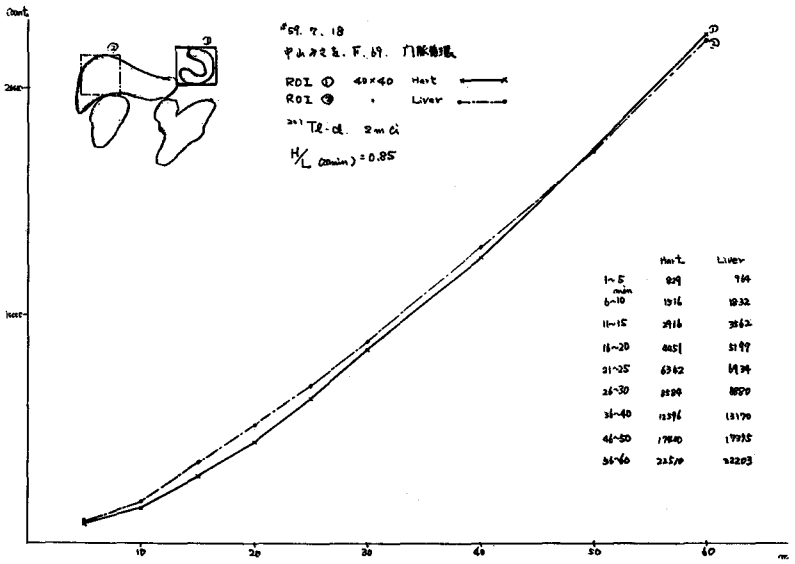


Fig. 7. Demonstration of portocaval shunt by the visualization of the left ventricular myocardium after intrarectal infusion of ^{201}TlCl.

developed during the next 15 years as convenient diagnostic means for the examination of varieties of disease conditions such as malabsorption syndromes, metabolic disorder of the liver, etc. (Table 2).

The breath test can be classified into two types on the basis of origin of enzymes which acts on the target bond of labelled compounds, namely organolytic and xenolytic breath tests.

An example of the former is lactose breath test for the diagnosis of lactase deficiency, which was developed by the author's group.

Diagnosis of lactose malabsorption

When lactose-1-^{14}C is ingested with carrier lactose, intestinal lactase splits it into glucose-1-^{14}C and galactose. Glucose-1-^{14}C is rapidly absorbed and metabolized. The end product of the metabolism, $^{14}CO_2$ is excreted into the expired breath.

The method consists of serial measurements of the specific radioactivity of $^{14}CO_2$ in the exhaled breath after oral administration of 5μCi of lactose-1-^{14}C together with 50g of carrier lactose. Specific radioactivity of $^{14}CO_2$ in the breath reaches its peak 3-4 hours after lactose ingestion. Lactase-deficient subjects expire significantly less $^{14}CO_2$ than lactose-tolerant subjects (Fig. 8).

Striking racial differences in the incidence of primary adult lactose malabsorption have been known. As shown in Fig. 9, milk tolerant Caucasians gave very high area under curve in ^{14}C-lactose absorption test. In contrast milk intolerant American Negroes showed significantly lower absorption of ^{14}C-lactose. Milk tolerant Japanese gave higher indices than milk intolerant Japanese but they were much lower than milk tolerant Caucasians.

Detection of bacterial deconjugation of bile salts.

The author and his group used glycine-1-^{14}C-cholate for the detection of bacterial deconjugation of bile salts, which is an example of the xenolytic breath tests.

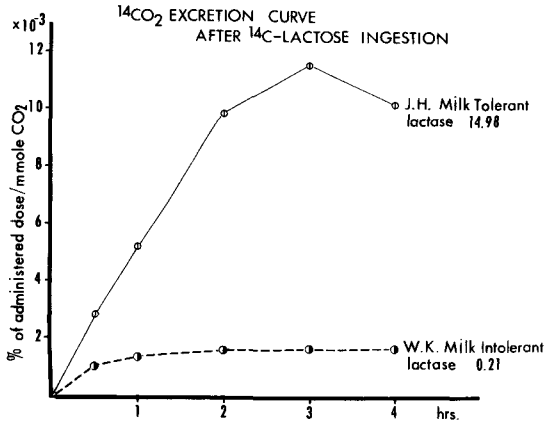


Fig. 8. $^{14}CO_2$ excretion in the breath after oral administration of 5μCi of lactose-1-^{14}C in representative milk tolerant and milk intolerant subjects.

