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Scintigraphy of the Gastrointestinal Tract

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SCINTIGRAPHY OF THE GASTROINTESTINAL TRACT

STATEMENT OF OBJECTIVES

The primary goal of this correspondence course is to increase the reader's knowledge and understanding of the various imaging procedures (and corresponding radiopharmaceuticals used therein) which collectively can be referred to as gastrointestinal (GI) scintigraphy. Throughout this discussion, information is presented that highlights the pathophysiology of various disease states as they can occur at different points along an individual's gastrointestinal tract (from mouth to rectum). Additionally, comparisons will be offered as to the advantages/disadvantages of scintigraphic procedures as compared to the other types of diagnostic testing. In select instances, this course will address various tangential issues (i.e., interventional techniques and/or interfering drugs or other modifiers) as they may pertain to a particular GI imaging procedure.

Upon successful completion of this material, the reader should be able to:

1. List several examples of nuclear medicine imaging procedures which can be considered subsets of gastrointestinal scintigraphy.
2. Describe the radiopharmaceuticals used in salivary gland imaging, as well as any concomitant interventional techniques.
3. Compare and contrast other types of diagnostic testing procedures relative to scintigraphy with respect to esophageal transit studies.
4. Explain the differences between single-swallow and multiple-swallow scintigraphic esophageal transit studies, relative to the type of information that is obtained.
5. Compare and contrast other types of diagnostic testing procedures relative to scintigraphy with respect to gastroesophageal reflux studies.
6. Describe the clinical manifestations of severe gastroesophageal reflux in pediatric patients.
7. List four important aspects of gastric emptying studies that must be considered at all times in order to achieve accurate quantitation.
8. Describe the pattern of emptying for liquids versus solids in normal patients.
9. Describe the proposed mechanisms for the emptying of solids from the stomach.
10. List several conditions that can result in abnormal rates of gastric emptying in patients.
11. Describe several examples of nonradionuclidic testing procedures that can be used to assess gastric emptying in patients.
12. List the characteristics of what would constitute an ideal radiopharmaceutical for use in gastric emptying studies.
13. List four examples of single- and multiple-radionuclide test meals for use in gastric emptying studies.
14. Compare the difference between the use of Tc-99m sulfur colloid and Tc-99m albumin colloid as a radiopharmaceutical for use in gastric emptying studies.
15. List five factors which can accelerate the rate of gastric emptying.
16. List four factors which can prolong the rate of gastric emptying.
17. Describe the effect of four different drugs which can either accelerate or prolong the rate of gastric emptying.
18. Describe a scintigraphic approach for assessing enterogastric reflux in patients.
19. Describe several factors which can contribute to a slowing, or an acceleration, of small bowel transit of a test meal.
20. Explain some of the reasons that can contribute to a false-negative test result for Meckel's diverticulum.
21. Explain some of the reasons that can contribute to a false-positive test result for Meckel's diverticulum.
22. List two examples each of slowly-extracted and rapidly-extracted radiopharmaceuticals for use in gastrointestinal bleed detection studies.
23. Describe the advantages/disadvantages for using slowly-extracted versus rapidly-extracted radiopharmaceuticals in gastrointestinal bleed detection studies.
24. Describe the three approaches to radiolabeling red blood cells with technetium Tc-99m sodium pertechnetate.
25. Describe a CO₂ breath test, and how it is used in the performance of gastrointestinal malabsorption studies.
26. List two of the radiopharmaceutical agents that can be used in assessing ileal dysfunction and bacterial overgrowth in the bowel.
27. Describe some of the radiopharmaceuticals that have been used to perform scintigraphic colonic transit studies.
28. Describe what a "nuclear enema" is and how it would be used in patients.
29. Describe what a "barium burger" is and what it would be used for in patients.

COURSE OUTLINE

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 - D. Intraabdominal Blood Flow

SCINTIGRAPHY OF THE GASTROINTESTINAL TRACT

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INTRODUCTION

A discussion of nuclear medicine procedures involving the **gastrointestinal (GI) tract** involves a wide array of subset organ areas of interest. In describing what constitutes the gastrointestinal system, this wide range of topics becomes clear. For example, foods, minerals, vitamins, and fluids enter the body by mouth, which represents the upper end of the gastrointestinal tract. In the mouth, food particles are broken down and mixed with secretions of three pairs of salivary glands (parotid, submaxillary, and sublingual) which open into the oral cavity [salivary imaging]. The lubricated food is then propelled through the pharynx, down the esophagus, and into the stomach [esophageal transit and gastroesophageal reflux studies].

In the stomach, food is stored and mixed with various gastric secretions (hydrochloric acid, mucus, pepsin, lipase, etc.) which continues the digestive processes. The partially digested food is released from the stomach at a controlled rate into the duodenum [gastric emptying studies], though the rate of gastric emptying depends on the nature of the stomach contents.

The small intestine can be divided into three areas, the duodenum, jejunum, and ileum. In this segment of the gastrointestinal system, the emptied stomach contents are mixed with various intestinal secretions, pancreatic juice and bile. It is in these regions that the partially digested foodstuffs continue on their journey [small bowel transit studies] and undergo complete breakdown, with the final products of digestion being absorbed from the small intestine into the blood and lymph [GI absorption studies, Meckel's diverticulum imaging, enterogastric reflux and GI bleed detection]. What remains following this absorption process is propelled from the ileum into the large intestine, or colon.

In the colon, absorption of water and minerals converts the remaining expelled contents into semi-solid feces. The colonic contents are then propelled from the ascending colon through the transverse, descending, and sigmoid colons into the rectum [colon transit studies, GI absorption studies and GI bleed detection].

From the rectum, the fecal matter is expelled through the anal orifice [rectal emptying studies], which represents the lower end of the gastrointestinal tract.

In this continuing education article, we will briefly examine

each of the GI nuclear medicine procedures noted here and, in doing so, explore various facets of clinical nuclear pharmacy practice as they relate to each of these scintigraphic studies.

SALIVARY GLAND IMAGING

Rationale for Use of Procedure

The salivary glands play a vital role in maintaining the integrity of the oral cavity mucosa, teeth and gums. Without the cleansing and protective action provided by saliva, these structures would undergo serious degeneration. Saliva is a mucus-rich secretion, primarily from the epithelial cells of the sublingual and submaxillary (submandibular) glands, that aids in protectively coating particles, lubricating the oral cavity, and facilitating swallowing (1).

The salivary glands have concentrating mechanisms for the group VII anions, including iodide and its analogues pertechnetate, thiocyanate, and perchlorate (2). The glands are innervated by the autonomic nervous system. The rate of secretion, as well as growth and integrity of the epithelium, is under the influence of the parasympathetic system and to a lesser degree, the sympathetic system. Stimulation of gland function and saliva production occurs by parasympathetic innervation and by food or drugs such as pilocarpine (1,2). Increase in blood flow is also under control of the autonomic nerves, and this may contribute to an increase in the rate of saliva formation. Anticholinergic drugs, such as atropine, markedly reduce saliva production and flow resulting in "dry mouth" (2).

Dry mouth can be a difficult symptom to assess clinically. Until radionuclide techniques became available, it was not possible to measure it by objective methods. The use of Tc-99m pertechnetate is useful in assessing patients with this symptom, and may be diagnostic in distinguishing genuine xerostomia from psychosomatic dry mouth (3).

The clinical potential of salivary gland imaging using Tc-99m pertechnetate was first introduced as an incidental evaluation during brain scanning. While we may tend to view salivary gland scintiphotos as a means of detecting and categorizing anatomic lesions (i.e., tumors, cysts and fibrosis), in fact, the imaging study does this poorly and often cannot delineate clinically palpable masses (1). Most of them have diminished activity and thus may be difficult to detect. Clinically, occult masses are not detected. Even if a mass is detected, the distinction between intra- and extraparotid lesions may not be possible (1). The computed tomography (CT) scan is a better noninvasive tool for detecting and categorizing mass lesions involving the parotid glands (1). Contrast sialography, although invasive and somewhat uncomfortable, also has a higher accuracy in this regard. However, salivary gland imaging does provide a unique and sensitive means for investigating salivary gland function and its derangement due to the physiologic effects of diffuse cellular infiltration, even in subclinical stages where detection sensitivity rivals biopsy techniques (1).

In a variety of systemic diseases, the salivary glands (and often the lacrimal glands) commonly undergo lymphocytic infiltration. If extensive, this leads to swelling and functional

obstruction, resulting in diminished secretory capacity, perhaps even atrophy if the involvement is severe and prolonged (1). These nonsuppurative histologic changes have been well documented, and the local findings of keratoconjunctivitis and xerostomia were recognized by Sjogren to be manifestations of a systemic disease, usually rheumatoid arthritis (4). In Sjogren's syndrome (or genuine xerostomia) there is reduced salivary gland function and no uptake of the radiopharmaceutical into the four glands, with no subsequent discharge into the mouth. Both of these phases of salivary function are normal in patients with psychosomatic xerostomia (4).

Salivary gland scans can be useful in documenting asymmetries between the salivary glands due to radiation damage or other inflammatory processes involving the parotid glands, such as viral disease, toxic alcoholic inflammation, radiation sialitis, iodide sialitis and, rarely, suppurative microorganisms (1). Both Warthin's tumors and oncocyotomas show an increased concentration of Tc-99m pertechnetate in salivary gland scintiphotos, whereas other tumors, including carcinoma, mixed tumors, and lymphoma are either "warm" or show decreased uptake (5).

Imaging Technique

Iodide in quantities sufficient to suppress the thyroid, but not salivary concentration of Tc-99m pertechnetate, has been used to prepare the patient for salivary gland imaging. However, such preparatory efforts are probably best omitted, since they would restrict one's ability to compare salivary gland and thyroid trapping (6).

A perfusion study is done with 10 mCi of Tc-99m pertechnetate to delineate gland vascularity. Images are made at 1-5 second intervals and an initial 300,000 to 500,000 count image made. At 5 minutes another view including the thyroid gland, as well as both 60-degree lateral oblique views are made (7). Use of a converging collimator enhances resolution over a parallel-hole collimator without causing any unnecessary delays in imaging time to the study (1,8).

This imaging procedure can also include an interventional component which involves the use of saliva secreting agents to clear radioactive saliva from the normal portion of the gland, but not from the abnormally warm spot, thus making the differential uptake by "hot" spots obvious (8). Pilocarpine has been used to increase uptake and retention of the radionuclide, whereas the administration of perchlorate results in washout of trapped pertechnetate from the glands (9,10). Other investigators have noted that the use of ascorbic acid (500 mg), or having patients suck on a tart piece of candy (i.e., lemon drop) can be employed to achieve the same washout effect (11).

The procedure for an interventional study is very simple. A scan of the patient is taken at 20-30 minutes following the intravenous administration of 15 mCi of Tc-99m pertechnetate. No prior preparation is necessary for this portion of the study except for having the patient rinse the mouth prior to imaging. This diminishes the unnecessary background from the oral radioactivity. Following the initial study, the patient is given a piece of candy to suck on for 5 minutes in order to discharge salivary gland contents into the mouth before images

are repeated. After a repeat rinsing of the mouth with water, another scan should be taken in the same projection as those before the patient was given the candy (continue imaging for another 45 minutes, acquiring 300,000 counts every 10 minutes). This will facilitate correct comparison.

Patients with infiltrative parotid disease show delayed and diminished peak trapping of Tc-99m pertechnetate and incomplete discharge because of an inability to increase salivary flow rate in response to physiologic or pharmacologic stimuli (1). Partial obstruction of a major duct, either mechanical or functional, leads to retention of activity in the salivary glands (12). Follow-up interventional studies with saliva secreting agents make the retention in the hot spot more obvious. Complete obstruction will lead to gland atrophy and diminished pertechnetate trapping (11).

A normal image shows the parotid and submaxillary glands. The sublingual and minor mucosal salivary glands take up Tc-99m pertechnetate in concentrations no greater than that for plasma and thus are generally not seen. Oral activity represents activity secreted from the major glands. Assuming normal thyroid trapping, parotid uptake ranges from slightly less to slightly more than thyroid gland activity, and there should be nearly complete discharge from the parotid glands following salivary gland stimulation (1).

ESOPHAGEAL TRANSIT STUDIES

Rationale for use of Procedure

In the evaluation of esophageal transit (and gastroesophageal reflux) radionuclide techniques have several advantages over other imaging and nonimaging modalities. For example, scintigraphic methods facilitate the ease of studying gastrointestinal function because they are quantifiable and generally do not require the use of tubes (or other foreign objects) into the organs being studied (13). Additionally, in comparison to barium fluoroscopic studies, the radionuclide techniques deliver a lower radiation dose, are usually brief in terms of the duration of testing, and thus meet with greater patient acceptance (14,15). Alternatively, other modalities may be relatively insensitive or invasive, or only serve as indirect determinants of organ function.

Conventional methods of assessing esophageal motor function include contrast esophagography, the acid clearance test, and esophageal manometry (16). Contrast esophagography (or cine-esophagography), though noninvasive, results in a relatively large radiation burden to the patient (17). The acid clearance test requires intubation with a pH electrode, and is only semi-quantitative at best (17). Esophageal manometry records intraluminal pressures. An accurate assessment of intraesophageal pressure changes can be obtained using this technique. This procedure assesses the amplitude, duration, and velocity of peristaltic contractions; lower esophageal sphincter (LES) pressure and relaxation; and coordinated relaxation of the upper esophageal sphincter (UES) (18). While specific criteria exist to define esophageal motility disorders, and manometry is generally considered the gold standard for diagnostic purposes, correlation of esophageal motor activity with transit has not been well established (17,18). None of the current techniques for

studying esophageal motor function, with the exception of the radionuclide technique, is quantitative for judging the degree of obstruction and/or the effects of therapy (19,29).

In 1972, Kazem (20) reported the use of a radiopharmaceutical and gamma camera to monitor swallowing. Since then several scintigraphic techniques have been described for the evaluation of esophageal motility (21-28) using quantitative parameters (21,22,24,26), functional imaging (23,28), or a combination and extension of these approaches (25,27). Each of the currently employed techniques is based upon the technique of Tolin, et al. (21), although the quantitative methods utilized for data evaluation differ somewhat. The application of scintigraphic techniques to the study of aboral and retrograde movement of luminal contents represents a major advance in the evaluation of upper gastrointestinal motor function (19).

The primary motor disturbances of the esophagus are achalasia, diffuse esophageal spasm, scleroderma and stricture (16). Achalasia is manifested in patients who demonstrate increased lower esophageal sphincter pressure, incomplete sphincter relaxation, lack of peristalsis of the entire esophagus, and in some cases, megaesophagus (16). Patients with diffuse esophageal spasm can be characterized by high-amplitude and nonprogressive peristalsis (16). Scleroderma is characterized by decreased lower esophageal sphincter pressure and low-amplitude peristalsis, whereas stricture is characterized by a localized intrinsic or extrinsic narrowing of the esophagus (16). Each of these conditions, when present, will result in altered peristalsis and prolonged esophageal transit times in patients.

Imaging Technique

As an inevitable consequence of the fact that there are a number of different ways in which esophageal transit studies can be performed, the very fact that this type of study lacks standardization can be most problematic in terms of interpretation of test results.

Usually these tests are performed with the patient taking only one or two radiolabeled swallows. However, some investigators believe that studies utilizing single swallows may show a considerable intra-individual variation (30-32). Therefore, it has been suggested that more than one swallow may be required in order to reliably diagnose (or exclude) esophageal motility disorders (33,34). For example, Tatsch and co-workers have developed protocols for acquisition and processing of multiple consecutive swallows (six swallows), which permit a combined quantitative and qualitative evaluation of esophageal transit during a single investigation (34).

Variability in test performance extends beyond the perceived concern of how many dry swallows a patient should take during testing. There is a wide range of methods by which data can be quantitatively analyzed, which generally can be looked at as being one of two major approaches based on analysis of time-activity curves for a given region of interest within the esophagus. First, measurement of the percentage of esophageal emptying after one or more swallows (18). Or second, the transit time required for the esophageal contents to drop below a specified low level (18). All in all,

these two approaches are somewhat equivalent in that a patient with an abnormally low percentage of esophageal emptying is quite likely to also display an abnormally long esophageal transit time.

Variations notwithstanding, there is a basic approach that can be taken for performing esophageal transit studies, as described by Malmud and Fischer (35). Following an overnight fast, patients are placed supine under an Anger gamma camera, affixed with a diverging-hole medium-energy collimator (on a standard field-of-view camera) or a parallel-hole collimator (on a large field-of-view camera), with radionuclide energy windows set at $140 \text{ keV} \pm 30\%$. While in the supine position, the patient is administered 30 uCi (11,000 kBq) of Tc-99m sulfur colloid through a straw and instructed to perform dry swallows on command at 15-second intervals for up to 10 minutes, with no further liquids being given during this time. The passage of the bolus is observed on the persistence oscilloscope. Regions of interest are established and data stored in the computer. The count rate within the established esophageal area of interest is used to determine the rate of esophageal transit by using the following equation (21):

$$C_t = \frac{E_{\text{max}} - E_t}{E_{\text{max}}} \times 100$$

Where: C_t = the percentage esophageal transit time at time "t"

E_{max} = the maximum count rate in the esophagus

E_t = the esophageal count rate at time "t"

Note: Esophageal Transit - Single Swallow (counts obtained per second for 15 consecutive seconds following initial swallow)

Note: Esophageal Transit - Multiple Swallows (counts obtained per 15 second interval following each swallow for 10 minutes)

In normal situations, the transit time of a liquid bolus from the pharyngoesophageal junction to the cardia is less than 10 seconds. In situations where there is extrinsic or intrinsic obstruction, accumulation of the radiopharmaceutical at the level of the obstruction is observed and the transit time is prolonged in direct proportion to the degree of narrowing (16). For example, in normal subjects, esophageal activity decreases rapidly with less than 10% of the activity remaining after the first 15 second interval. After eight swallows, esophageal transit (in terms of % bolus cleared) in patients with achalasia was $27\% \pm 11\%$; in patients with scleroderma, $24\% \pm 15\%$; and, in normals $93\% \pm 1\%$. Patients with diffuse spasm had an esophageal transit of $76\% \pm 11\%$ after eight swallows (transit rates were significantly reduced during the first half of the study, but approached normal values after approximately 20 minutes) (21). In patients with the syndrome of symptomatic gastroesophageal reflux, the esophageal transit was diminished after serial swallows (see Table 1). In general, it is important to note that esophageal transit studies can be repeated as often as necessary and therefore this procedure becomes a useful tool in the

evaluation of patient therapy. This type of testing may also reveal the presence of esophageal fistulas before they are readily apparent in radiologic examinations, primarily due to the fact that the liquid radiopharmaceutical is less dense and viscous than are most contrast media agents (16).

Table 1. Quantitative Esophageal Scintigraphy in Different Disease States

Patient Type	% Transit After 8 Swallows	% Transit After 40 Swallows
Normals	$93\% \pm 1\%$	$95\% \pm 4\%$
Achalasia	$27\% \pm 11\%$	$31\% \pm 10\%$
Diffuse Spasm	$76\% \pm 11\%$	$93\% \pm 3\%$
Scleroderma	$24\% \pm 15\%$	$42\% \pm 15\%$
Symptomatic Gastro- esophageal reflux		
-with motor disorder	$74\% \pm 4\%$	$81\% \pm 4\%$
-without motor disorder	$86\% \pm 3\%$	$92\% \pm 3\%$

(adapted from Malmud LS³⁵)

In a study by Russell et al. (22), an attempt was made not only to measure the esophageal transit time, but to observe the dynamics of the bolus progression as well. The technique used by these investigators called for dividing the esophagus into three regions of interest, namely the proximal, middle and distal thirds. Time-activity curves were plotted and the resultant data used to describe the transit of the bolus through each of the areas of interest. Using this technique, it was possible to differentiate achalasia from scleroderma. For example, in patients with scleroderma, most of the bolus entered the stomach within the 15 second study period, whereas in patients with achalasia the bolus was delayed. Additionally, patients presenting with diffuse esophageal spasm were able to be separated from those with nonspecific motor abnormalities (22).

Tatsch et al. (34) evaluated esophageal motility by analyzing six consecutive swallows, with a summation image being generated that contained the information for the entire study, allowing for combined quantitative and qualitative evaluation of esophageal motility disorders. Esophageal transit times and characterization of the bolus behavior was derived from the summation image and the single swallow data. Liquid and solid phase studies showed remarkable variation for single swallow data in normal patients (10% for liquid; 14% for solid), which was even higher in patients with disorders (31% for liquid; 25% for solid). Sum images tended to yield results that compensated for this intra-individual variation, where false-positive (16% liquid; 25% solid) or negative (36% liquid; 27% solid) single swallow findings are reduced. Quantitative data was evaluated for each single swallow, as well as the sum image (representing a mean emptying rate for the whole study). Assuming that the esophagus may not be cleared of residual activity between consecutive swallows in patients presenting severe motility disorders, background correction was performed using the following equation:

$$\text{esophageal emptying \%} = \frac{\text{cts}_{\text{max}} - \text{cts}_{10 \text{ sec}}}{\text{cts}_{\text{max}} - \text{cts}_{\text{min}}} \times 100$$

Where: cts_{max} = maximal count rate observed in the columns of a condensed image

$\text{cts}_{10 \text{ sec}}$ = count rate 10 seconds after t_{max}

cts_{min} = mean residual activity calculated as mean count rate of the first five columns (=frames) prior to each swallow

Using this approach Tatsch et al. (34) showed that, in particular cases, the emptying rate of a single swallow may exceed the value of 100% (if the residual activity from a preceding swallow was cleared with the following one).