Bile salts conjugated with glycine or tauline is indispensable for fat absorption, as they form mixed micells with fatty acid which allow absorption of fatty acid through intestinal mucosa.

Certain bacteria have enzymes to deconjuate bile salt to form the amino acids and free bile acids. The free bile acids without its magic mantle are disabled to form water soluble micells for fat absorption.

In patients with abnormally increased colonization of bacteria in the small intestines, large amounts of ^{14}C-glycine-cholate are deconjugated by the bacteria. Ileal resection, bypass and dysfunction allow much of ^{4}C-glycine-cholate to escape absorption in the ileum and pass into the

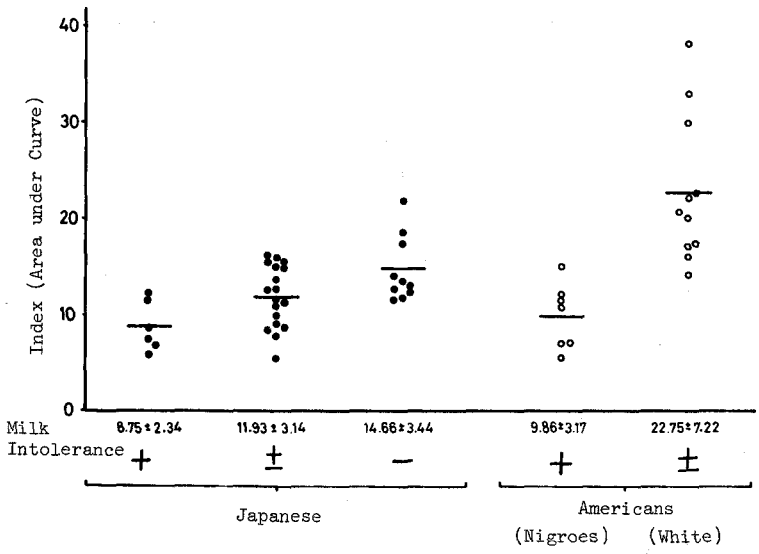


Fig. 9. Racial differences of lactose malabsorption studied by ^{14}C-lactose breath tests.

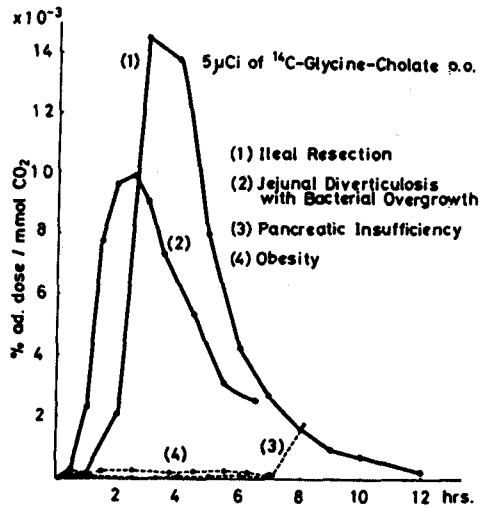


Fig. 10. $^{14}CO_2$ in the breath after oral administration of 5μCi of glysine-1-^{14}C-cholate. The remarkable peaks are demonsrated in patients with bacterial overgrowth and ileal resection, which indicates bacterial deconjugation of bile salts in the intestine.

colon, where deconjugation is taken place. Both conditions may result in fat malabsorption due to inadequate concentration of conjugated bile salt to form mixed micelles.

^{14}C-breath test can detect the conditions by abnormally increased excretion of $^{14}CO_2$ in the breath. In contrast control subject shows a flat curve (Fig. 10).

When the breath test is repeated after treatment with oral antibiotics, $^{14}CO_2$ excretion is markedly reduced and curves become flat. The examples of two cirrhotic patients with bacterial overgrowth in the small intestine are shown in the slide (Fig. 11).