Taillefer et al. (29) recently compared the radionuclide esophageal transit study (RETS) to esophageal motility studies (EMS) involving manometry (as a gold standard) in 109 patients presenting with various esophageal diseases. Based on final diagnosis, patients were divided into three groups, those with primary esophageal motor disorders (Group I), reflux disease (Group II), and non-cardiac chest pain and/or dysphagia (Group III). Using EMS as a standard, the results of RETS in terms of the sensitivity for the detection of motor dysfunction was 97%, 92%, and 77% for Groups I, II, and III respectively, whereas the specificity for Group II was 91% and for Group III it was 100%. In this study, no clinically significant motor disorder was missed using the RETS technique.

Radionuclide esophageal transit studies can be performed with the patient in either the upright or supine position (see Table 2). However, it has been noted that studies done with patients in the upright position provide a more physiologic evaluation relative to the normal position for swallowing, as compared to outcomes when the test is performed with patients in the supine position (35,36). On the other hand, by partially removing the effects of gravity, esophageal contractions by themselves become responsible for esophageal emptying. Additionally, esophageal motility disorders are easier to demonstrate when patients are in the supine position, particularly in the early disease stages when tests results done in patients in an upright position can yield normal results (36). Some investigators have advocated the use of the posterior projection during the performance of the study in order to provide a relatively uniform attenuation of radioactivity throughout the entire length of the esophagus, thereby avoiding any attenuation caused by the heart (37).

While it can be stated that the esophageal motility study measures the duration, velocity and pressure of the esophagus and sphincters, the radionuclide esophageal transit study evaluates the combined effects of these factors in both segmental and global esophageal emptying (18,29). However, barium radiographic studies and/or endoscopy should also be performed when screening patients for esophageal motility disorders, in order to rule out the likelihood of mechanical obstruction, stricture or malignancy (16). These lesions cannot be distinguished from the presence of a esophageal motor disorder alone using the radionuclide testing method.

Table 2. Effect of Patient Position on Esophageal Emptying or Total Clearance Time of Radionuclide Marker

Patient Position	Transit Time (sec)	Total Clearance Time (sec)	Ref
Supine	42% at 3 sec	9 sec	21
Supine	83% at 15 sec	60 sec	17
Sitting	65% at 10 sec	60 sec	343
Supine	- - -	6 ± 2 sec	25
Sitting	50% at 5 sec	6-8 sec	344
Supine	- - -	9.5 ± 1.5 sec	10
Upright	- - -	7 ± 2 sec	
Standing	95% at 60 sec	- - -	

(adapted from Lichtenstein GR⁴²)

When comparing esophageal transit study data obtained in patients to that obtained in normal subjects, one cannot help but wonder if normal volunteers always empty the esophagus, to a substantial degree, under the action of a single initial swallow, as has been stated by some investigators (38,39). Or, do they sometimes fail to do so as reported by others (33,40), raising the question that this is a matter of intrasubject rather than intersubject variation (33,34). It is quite likely that aberrant swallows occasionally occur in normal subjects (32). A possible explanation for this type of event would be the inhibition of peristalsis when the interval between successive swallows is too short, such as less than 10 seconds (31). Detection of such events may be possible by examining either "condensed" standard dynamic images, or analysis of time-activity curves with special attention being paid to the proximal regions of interest.

The multiple swallow technique, as described by Tatsch et al. (34), inherently presents a problem of background correction from one swallow to the next. Subtracting the inter-swallow radioactivity in a given esophageal region of interest has the shortcoming that residual activity from a preceding swallow can be cleared with the following one and lead to an impossibly high calculated emptying value for any given individual swallow, implying that the patient had a delayed esophageal transit clearance or reflux (false-positive) (22,34). In order to avoid this, it is helpful to include the patient's mouth in the field of view in order to determine when the radionuclide bolus leaves the patient's mouth. A second possible source of error (leading to false-positive test results) may occur when a patient has a large hiatal hernia, since this condition can easily be mistaken for the presence of a dilated distal esophagus. An attempt to empty the esophagus more completely between boluses, using multiple dry swallows in the erect position over a sufficient time interval, could possibly diminish the effect that residual activity can have on test outcomes. Additionally, use of a multiple swallow test using a short half-life radionuclide, such as Kr-81m (13 seconds) or Au-195m (30 seconds) would solve the problem of residual activity, but does not address the concomitant problem of residual volume (26,43). However, there is the remaining advantage that either of these two alternative

radionuclides provide for high count rates to facilitate data acquisition and analysis, and presents a lower radiation burden to patients, but at the apparent loss of convenience and economy of using Tc-99m (26).

Several authors have proposed that the sensitivity of testing using radionuclide techniques can be improved by using such adjunctive measures as abdominal compression (44), Trendelenburg or prone position (45), and/or various drug provocations (46). Anticholinergics, nitrates, calcium channel blockers and cimetidine have been reported to have an effect on both esophageal transit and resting lower esophageal sphincter pressure gradients (21,22,32,47-49). It has also been shown that changing the patient's position from prone to supine (or vice versa) can have an important effect on esophageal transit. It should also be mentioned that the rate of transit is dependent upon other extrinsic factors besides positioning, such as the density of the bolus that is swallowed (solid or liquid) (50). A majority of the published results of esophageal transit studies describe the use of a liquid as their radiolabeled vehicle. Solids, however, are felt to be more representative of physiologic states in patients with esophageal disorders (specifically individuals with achalasia), since patients often complain more frequently about dysphagia for solids than they do for liquids (51,52).

Clinically, esophageal scintigraphy using any of the methods described above is a simple quantitative and noninvasive test of esophageal transit. The technique permits detection of disturbances in esophageal transit, both in patients with radiologically proven motor abnormalities, as well as those with nonspecific symptoms and normal radiographs, or subtle transient abnormalities as demonstrated by manometry (53). Scintigraphy is more sensitive to minor disturbances of esophageal transit than is either radiography or manometry alone. Those investigators who recognize that esophageal manometry is often the diagnostic technique of choice for patients with suspected esophageal motility disorders have questioned the cost-effectiveness of the procedure. Specifically, concern centers around the type/quality of data obtained from testing in relation to the level of expertise and time needed in order to derive conclusive results (54).

Acid clearance testing is another technique that has been used, but it appears to be limited in sensitivity compared to both manometry and scintigraphy. The acid clearance test requires intubation with a fragile pH electrode and is unphysiologic in that the indwelling electrode can interfere with esophageal transit, not to mention that acid must be instilled into the esophagus which can affect esophageal motor function (55). As a consequence, it is important to note that esophageal scintigraphy can be adapted to study the transit, not only of acid solutions, but of most any material that can be successfully labeled with a gamma-emitting radionuclide (17,38).

The use of esophageal scintigraphy, within the overall diagnostic algorithm for evaluation of esophageal motor disorders, is ideally suited not only for the evaluation of patients with possible abnormalities in esophageal transit, but also for the quantitative reevaluation of patients following the use of any number of therapeutic measures (17).

GASTROESOPHAGEAL REFLUX

Rationale for Use of Procedure

In the 1970's, gastroesophageal scintigraphy was developed as a technique to enable the detection and quantitation of reflux from the stomach into the esophagus (56). Movement of gastric and duodenal contents across the gastroesophageal junction contributes to inflammation of the esophageal mucosa, which results in symptoms including heartburn, regurgitation, bleeding, and vomiting. Many times, patients with these types of symptoms (or history) do not necessarily have reflux disease. These symptoms are, in themselves, nonspecific for reflux disease. Detection of reflux is often problematic, especially in the patient with an atypical history. Exclusion of reflux can also be a problem in light of other conditions which may mimic the symptoms of reflux, such as angina pectoris, diffuse esophageal spasm (which causes angina-like pain and/or difficulty with swallowing, and which can either be precipitated by reflux or occur spontaneously, or in association with achalasia or carcinoma), achalasia, carcinoma of the cardia, peptic ulcer or pyloric stenosis (3). Consequently, gastroesophageal scintigraphy is of value, particularly when the need arises to evaluate therapy in those patients in whom therapeutic response has been poor (56).

In addition to scintigraphic techniques, a number of other methods can be used to evaluate reflux disease (see Table 3). These include the use of barium esophagography (57), barium cine-esophagography (58), endoscopy (59), esophageal manometry (to measure lower esophageal pressure gradient) (60), esophageal mucosal biopsy (61), the acid perfusion test (62), the acid clearance test (63), and the acid reflux test (64).

Table 3. Evaluation of Gastroesophageal Reflux in 30 Symptomatic Patients Using Different Diagnostic Testing Techniques

<u>Diagnostic Testing Technique</u>	<u>% of Positive Test Result</u>
Acid Perfusion Test	63%
Endoscopy	40%
Fluoroscopy	50%
Gastroesophageal scintigraphy	90%
Histologic examination (esophagitis)	47%
Manometry (LES pressure < 10 mm Hg)	57%
(LES pressure \leq 15 mm Hg)	77%
Phenol Red Reflux Test	47%
Radiographic (barium) hiatal hernia	60%

(adapted from Malmud LS[®])

Any satisfactory process used to investigate the presence of gastroesophageal reflux in patients requires the use of a simple, acceptable, and reproducible test that yields both a low false-positive and low false-negative detection rate (3).

Each of the nonscintigraphic techniques mentioned above offers specific strengths and limitations, in terms of their use in detecting gastroesophageal reflux. For example, barium esophagography (either fluoroscopic or with cine), is recognized to be insensitive in detecting gastroesophageal reflux or aspiration, due largely to the limited time of

fluoroscopic observation; a prolonged procedure can impart a large radiation burden to the patient (65). The causes of false positive diagnosis of reflux, using the barium swallow approach, include excessive crying (by the patient) during testing, excessive pressure on the abdomen, and a too aggressive interpretation of small signs of barium reflux (on the other hand, the use of too little barium may result in a false negative examination in patients with reflux). There is also the water siphon test (use of the head down position) that can be performed, but this procedure is also a source of false positive results, despite the fact that it is nearly guaranteed to produce reflux (70). However, radiographic techniques have an essential role in terms of evaluating anatomic gastrointestinal abnormalities that can mimic the symptoms of gastroesophageal reflux in patients (66).

The acid reflux test detects reflux directly, and is thus often used as a standard for comparing results obtained from the use of other diagnostic modalities. While this procedure is somewhat simple in principle (though often fraught with technical problems) and highly sensitive for the detection of reflux, it does require sedation and placement of a pH probe into the distal portion of the esophagus. In some studies, the pH electrode is positioned fluoroscopically or placed to the desired depth within the esophagus by using a formula for estimating esophageal length based on actual patient height. However, both approaches can be somewhat inaccurate, especially in patients where esophageal anatomy is abnormal (1). For example, the extent of acid exposure dramatically decreases as the pH of the more proximal esophagus is monitored; therefore, the higher in the esophagus the tip of the probe is placed, the higher the risk of obtaining a false-negative test outcome (70). In some respects, deficiencies in acid clearance may be expected to perpetuate gastroesophageal reflux (74,75). Additionally, the results of continuous pH monitoring are prone to wide variation, depending on any number of conditions under which the test is performed. For example, factors that are important are: patient positioning (with esophageal acid clearance being longer, requiring more peristaltic sequences, when a patient is in a supine rather than erect position) (71,76), the frequency of feeding (72), the acidity and physical position of the patient (73), gastric acidity (63), medications, and the exact nature of the pH electrode in the esophagus (70). Therefore, this technique is invasive, nonphysiologic and should not be used when trying to detect aspiration (67,68).

Endoscopy can be used, along with esophageal biopsy, to determine if esophagitis is present, as well as peptic ulceration and pyloric stenosis (66). However, abnormal findings may or may not be attributable to reflux, and some investigators report that this technique satisfactorily provides evidence of esophagitis in only 40% of symptomatic patients, when reflux is demonstrated by the acid reflux test (66).

Esophageal manometry is another technique that has been utilized to evaluate symptomatic reflux. However, it has been shown that abnormal manometric determinations are not necessarily related to gastroesophageal reflux, but rather correlate with low LES pressure as a result of decreased resistance (including peristaltic abnormalities) at the

gastroesophageal junction (69). As a result, manometry is neither specific nor sensitive for detecting the presence of reflux and, like other nonradiologic testing methods, should not be used when trying to quantitate reflux or detect aspiration.

The acid perfusion test often yields variable results when compared to data obtained from the acid reflux test (62,66). While this testing approach has not been widely used in children, it does show some promise in evaluating the sensitivity of the esophageal mucosa to acid, more so than its ability to detect the presence of reflux (66).

In relation to each of these other approaches, gastroesophageal scintigraphy can quantify reflux and be used to follow the response to medical or surgical therapy (56). It is limited in that anatomic detail is not well defined, and studies involving patients with hiatal hernia often give conflicting results (68,77). However, when both radiographic and scintigraphic techniques are combined, together most abnormalities are adequately detected.

Imaging Technique

A wide variety of test meals have been proposed for the performance of gastroesophageal scintigraphy in both adult and pediatric patients alike. Since there are some subtle differences to take into account when performing this test in children compared to adults, attention will first be directed toward the adult patient population.

In a generalized approach, 100 uCi to 300 uCi of Tc-99m sulfur colloid (or DTPA) is placed into: 300 ml of saline; orange juice and water (150 ml each); or some other liquid vehicle such as 0.1 N HCl (150 ml) added to saline (56,78). A nasogastric tube is generally not necessary. During testing, the patient is typically studied while in the supine position in order to remove the counter-reflux effect of gravity (16). An acid load to the stomach is employed in order to relax the lower esophageal sphincter pressure gradient. Finally, augmentation of reflux is achieved by use of an abdominal binder which, when inflated up to 100 mm Hg, raises the pressure across the lower esophageal sphincter from 10 to 35 mm Hg. Without the use of such a technique, the test would be far less sensitive under resting conditions. Using a computer-interfaced gamma camera, the gastroesophageal scintiphotos are obtained for a 30-second exposure at each 20 mm Hg pressure gradient up to 100 mm Hg. Reflux is typically measured with regions of interest placed over the lower esophagus and stomach and expressed as a percentage of gastric counts which offers some allowance for any losses in activity due to gastric emptying (3).

The test is positive if significant counts are observed at any point in the esophagus; the overall percentage of gastric contents that are refluxed serves to quantitate the overall severity of disease. In general, reflux greater than 4% is visible without any significant data processing and is considered to be abnormal (78). If no reflux is demonstrated, the test may be repeated using 300 ml of a designated liquid vehicle, containing the Tc-99m sulfur colloid in weak acid. It has been suggested that patients with a typical history for gastroesophageal reflux could proceed onto a trial course of appropriate therapy without having to undergo any further

diagnostic investigation (68). However, should testing still be called for, the highest diagnostic accuracy in the detection of reflux would likely come from the radionuclide scan, the acid perfusion test and/or esophageal pH measurements. If a patient presenting with an atypical history makes the immediate consideration of reflux less likely, with perhaps more specific indications pointing towards the presence of peptic ulcer or carcinoma of the cardia, then radiography and endoscopy would be the investigative techniques of choice. The radionuclide scan would prove useful in monitoring the effectiveness of various therapies (i.e., alginate acid compound) (80). If, on the other hand, some esophageal motility disorder (i.e., spasm or achalasia) is suspected, radionuclide transit studies should be made prior to scintigraphic studies for reflux itself, thus eliminating the need for performing manometry (22).

Data accumulated from radionuclide testing is processed and an index of gastroesophageal reflux is computed by using a simple area-of-interest analysis and the following equation:

$$R = \frac{(E_t - E_b)}{G_0} \times 100$$

where R equals the percentage gastroesophageal reflux index; E_t equals the esophageal counts at time "t"; E_b equals the esophageal background counts, and G_0 is equal to the gastric counts at the beginning of the study. Using this formula, an R value of 4% or greater would be indicative of reflux abnormalities.

Pulmonary aspiration of gastric contents may occur with or without clinical symptoms of reflux. This event has been implicated in the etiology of asthma and of pulmonary fibrosis (82). Silent gastropulmonary aspiration may be suspected, but rather difficult to prove, especially if radiologic techniques are employed which may, in themselves, demonstrate the consequences but not the actual cause of the anomaly (82).

The procedure for detecting pulmonary aspiration of gastric contents is relatively simple and non-invasive, but may need to be repeated more than once in order to detect intermittent nocturnal aspiration. For example, 10 mCi of Tc-99m sulfur colloid is administered the night before testing by placing it into a large glass of water and having the patient drink it. Eating other foods should not interfere with the course of testing. The day following ingestion of the test meal, scintiphoto images are obtained in the anterior, posterior and right lateral positions (100,000 counts per image) using a gamma camera. Any cross-activity coming from the patients upper abdomen should be excluded (83). To a large degree, localization of aspirated activity will depend on the position in which the patient normally sleeps.

In pediatric situations, vomiting or spitting up is a very common problem, and in a majority of patients, it is a benign, self-limiting condition. However, in older children, severe complications can ensue should vomiting continue as a result of gastroesophageal reflux (i.e., death due to respiratory arrest) (85-87).

Since the initial description of gastroesophageal reflux in infants (88), there have been numerous reports characterizing the clinical manifestations of severe reflux. Some of these signs are esophagitis, esophageal stricture, hematemesis,

failure to thrive, torsion spasm of the neck, iron deficiency anemia, intermittent wheezing, recurring acute respiratory distress, aspiration pneumonia, nocturnal cough or sudden infant death syndrome (89-92).

Several suitable radionuclide techniques have been described in the literature in order to detect gastroesophageal reflux in pediatric patients. In general, 200 uCi to 1 mCi of Tc-99m sulfur colloid is placed into either fruit juice (93), milk (94), formula (95), or glucose water (96), or the tracer can be placed directly into the stomach by way of a nasogastric tube (35). The patient is positioned supine under a gamma camera with a parallel hole collimator. During a 30 minute to 60 minute period, data is being accumulated at 30-second intervals, with an area of interest selected over the esophagus with computer and time-activity curves being calculated. At two hours after radiotracer injection, images are obtained of the thorax in order to determine if aspiration had taken place.

According to some investigators (16), compression of the abdomen in infants and children may actually decrease sensitivity for detecting gastroesophageal reflux. Several technical suggestions have been made in order to improve imaging, including 1) immobilization to prevent artifactual spikes in recorded activity, 2) selection of a region of interest in the middle of the esophagus in order to eliminate artifacts due to gastric motility, and 3) frame summing and the use of other computer enhancement techniques (16). Following such recommendations, it has been noted that the accuracy of detecting gastroesophageal reflux in children is between 80% and 90%.

Gastroesophageal reflux is not only a useful technique in the diagnosis of reflux esophagitis, but also as a tool for quantitatively evaluating a patient's response to therapy (17,80,98,99). Use of this approach has also permitted the study of the relationship between lower esophageal sphincter pressure and reflux (35). This has been done for the most commonly prescribed therapeutic approaches, namely, positional therapy (upright versus supine) (35), Gaviscon antacid (an antacid-alginate acid compound) (80), bethanecol (or urecholine) (17,99) and surgery (102).

In scintigraphic studies of patients in the supine versus upright position, it was noticed that reflux was quantitatively reduced in the upright position, with no comparable change in the lower esophageal sphincter pressure. Following the use of antacid therapy, reflux was reduced at all time points heading toward 30 minutes post-antacid administration, with no evidence of a reduction in lower esophageal sphincter pressure until 30 minutes after the antacid was given. The predominant pharmacologic action of antacids is the reduction of intragastric pH. Therefore, the efficacy of antacids in the management of reflux may be due to an indirect increase in lower esophageal sphincter pressure resulting from reduced stomach acidity (101). Bethanecol significantly increased lower esophageal sphincter pressure at all time points following initial drug administration (up to 45 minutes later), with a corresponding decrease in gastroesophageal reflux indices. Atropine, an anticholinergic, significantly decreases lower esophageal sphincter pressure, while demonstrating an increase in the maximal gastroesophageal reflux indices.

Table 4 summarizes the effects of various treatment approaches of gastroesophageal reflux and lower esophageal sphincter pressure.

Table 4. Effect of Therapy (Tx) on Gastroesophageal (GE) Reflux and Lower Esophageal Sphincter (LES) Pressure

Treatment/Therapy	GE Reflux Index (%)		LES Pressure (mm Hg)	
	Before Tx	After Tx	Before Tx	After Tx
Antacid	11	8	9	17
Atropine sulfate	8	10-13	11	5-7.5
Bethanecol	12	6-8	10	14-18.5
Gaviscon (alginic acid/ antacid)	10	6.5	10	11
Nissen Fundoplication	17.5	3	8	12
Positional change (supine to erect/upright)	15	7.5	8.5	6

(adapted from Malmud LS³⁵)

The study of gastroesophageal reflux has been hindered somewhat by the lack of an appropriate animal model, and the very fact that some reflux occurs in all normal individuals. However, by continual study of normal infants, children and adults, it is becoming increasingly clear that an understanding of acid clearance abnormalities (especially during sleep periods when in the supine position), may be all critical in order to better understand gastroesophageal reflux. As more is learned about what constitutes "normal" reflux, it will be possible to further refine current techniques (and likely develop new ones) that will permit more accurate diagnosis of gastroesophageal reflux.

GASTRIC EMPTYING STUDIES

Rationale for Use of Procedure

Since the early 1970's, radionuclide techniques for evaluating gastric emptying have been employed, with measurement of small bowel and colonic transit beginning to emerge in the 1980's, along with other scintigraphic approaches that permitted the evaluation of rectal emptying (103). Common to all these techniques is the need for having a suitably labeled physiologic marker that remains in the desired compartment long enough to permit completion of the testing/measurement procedure. For example, it would be desirable to use a radiopharmaceutical that remains in either the liquid or solid phase during gastric emptying studies, or an agent that would maintain the consistency of the stool during rectal emptying studies (103). Equally important is the need for having the radiopharmaceutical maintain its integrity throughout the study and not be subject to the various chemical and enzymatic conditions in the GI tract. In this regard, gastric emptying agents must maintain their integrity in the acid and pepsin environment of the stomach. Agents used for small bowel transit studies must be stable at neutral to alkaline pH, and agents used for colonic transit studies must not be digested by the bacteria generally found within the colon (103). Finally, agents used for these

types of imaging procedures must not be absorbed within the gastrointestinal tract, nor should they be excreted through the GI mucosa (103).