Cumulative specific activity obtained as area under $^{14}CO_2$ curves is used as the index for the deconjugation of bile salts. Normal controls and patients with steatorrhea unrelated to abnormal bile salts metabolism excreted small amount of ^{14}C in the breath in 6 hours. In contrast patients with bacterial overgrowth and ileal resection showed markedly increased excretion of $^{14}CO_2$. The test is simple means for the diagnosis of malabsorption due to interupted enterohepatic circulation of bile salts (Table 3).

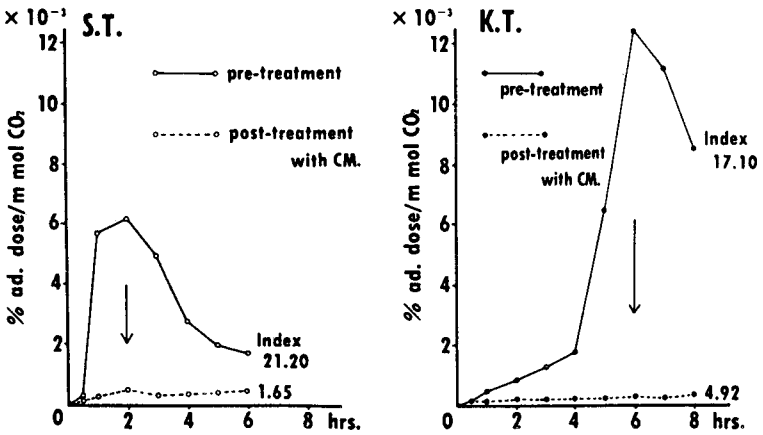


Fig. 11. Antibiotic effects on $^{14}CO_2$ excretion in two patients with liver cirrhosis with bacterial overgrowth in the small intestine.

Table 3. $^{14}CO_2$ Output after Oral Administration of Glycine-1-^{14}-C-cholate

	Area under curve (m + 1 S.D.)	
	Americans	Japanese
I. Normal control	4.4 ± 3.2 (n=7)	3.07 ± 1.38 (n=9)
II. Steatorrhea unrelated to abnormal bile salt metabolism	2.9 ± 2.3 (n=10)	–
III. Ileal resection	62.0 ± 23.9 (n=7)	39.1 ± 24.55 (n=8)
IV. Bacterial overgrowth syndromes	53.2 ± 26.5 (n=4)	

Application a stable isotope ^{13}C

Use of organic compounds labeled with a β-emitting radionuclide of long physical half life requires strict selection of the patients to be studied, even though the radiation dose is estimated to be very low. In this respect use of a stable isotope ^{13}C in place of ^{14}C is advantageous. In recent years the keen interest in medical application of stable isotopes and progress in stable isotope technology have expanded the applicability of breath test to pregnant women, infants, young adults and mass survey of the healthy population.

A mass spectrometer has been used for the measurement of isotope ratio of $^{13}CO_2/^{12}CO_2$ in the breath.

We have been using on infrared analyzer designed specifically for breath test.

A patient with jejuno-colostomy after surgery for ileus was studied with ^{13}C-breath test before and after the surgical correction of the bypass.

Preoperative $^{13}CO_2$ curve shows significant early peak. Whereas postoperative examination revealed flat curve.

A patient with choledocho-colostomy and resultant vitamin K deficiency showed a continuous rise of $^{13}CO_2$ excretion. The condition was reproduced in an animal model.

In addition to the breath tests I have now described varieties of tests have been reported for the studies of gastrointestinal and liver diseases. ^{13}C-compounds have been applied to some of those tests.

For a long period of time we did not think breath tests could ever be related to imaging examinations. Now after 15 years, the development of PET with ^{14}C labeled compounds makes me predict that the day would come when regional tissue metabolism is evaluated with PET while whole body metabolism is assessed by a breath test. This is a marvelous thing to me as an old Japanese proberb says "windy weather brings a fortune to tub makers" meaning matters apparently not related at all may have hidden logics of correlation, that brings a surprising outcome to you.