Radionuclide gastric emptying studies measure the rate of removal of radiolabeled liquids and solids from the stomach. These types of studies generally permit the evaluation of gastric physiology as a result of their noninvasive nature. Generally speaking, liquids clear faster than solids (2).

Gastric emptying studies are relatively simple to perform, but in order to achieve accurate quantitation, there are several aspects of this type of imaging procedure that must be considered at all times, such as 1) the radionuclide markers used must have a high labeling efficiency and remain stable in vivo during the entire course of patient testing, 2) the meal size and composition should be standardized, 3) patient position and posture should remain constant during the entire course of testing, and should also be standardized in order to facilitate the comparison of acquired information between patients, and 4) correction techniques should be applied (whenever needed) in order to compensate for radiopharmaceutical decay, potential photon interferences which may occur when more than one type of radiolabeled compound is used in the study, geometry changes, septal penetration and scatter from high energy gamma rays (2).

After food passes through the esophagus and lower esophageal sphincter, it arrives at the stomach where it is mixed with various gastric secretions. The stomach consists of two major parts in terms of its motor function; the proximal receptacle (which includes the fundus and body), and the distal portion with the antrum and pylorus (104). Regular, slow contractions of the fundus and peristaltic waves in the body propel the food toward the antrum, where weaker waves fade, but stronger ones result in contractions of the antrum and coordinated duodenal muscle activity (105). The pylorus, being a major component of duodenal gastric resistance, may be the principal antireflux control device in man. Therefore, it can be stated that it is the fundus that controls the emptying rates of liquids, whereas the role of the antrum is to help control solid emptying (although antral contractions, triggered by the presence of solid material, may also play a role in the emptying of liquids) (105).

Gastric emptying of liquids is also dependent upon the gastroduodenal pressure gradient. However, because the fundus of the stomach is able to relax in response to an increased volume, there is not a direct relationship between increased gastric volume and the rate of gastric emptying (although an indirect relationship has been demonstrated) (106).

The control of gastric emptying is multifactorial in that it is influenced by the pH, osmolarity, volume, chemical composition and size of the meal (see Table 5) (3). For example, large meals empty slower than smaller ones, and meals high in carbohydrate empty faster than those primarily made of protein or of fat. Fat, in fact, empties slower than either carbohydrate or protein (3). Water taken with meals will have an effect on volume and osmotic pressure, but has no other effect on the rate of gastric emptying per se. The osmotic pressure of gastric contents emptied into the duodenum will affect the rate of emptying via the enterogastric

reflex, where fluids of higher osmotic pressure tend to empty more slowly, but overall this process is much more complicated (3). The pH of the gastric contents can influence the rate of emptying as an indirect function of the neutralizing ability of the duodenum. In general, the more acidic the contents, the slower the rate of emptying (3). Gastric emptying can also be influenced by patient position and by the presence of certain drugs.

In addition to the characteristics of the meal itself, electrical activity also controls gastric emptying and appears to be mediated by both autonomic and higher neural activity (107,108), as well as by hormones such as enterogastrone, gastrin, cholecystokinin (CCK), and secretin which may affect gastric motility on either a physiological or pharmacological basis (see Table 5). Gastrin, CCK, and secretin delay gastric emptying, although gastrin and CCK increase antral activity, whereas secretin decreases antral activity while increasing pyloric pressure (108). Glucagon is able to inhibit gastric motility, but only at pharmacological doses (104).

Table 5. Factors Which Can Affect Gastric Emptying Rates in Patients

<u>Accelerate Emptying</u>	<u>Delay Emptying</u>
Alcohol	Acidity (0.1 N HCl)
Duodenal ulcer	Amyloidosis
Exogenous hormones	Atrophic gastritis
-somatostatin	Cigarette smoking
Hyperthyroidism	Diabetes mellitus
Liquids	Electrolyte imbalance
Obesity	Exogenous hormones
Pharmacologic agents	-cholecystokinin
-alcohol	-gastrin
-beta adrenergic antagonist	-glucagon
-cholinergic agonists	-insulin
-dopaminergic antagonists	-motilin
(metoclopramide, domperidone)	-secretin
-nicotine	Fat (olive oil, sodium oleate)
-salicylates	Gastric ulcers
Postsurgical (hemigastrectomy, pyloroplasty, etc.)	Hypothyroidism
Small food particle size/volume	Intra-abdominal inflammation
Zollinger-Ellison syndrome	Meal Composition
	-increased acidity
	-increased caloric content
	-increased fatty acid chains
	-increased osmolality
	-increased food particle size/volume
	Myotonic dystrophy
	Nausea of any kind
	Pharmacologic agents
	-beta adrenergic agonists
	-cholinergic antagonists
	-dopamine
	-dopaminergic agonists
	-epinephrine
	-hypertonic amino acid soln.
	-hypertonic glucose solutions
	-metoclopramide
	Position change (supine to erect)
	Progressive systemic sclerosis
	Pyloric stenosis or ulcer
	Solids (large food particles/volume)
	Stomach cancer
	Trauma
	Tumor (i.e., brain)

The mechanisms that are involved in gastric emptying of solids are still not fully understood or recognized. However,

there appears to be at least three interacting processes that can be described: the grinding pressure waves of the distal antrum; the discriminatory mechanisms of the pylorus; and the propulsive forces of the fundus, each of which pushes fluids and small suspended solid particles into the duodenum. The pylorus serves to prevent reflux of duodenal contents and restrict the rate of gastric emptying of solids and other particulate matter, whereas the liquid portion of a meal would empty more rapidly. While the antral activity propels the solid food toward the pylorus, the pyloro-duodenal contractions retro-pulse solids back to the fundus, presumably because the fundus is closed (or nearly so), permitting the passage of liquids and very small particulate matter. This coordination of antral and pyloric function probably limits postprandial emptying of solids to very small particles, but allows the passage of larger inert substances during the interdigestive phase (104).

Abnormal rates of gastric emptying are associated with several gastrointestinal disorders (see Table 5). Too rapid emptying may play a role in duodenal ulcers and is a frequent complication of gastrectomy and postgastrectomy reconstruction procedures, which can be manifested by the presence of the "dumping syndrome" (16). Slow emptying is associated with gastric ulcers, pyloric stenosis, vagotomy, diabetes, various malignancies, atrophic gastritis, and following surgery (16). Gastric stasis may occur after surgery characterized by the patient complaining of epigastric fullness and vomiting. In all of these conditions, information about the rate of gastric emptying is of value, such that it may not alter the clinical diagnosis, but can be of significant help in deciding the correct course of therapy. However, changes observed in gastric emptying following surgery can only be generalizations (at best), and the overall value of the technique itself lies in the assessment of the individual patient, particularly in relation to his/her own symptoms (109). For example, following vagotomy and pyloroplasty, the rate of emptying of the liquid component of the meal tends to be changed very little by the surgery, except in those who experience the dumping syndrome or diarrhea, where the early rate of emptying can be much faster than that seen prior to the surgery (109,110). In most patients, solid meals tend to empty slower following surgery, particularly in the early post-operative period with a gradual return to pre-operative emptying times after some several weeks or months of recovery (111).

Several nonradionuclide tests for measuring gastric emptying time have been proposed over the years (see Table 6). The one most commonly used by gastroenterologists is the saline load test (an intubation test), in which the patient is given 500 ml to 700 ml of saline solution through a nasogastric tube. Thirty minutes later, the gastric contents are aspirated, and the retained volume measured (16). In this manner, only the emptying rate of liquid meals can be assessed, and repeated testing over a number of days is often required in order to acquire enough data points in order to adequately plot the pattern of emptying. This process can be very time consuming and highly uncomfortable to patients, but it is most reliable and reproducible (3). Radiologic techniques employing barium are relatively insensitive to subtle motor disturbances of the stomach, and are associated with a

significant radiation burden to the patient. Generally speaking, there are three types of radiographic tests employing the use of barium: barium liquid, barium enteric coated granules, and the "barium burger" (114). In general, such techniques only estimate the total emptying time (not very quantifiable), and the measurements are crude and open to wide error. Barium liquid is unphysiologic since the barium itself may precipitate out and irritate the gastric mucosa (114). Barium enteric coated granules were developed in order to overcome the problem of gastric irritation seen with barium liquid, but they rely upon complete gastric emptying to occur, otherwise the test results cannot be accurately quantitated (115).

Table 6. Methods for Measuring Gastric Emptying

- 1) Intubation methods
 - Multilumen tube perfusion and aspiration
 - Saline load test
 - Serial intubation and aspiration
- 2) Radiologic methods
 - Barium burger
 - Barium enteric coated granules
 - Barium (liquid) studies
- 3) Radionuclide methods
 - Single isotope, single phase
 - Dual isotope, solid-liquid phase

(adapted from Malmud LS¹⁰⁴)

Many radionuclide methods have been described, and these are usually favored because they are quantitative, noninvasive, reproducible and require the use of equipment that is readily available in almost all instances. Radionuclide tests for gastric emptying were first introduced in 1966 by Griffith et al. (using a Cr-51 labeled porridge and an external probe for quantitation) (116), and the approaches taken provided for great flexibility and allowed for the assessment of more than one component of the meal, namely both liquids and solids (112). Many different radiolabeling techniques of various test meals, as well as methods for quantitation using various pieces of counting equipment (i.e., simple probes, rectilinear scanners, dual scanner, gamma camera, etc.) have been described, and at present there is no clear consensus of agreement among investigators as to a "standardized" meal, study methodology or interpretation of test results. However, some aspects involving radionuclide methods of gastric emptying determination seem to be universally agreed upon. For example, it is clear that the test meal itself can be either liquid, semisolid or both. Gastric emptying of liquids and solids represent separate physiologic functions in that, in normals, it is clear that liquids empty faster than solids, and liquid emptying tends to be exponential while solid emptying tends to be linear. But the rates vary with the different radionuclides that have been used, probably as a result of varying affinity of the different labels for the meal itself (113). Whatever labels are used, it is important to ensure that there

is no transfer of the label itself from the liquid to the solid component of the meal, and vice versa, either as a result of inadequate labelling or digestion (113).

Results obtained from gastric emptying studies are usually expressed as gastric emptying half-time (or gastric half-emptying time) (T1/2), that is the amount of time needed for the volume of the meal remaining in the stomach to empty by one half of the total amount. Use of such values are, in themselves, not truly satisfactory since the emptying curve cannot be adequately described by a single exponential given the many multifactorial aspects which come into play in determining the emptying of a meal (both liquid and solid components) from beginning to end. Nevertheless, investigators have found the use of the T1/2 value convenient and simple, and most feel that the advantages of reporting data in this fashion outweigh the disadvantages (104).

Radiolabeled Meals and Imaging Techniques

The major limitation in many radionuclide approaches to studying gastric emptying lies in the fact that there can be dissociation of the radionuclides employed from the food with which they were administered, giving results that would overestimate the rate of gastric emptying. In general, the characteristics for what would constitute the ideal radiopharmaceutical meal for use in studies of the gastrointestinal tract are as follows (117):

- 1) It should be nonabsorbable and nonadsorbable.
- 2) It should not interfere with the osmolality of the intestinal contents.
- 3) It should be nontoxic and inert.
- 4) It should be homogeneously mixed with the digesta and should have a particle size comparable to that of the solid phase digesta.
- 5) It should bind the radionuclide irreversibly.
- 6) It should not expose the patient to a high radiation dose.
- 7) It should have radiation characteristics similar to those of Tc-99m.
- 8) It should be easily prepared and economical.

Two types of radionuclide markers are used for gastric emptying studies, liquid markers and solid markers. Liquid markers are soluble radiopharmaceuticals that are miscible with aqueous liquids and will trace movement of liquids from the stomach (2). Commonly used liquid markers, those that are both stable and nonabsorbable, include DTPA labeled with Tc-99m, In-111 or In-113m, as well as Tc-99m sulfur colloid. Tc-99m pertechnetate is not used because it is secreted by the mucous cells of the gastric glands (2). Solid food markers are radionuclides bound to a solid food such as chicken liver, scrambled eggs, or oatmeal, to name a few.

The problem of radionuclide dissociation was overcome in 1976 by Meyer et al. when they administered Tc-99m sulfur colloid to live chickens, slaughtered the chickens, harvested their livers and fed the intrinsically-labeled cooked chicken

livers to patients (118). Since that time, recommendations from many investigators have led to the development of a variety of dual-label techniques (16,104), proposing the use of Cr-51 sodium chromate, I-131 HSA, Tc-99m sulfur colloid, Tc-99m DTPA, Tc-99m tin colloid, Tc-99m polystyrene resin, In-111 DTPA, and Cs-129 as radionuclide sources. Emptying time of the liquid and solid phases of a meal can then be determined simultaneously by labeling each phase with distinctly different radionuclides, e.g., labeling one phase with Tc-99m and the other with In-111. As noted previously, the liquid phase of a mixed meal tends to empty in an exponential fashion, whereas, because it takes time for the solid phase of a mixed meal to be reduced in size in order to be emptied by the pylorus (needing approximately 20-30 minutes to reduce food particles down to 2 millimeters in size), the solid phase of the mixed meal empties in a linear fashion (119).

At the present time, there is no consensus among nuclear medicine physicians (or gastroenterologists) regarding what constitutes an optimal meal and testing methodology for routine clinical gastric emptying studies. Several different types of radiolabeled meals can be prepared and administered to patients, designed to facilitate not only gastric emptying studies, but studies involving the rest of the gastrointestinal tract including gastroesophageal reflux studies. Table 7 lists a representative sample of some of the many different types of radiolabeled meals that have been described in the literature. Additionally, there are several different pharmacologic agents that have been shown to either accelerate or delay the rate of gastric emptying in patients. Some of these drug agents are listed in Table 8, though additional discussion of this topic is forthcoming in this article.

One of the most elegant approaches to preparing a radiolabeled meal for use in gastric emptying studies was described by Meyer et al. (118) and Fisher et al. (120) in which 1 mCi of sterile, pyrogen free Tc-99m sulfur colloid was injected into the wing vein of a live chicken. After one hour, the chicken was sacrificed and the liver removed. The liver was placed into a water bath and agitated for 5 minutes in order to remove any radionuclide on the surface, then it was wrapped in aluminum foil and cooked in a pre-heated boiler for 20 minutes at 350°F. After cooking, the liver was removed and diced up into 0.5 cm cubes and then added to an unlabeled meal, such as an 8 oz can of chicken stew. This is truly an intracellular label of a physiologic solid marker.

More commonly, the solid marker used for gastric emptying studies that has received much attention is Tc-99m sulfur colloid added to eggs which are then scrambled and cooked to a firm consistency and eaten with other components of a mixed meal such as bread or meat of some kind. Other investigators prefer to use Tc-99m sulfur colloid labeled liver (in which the radiopharmaceutical is injected into the center of commercially prepared chunks of liver meat, either chicken or beef in origin) or pate (121). The liquid component of a mixed meal is usually 125-250 uCi of In-111 DTPA in approximately 120-200 ml of water or milk (122). An alternative marker of liquid and solid emptying could be the use of 500 uCi Tc-99m sulfur colloid in 60 gm of Egg Beaters® cooked to a firm consistency, 30 gm of Canadian bacon, a slice of white bread with 5 gm of margarine and 20

gm of grape jelly; and the liquid component of the mixed meal containing 250 uCi In-111 DTPA in 60 gm of Ensure and 60 gm of skim milk (103). This meal yields a composition of 57% carbohydrates, 25% protein and 18% fat with 293 calories (103). These markers are selected because they are easy to prepare, they do not break down in the stomach, and they maintain their relationship to their appropriate phase (123).

Table 7. Examples of Single and Multiple Radionuclide Gastric Emptying Test Meals

<u>Single radiotracer</u>	<u>Meal component(s)</u>
Chromium-51 chloride	Milk, soluble protein, sugar
Chromium-51 sodium chromate	Eggs, oatmeal
Chromium-51 sodium chromate	Cornflakes, milk, eggs
Indium-111 DTPA	Orange juice
Indium-113m chloride	Instant breakfast
Indium-113m DTPA	Cornflakes, milk, sugar
Indium-113m DTPA	Orange juice
Indium-113m DTPA	Instant mashed potatoes
Iodine-131 sodium iodide	Cellulose fiber
Iodine-131 triolein	Milk and cream mixture
Technetium-99m albumin colloid	Instant Oatmeal (unflavored)
Technetium-99m chelex resin	Oatmeal
Technetium-99m DTPA	Kool Aid
Technetium-99m DTPA	Cornflakes, milk
Technetium-99m DTPA	Bread
Technetium-99m FeOH	Potatoes
Technetium-99m FeAscorbate-DTPA	Instant breakfast, milk, powdered eggs, water
Technetium-99m ovalbumin	Eggs
Technetium-99m triethylenetetramine	Polystyrene beads
Technetium-99m triethylenetetramine	Oatmeal
Technetium-99m sulfur colloid	Pate
Technetium-99m sulfur colloid	Beef stew, chicken liver
Technetium-99m sulfur colloid	Instant mashed potatoes
Technetium-99m sulfur colloid	Beef stew
Technetium-99m sulfur colloid	Chicken liver
Technetium-99m sulfur colloid	Cornflakes
Technetium-99m sulfur colloid	Orange juice
Technetium-99m sulfur colloid	Scrambled eggs
Technetium-99m tin colloid	Cream
<u>Multiple Radiotracers</u>	<u>Meal Component(s)</u>
Chromium-51, Cobalt-57 and Technetium-99m pertechnetate	Floating capsules, or sinking capsules and water
Indium-111 DTPA, Tc-99m sulfur colloid	Cooked liver, pizza, Kool Aid
Indium-111 DTPA, Tc-99m sulfur colloid	Cooked liver, beef stew, Kool Aid
Indium-111 DTPA, Tc-99m sulfur colloid	Milk, cornflakes
Indium-111 DTPA, Tc-99m sulfur colloid	Chicken livers, water
Indium-111 DTPA, Tc-99m sulfur colloid	Chicken liver chunks
Indium-113m DTPA, Tc-99m sulfur colloid	Milk, cornflakes
Indium-113m DTPA, Tc-99m sulfur colloid	Milk, Readybrek

Using a mixed meal approach in gastric emptying studies seems to have gained much favor over the years, but some technical considerations from an imaging standpoint are equally important to remember. After administering the radiolabeled meal to the patient, the subject should be placed supine under a dual window, large field of view gamma camera with a parallel hole, medium energy collimator. Studies can also be done with the patient in a reclining or upright position; regardless of the patient position used, this

aspect of the study should be standardized. The technetium window should be set for 140 keV with a 10 keV window. The indium window is set to 171 keV also with a 10 keV window. Imaging is begun as soon as the patient completes the mixed solid-liquid meal. Images should be obtained for 60 seconds at 15 minutes intervals for a period up to 3 hours. During the 14 minute period between images, the patient can be permitted to sit upright. Imaging involving each radionuclide is done separately. If the Tc-99m/In-111 activity ratio is 6:1 or greater, down scatter of In-111 counts into the Tc-99m window is minimized, in which case down scatter correction may not be necessary. Otherwise, data processing including a correction factor for In-111 Compton scatter into the Tc-99m window (approximately 23%), as well as Tc-99m scatter into the In-111 window (approximately 8%) is necessary. Depth and attenuation corrections may not be significant in most slender to normal-sized patients (though half-emptying times may occasionally be seriously overestimated without the use of such corrections).

Table 8. Drugs That May Affect the Rate of Gastric Emptying (GE)

<u>Accelerates GE</u>	<u>Possible Mechanism of Effect</u>
Bethanecol	Parasympathetic stimulation
Domperidone	Dopamine antagonism
Ethanol	Possible calorigenic effect and/or osmoreceptor insensitivity
Metoclopramide	Parasympathetic stimulation and/or dopamine antagonism
Propranolol	Sympathetic antagonism
<u>Prolongs GE</u>	<u>Possible Mechanism of Effect</u>
<u>Antacids</u>	Possible effect on calcium fluxes in GI smooth muscle
Atropine sulfate	Parasympathetic antagonism
Caerulein	Not known.
Chloroquine	Possible direct anesthesia effect on gastric smooth muscle
Desmethylimpramine	Parasympathetic antagonism
Ethanol	Possible calorigenic effect and/or osmoreceptor insensitivity
Hexamethonium	Ganglionic blockade
Isoprenaline	Sympathetic effect
Librax	Not known.
Methylatropine nitrate	Parasympathetic antagonism
Morphine and narcotic analgesics	Action upon cholinergic, tryptaminergic and enkephalinergic GI receptors
Phenytoin	Not known.
Proprantheline	Parasympathetic antagonism
Salbutamol	Sympathomimetic effect
Trihexylphenidyl	Parasympathetic antagonism

In normal subjects, when the amount of remaining radionuclide activity is plotted as a function of time, the liquid component of a mixed meal empties more rapidly from the stomach than does the solid component (35). Thus, liquid emptying approximates a monoexponential curve, whereas, the

solids empty in a zero-order fashion (or straight line) (35). However, when the data representing gastric emptying of the components of a mixed meal are expressed semilogarithmically, as a function of time, a different pattern of emptying for the liquid and solid fractions is seen. Liquids empty in a monoexponential fashion and solids empty in a biphasic fashion (35). The solid part of the meal appears to go through an active digestive phase, in which large food particles are reduced in size via normal processes until the liquids and solids are blended and then proceed to empty at a similar rate (124). Some investigators have suggested that it may be necessary to label only liquids, or only solids, in order to accurately quantitate the rate of gastric emptying (125,126).

Recently, other alternate approaches to gastric emptying have been described. Although Pitman et al. (127) described the in vitro instability of Tc-99m albumin colloid in simulated gastric juice, and suggested that this radiopharmaceutical could not be used for gastric emptying studies, other investigators have found this not to be so. Harwood et al. (128) described satisfactory outcomes when 0.5-1.0 mCi of Tc-99m albumin colloid was placed into 70 ml of tap water and then added to a 1.5 oz package of Quaker Instant Oatmeal (regular flavor). No activity above normal soft tissue background was identified in any of the patients they studied. There was no detectable activity in the bladder in the early images, and less than 2% on images taken at 24 hours post-ingestion of the radiolabeled meal. Blood and urine samples collected over a 24 hour period contained less than 0.1% and 1.0% of the total dose, respectively. Activity observed in the bladder at 24 hours into the study was thought to be due to underlying activity emanating from the sigmoid colon. Though chemical or physical analysis of the material present within the gastrointestinal tract was not performed, the most logical breakdown product would have been increased amounts of free Tc-99m pertechnetate (which, following oral administration is rapidly absorbed from the GI tract and reaches blood levels of 50% of that seen when the radionuclide is otherwise given intravenously). However, no increases in activity levels were noted in the blood, urine or thyroid gland analyses.

Taillefer et al. (100) also compared the performance of Tc-99m sulfur colloid- and Tc-99m albumin colloid-labeled scrambled eggs in 20 healthy volunteers. In vitro studies were performed to evaluate the labeling efficiency and stability in hydrochloric acid and in human gastric juice of intracellularly-labeled chicken liver and scrambled eggs labeled with Tc-99m sulfur colloid (SC) or Tc-99m albumin colloid (AC). When stability in hydrochloric acid was examined, there was no significant differences between either of the two radiopharmaceutical preparations in terms of meal labeling efficiency (chicken liver: 98% ± 1% for Tc-99m SC and 96% ± 2% for Tc-99m AC; scrambled eggs: 92% ± 2% for Tc-99m SC and 91% ± 3% for Tc-99m AC). When analysis was done in human gastric juice the overall stability was lower for both chicken liver (97% ± 2% for Tc-99m SC and 94% ± 3% for Tc-99m AC) and scrambled eggs (88% ± 2% for Tc-99m SC and 85% ± 4% for Tc-99m AC). Gastric emptying curves from both meals were also similar, with a mean half-emptying time of 85 ± 13 minutes and 87 ± 16 minutes for the meals containing Tc-99m sulfur colloid and

Tc-99m albumin colloid respectively.

Gastric emptying studies using radiolabeled liquids and solids are subject to relatively large inter-individual and intra-individual variability on different study days. While the imaging method itself remains an important factor, normal day-to-day variation must be taken into account when interpreting individual study results. Brophy et al. (129) have examined this question in healthy volunteers who were tested repeatedly over a period of 4 days using a standard 300 gm meal (Tc-99m sulfur colloid in pate as the solid-phase marker, and In-111 DTPA in orange juice as the liquid-phase marker). The mean half-emptying time for solid food was 58 minutes and the mean liquid half-emptying time was 24 minutes. There was moderate intrasubject variability for solid emptying and high variability for liquid emptying.

Mean half-emptying times can vary significantly depending on the type of radiolabeled meal that is being utilized. For example, some investigators (130,131) have reported normal half-emptying times of 37 ± 5 minutes for Tc-99m DTPA in cornflakes and milk and 12 minutes for Tc-99m sulfur colloid in saline. A meal of instant breakfast and powdered eggs resulted in a mean half-emptying time of 55 ± 15 minutes, and the use of Tc-99m DTPA in saline gave a half-emptying time of 12 ± 3 minutes (16). With yet another meal (described previously), the normal value for the liquid T1/2 is 43 minutes (ranging from 33 to 75 minutes) and, for the solid T1/2, 129 minutes (ranging from 71 to 190 minutes) (103).

Non-Drug Related Factors Affecting Gastric Emptying

As noted in the early portions of this discussion on gastric emptying, there are a number of factors that can have an affect on the outcome of testing by either accelerating or delaying the rate of emptying.

For example, dietary fat, although insoluble in water, is digested within the aqueous environment of the GI tract. While it is not generally understood how the stomach processes fat, it is known that fatty acids slow gastric emptying and that the mechanism for this may involve stimulation of duodenal receptors and jejunal receptors that are sensitive to the hydrolytic products of triglycerides. After a fatty meal, a braking effect on gastric emptying could retard selectively the exit of fat or, alternatively, delay the emptying of all constituents of a mixed meal equally (132). Recent studies suggest that a small proportion of extracellular fat layers on top of gastric contents, and that the majority is either stabilized in an aqueous emulsion or adheres to solid food particles as they empty from the stomach (133-135). This layering of an oil phase above water, and the effect of gravity and bodily position, have been proposed as being crucial to relative gastric retention of lipids (136). At the present time, there is no satisfactory radionuclide (or alternative) technique for measuring gastric emptying of fat, although Cunningham et al. (137) have reported some very promising results using Tc-99m(V)-thiocyanate in measuring the gastric emptying of extracellular fat. Using a low-nutrient soup labeled with In-113m DTPA and mixed with Tc-99m(V)-thiocyanate labeled oil, they noticed in six human volunteers that the oil emptied much more slowly (mean T1/2 = 198 minutes) than the aqueous component (mean T1/2 = 30 minutes) (137). Similar

results have been reported by Cortot et al. (134). It appears that the emptying of dietary fat will be slowed relative to water if two conditions are met: 1) the ingested fat must be capable of being hydrolyzed, explainable on the basis that fatty acids, and not triglycerides, stimulate duodenal receptors that inhibit motility (138,139), and 2) the fat must be ingested in a physical form that allows it to dissociate from water in the stomach because fat is not capable of inhibiting its own emptying under certain conditions, such as when mixed with water (since an emulsified mixture of fat and water will leave the stomach faster than fat alone, but slower than water alone (134,138,139)). Whether the inhibitory effect of fat on gastric emptying is humoral or neural is not well understood. Recent studies by Kroop et al. (140) have shown that fat inhibits solid emptying in both normals and patients with truncal vagotomy, antrectomy and gastrojejunostomy. In Billroth II patients, the inhibitory effect of fat overcomes an early washout effect from water, thus the finding suggests that a nonvagal-mediated mechanism, independent of antral-pyloric function, exists for control of gastric emptying of solids in these patients, and perhaps in normal subjects as well (140).

Tothill et al. (141) found that gastric emptying times tend to be overestimated if serial counts are taken from the anterior position alone. Passage of the labeled meal from the fundus to the pylorus proceeds in a postero-anterior direction with decreasing attenuation seen in anterior detection. They found that greater accuracy is achieved by using smaller meals, which are less subject to this sort of error, as well as by taking the geometric mean of the anterior and posterior counts. Additionally, it was their opinion that high energy gamma-emitting nuclides such as In-111 are less subject to measurement errors because their detection is less influenced by changing attenuation as the meal passes through the stomach.

The gold standard for addressing problems associated with tissue attenuation for gastric emptying is the geometric mean of the bolus counts from the anterior and posterior views. Geometric-mean correction of gastric radioactivity can be used to correct for the distribution, depth, and attenuation of the radionuclide (142).

Other investigators also report that an overestimation of the half-emptying times is possible using only anterior data (143). The largest variations between anterior and geometric-mean data for determining gastric half-emptying times seems to occur with use of the large meals and, as expected, the lower energy-emitting radionuclides.

Obtaining both anterior and posterior images of the stomach and proximal lower GI tract, especially in institutions without a dual-headed camera, relying on drawn regions of interest and calculating gastric movement can be a long a tedious task. Because of this, many nuclear medicine departments seem to acquire only a single anterior view, even though this approach overestimates the half-emptying time by an average of 15% (144). To avoid this problem, other investigators have reported that a single projection, either a depth-corrected anterior view (143), left lateral view (144), or the left anterior oblique (LAO) view (145,146) can be used to

compensate for tissue attenuation, thus allowing for a more accurate gastric emptying time calculation (the LAO view being touted as the one that more closely approximates gastric motility involving a solid meal in a patient with normal gastric anatomy).

There are few studies of age-related changes in gastric motility and emptying; the remarks that do appear are not well documented and imply that emptying slows with age. Moore et al. (147) describe a dual-isotope method to study the rate of gastric emptying of a standardized meal (900 gm with a liquid marker of In-111 DTPA and a solid marker of Tc-99m tagged liver) in two groups of male subjects, the average age in the first group being 31 years, and that of the second group being 76.4 years. They found that there was no significant differences in solid food emptying rates between the two age groups, but that a delay in liquid emptying was observed in the older age group.

Several investigators have looked at how varying meal weight and composition affected gastric emptying rates. Moore et al. (148) studied the effect of meal size on gastric emptying of Tc-99m sulfur colloid-labeled chicken liver and In-111 DTPA simultaneously as solid-phase and liquid-phase markers, respectively. Data analysis was done using the geometric mean compared to anteriorly-obtained data only. The average half-emptying times for solid food from meals weighing 300-, 900-, and 1692-grams was 77, 146, and 277 minutes for the geometric-mean data and 85, 196, and 329 minutes respectively for the anterior data. With the liquid phase of the same test meal weights, average half-emptying times were 38, 90 and 178 minutes for the geometric-mean data and 41, 86, and 205 minutes respectively for the data processed from only the anterior projection. Using a 185 gm meal, Heading et al. (149) report a solid-phase marker T_{1/2} of 120 minutes. Meyer et al. (118) found a solid-phase T_{1/2} of 170 minutes and 80 minutes for meals of 850 gm and 425 gm respectively. MacGregor et al. (150) found a solid-phase T_{1/2} of 107 minutes for a meal weighing 425 gm. Thus, it appears that the longer half-emptying times are associated with meals of a larger total weight. But meal weight is but one of several variables that may have an influence on gastric emptying. It is probable that meals of the same weight, yet different compositions, will empty at different rates.

This observation has been borne out by published reports that have shown that gastric emptying of liquid meals (ml/min) in man were slowed with increasing caloric density (kcal/g). Hunt and Stubbs (151) demonstrated that meals of equicaloric concentrations of lipid only, carbohydrate only, or protein only produced equal slowing of gastric emptying rates. The pattern of liquid emptying appeared to be dependent on its nutrient content. Nonnutrient saline meals emptied rapidly with exponential (first-order) kinetics while nutrient meals, after an initial period of emptying that loaded the duodenum, emptied in a more linear (zero-order) manner, with the degree of slowing being directly related to meal caloric density (total meal kcal/total meal weight or volume)(151). Moore et al. (152), in considering both meal weight and caloric content, sought to determine how both of these variables affected the emptying of liquids and solid meals taken together. They fed healthy subjects meals that consisted of lettuce and water (50,

300 and 900 gm in weight), adjusted to either 68, 208 or 633 kcal, respectively, with added salad oil. The conclusions that they drew from this study were that: 1) absolute emptying rates (grams of solid food emptied from the stomach per minute) increased directly and significantly with meal weight, 2) increasing meal total caloric content significantly slowed solid food gastric emptying, but did not overcome the enhancing effect of meal weight, and 3) liquid emptying rates were uninfluenced by meal total kcal amount. It was not possible, however, to determine whether the slowing was due to incoming meal weight, total caloric content, caloric density, or to varying proportions of lipid, carbohydrates, and proteins.

Hyperosmolar glucose solutions have been noted to slow gastric emptying in man (153,154), however, extent of slowing due to this variable has not been well established in the literature using scintigraphic approaches. Phillips et al. (155) performed a total of 12 gastric emptying studies on normal subjects using a hyperosmolar glucose solution (400 kcal) commonly used for diagnosing diabetes, and a more dilute 200 kcal glucose solution. The gastric half-emptying times of both glucose solutions were greatly prolonged compared to the 8-12 minute half-emptying time reported for gastric emptying of saline (156): 107 minutes for the 400 kcal glucose solution and 66 minutes for the more dilute 200 kcal solution. Although the 200 kcal solution contained only one-half of the amount of glucose (50 gm) as compared to the 400 kcal solution (100 gm), the blood glucose values obtained during a 2-hour period were only slightly lower with the 200 kcal solution (155). The half-emptying times for both glucose solutions were, as previously stated, greatly prolonged. Prior to the study by Phillips et al., other investigators had shown that elevated blood glucose values could be associated with delayed gastric emptying. For example, Groop et al. (157) demonstrated that delays in gastric emptying in normal volunteers could be due to the intravenous glucose solutions that they received. Aylett (158) observed delayed gastric emptying associated with elevated blood glucose levels. Both of these investigators had postulated that the prolongation in gastric emptying noted for solid foods may be related to the number of calories in the solid food or to the elevation of blood glucose secondary to the ingestion of the solid food itself.

Velchik et al. (159) also studied the effects of calories on gastric emptying. They looked at three different solid meals containing 150 kcal, 300 kcal, and 600 kcal; each was composed of 40% carbohydrate, 40% protein, and 20% fat. They found a significant inverse relationship between the number of calories in a meal and the rate of gastric emptying. It is interesting to note that the liquid 400 kcal glucose solution used in the study by Phillips et al. (155) had a longer gastric half-emptying time than did the 600 kcal solid meal used by Velchik et al. (159). There may be some relation between the meal types in these two studies relative to the high elevation of blood glucose with the use of oral glucose solutions. It is a well known fact that a mixed meal does not increase the blood glucose as much as an oral glucose solution (160).

Dubois et al. (161) studied the effects of total body gamma irradiation on gastric emptying in dogs and primates, as well as the effects of certain drugs used to ameliorate the nausea and

vomiting that often occurs following gamma irradiation. They noticed that, in dogs, gastric emptying was suppressed for at least 3 hours following exposure to 8 Gy Cobalt-60, and that pretreatment with domperidone could prevent post-irradiation vomiting in these animals without improving gastric emptying. In the primate model, the investigators found that total-body gamma irradiation abolishes gastric emptying, and will produce vomiting. However, unlike the effects seen in the dog, domperidone did not prevent radiation-induced vomiting, and still did not improve the delay seen in gastric emptying. On the other hand, administration of metoclopramide did prevent vomiting and did cause an improvement in gastric emptying of water, but abolishment of gastric emptying of a mixed liquid-solid meal remained.

Variations in acidity, osmolarity and fat content of stomach contents inhibit gastric emptying to varying degrees by neurohumoral means (201). Fat has no inhibitory effect in patients with pancreatic insufficiency, which implies that the products of fat digestion, rather than triglyceride, are important in affecting gastric emptying in patients (201).

Drugs Which Modify Gastric Emptying

In having made reference above to the effects of metoclopramide on gastric emptying, it is important to emphasize that many different drugs have been found to alter the rate of gastric emptying, some of which are listed in Table 8. Not all of the drugs agents that can be noted have a detrimental effect on gastric emptying rates; many examples cited carry an interventional aspect with them. For example, Lamki and Sullivan (162) have studied the effects of the powerful, nonselective and short-acting opiate agonist etorphine and the opiate antagonist naloxone on gastric motility. Etorphine delayed gastric emptying (when administered in a dose equivalent to 5 mg of morphine), while naloxone had no effect. This raises the prospect that several subtypes of central and peripheral opiate receptors might be involved in gastric secretory/emptying. When the two drugs were given in combination, the inhibitory effect of etorphine on gastric emptying was incompletely prevented, while the central subjective effects (gastric acid secretion and motility, and etorphine distress symptoms) were completely abolished. These results indicate that while there are receptors (μ) that are important in terms of regulating gastric secretion/emptying, there are other receptors (non- μ , such as κ , σ , δ and ϵ) that also come into play. In this case, radionuclide techniques were useful in studying physiological effects of drugs on the GI tract.

Many of the pharmacologic agents used in the treatment of gastric stasis operate via a cholinergic and/or anti-adrenergic (or anti-dopaminergic) mechanism. It is not clear whether impaired stomach emptying results primarily from a deficiency of cholinergic stimulation or rather from other inhibitory influences (i.e., inhibitory and excitatory effects on the stomach from parasympathetic nerves, or inhibition of emptying by the absence of vagal stimulation due to an absence of sympathetic discharge) (163,164).

In a study by Dubois et al. (165), the cholinergic drug bethanecol was shown to increase stomach motility when used in the acute treatment of gastroparetic disease. However, the

emptying rates measured after bethanecol administration were still below normal (control) values. Atropine, being anticholinergic in nature, delays gastric emptying (166). This same property is also seen in other drugs with anticholinergic activity such as propantheline, trihexylphenidyl, methyl atropine nitrate, and desmethyimpipramine (167-169).

There are a number of drugs which inhibit gastric emptying. Rees et al. (170) have investigated the influence of beta adrenergic agonists and antagonists. Salbutamol and isoprenaline delay gastric emptying. Propranolol increases stomach motility and, when administered prior to isoprenaline, will prevent gastric stasis. It is possible that beta-adrenoreceptor drugs affect emptying partly by altering gastrin levels. However, the effect of gastrin on the regulation of stomach emptying has been questioned by Cooke (171), who states that there is little evidence that gastrin plays any role in this process.

The action of metoclopramide on gastric motor function has been examined by many investigators. The drug has been shown to promote the emptying of stomach contents into the small bowel. The effect is only seen in gastroparetic disease, as no acceleration in emptying rates have been observed when the drug was administered to normal subjects. Metoclopramide promotes gastric emptying by increasing the tone and amplitude of gastric contractions, relaxing the pyloric sphincter and duodenal bulb, and increasing peristalsis of the duodenum and jejunum. Pharmacologically, metoclopramide is a cholinergic agonist. It may stimulate local acetylcholine release and/or sensitize the stomach smooth muscles to parasympathetic influence (172). However, metoclopramide appears to have sympathetic activity also. It can stimulate gastric activity independently of vagal innervation, and it is postulated to be a dopamine antagonist (173,174). This possible bi-mechanistic effect of metoclopramide on gastric emptying may serve to explain why some clinicians have reported a wide range of variable response in the use of this drug in patients.

Gastric emptying studies have been very useful in monitoring therapy with metoclopramide. To determine organic or functional pyloric obstruction in patients with suspected gastric retention, Shih et al. (197) studied the use of the drug in patients who, after a 12 hour fast, were given 150 μ Ci of Tc-99m labeled TETA resin in cereal while in a sitting position. In most of their patients suffering from prolonged gastric emptying (including patients with diabetes mellitus, gastritis, postsubtotal gastrectomy, and short bowel syndrome), there was a good response (acceleration of gastric emptying) by using metoclopramide. A partial response was seen in some patients; emptying rates were decreased from previous values (when no concomitant drug was given with the radiolabeled meal), but still the emptying half-time was longer than 85 minutes. There was no response seen in those patients who had undergone subtotal gastrectomy and another patient who was affected by the Zollinger-Ellison syndrome. In the patients who showed a good response to the drug, gastric emptying studies were useful for differentiating organic from functional disease in pyloric obstruction and for planning therapy.

In a study by Domstad et al. (194), intravenous

metoclopramide significantly shortened the biologic gastric emptying time in eight of 12 patients suffering from diabetic gastroenteropathy. In a similar study involving patients with scintigraphically-proven gastroparesis, metoclopramide resulted in improved gastric emptying in 60% of patients who had no previous surgery, and in 75% of patients who had undergone surgery (195). Other investigators have found that interventional studies using metoclopramide have been useful in predicting therapeutic efficacy in patients with anorexia nervosa (196) and bulimia (197). Metoclopramide also increases the resting tone of the lower esophageal sphincter, and contributes to improvements in patients with gastroesophageal reflux (198). It should be noted, however, that concomitant use of narcotics and other analgesics, or mechanical obstruction, can counteract the effects of metoclopramide on gastric motility (80).

The effect of dopaminergic activity on gastric emptying has been demonstrated by Broekaert (175). The administration of apomorphine resulted in delayed emptying. This effect was reversed by domperidone, a dopamine antagonist. Domperidone given alone markedly increased the rate of emptying.

Hexamethonium, a ganglionic blocking agent, inhibits the transmission of impulses through both sympathetic and parasympathetic neurons. The resultant gastrointestinal hypomotility is accompanied by a marked delay in the onset and completion of stomach evacuation (176).

The effect of antacid preparations on the rate of gastric emptying in humans has not been convincingly demonstrated. Data derived from animal studies indicates that stomach emptying is retarded by aluminum-containing antacids (177). It is believed that aluminum ions inhibit motility by interfering with the cellular calcium fluxes which occur during smooth muscle contraction (178). Stomach hypomotility following antacid therapy has been observed in human subjects also (177). Some questions have been raised as to the accuracy of this observation in that it is believed that antacids themselves do not have a direct effect on the gastric emptying rate, but, instead expand the volume of intragastric contents resulting in a prolonged emptying of total stomach contents (179).

Crone and Ardran (180) observed that after the administration of morphine, there is an immediate increase in gastric motility followed by a more prolonged inhibitory phase which begins approximately 30 minutes later and may persist for several hours. Meperidine and pentazocine have inhibitory actions upon gastric motility similar to morphine (172), whereas naloxone, an opiate antagonist, causes a non-significant acceleration of solid food emptying (181).

The gastric stasis produced by narcotic analgesics is associated with an increase in antral and duodenal smooth muscle tone. This condition results from the actions of morphine and related compounds upon cholinergic, tryptaminergic, and enkephalinergic receptors in the gastrointestinal tract. Stomach emptying is inhibited also by the activity of these pharmacologic agents in the central nervous system (182).

Ethanol may accelerate or retard gastric emptying. Cooke (183) observed that small amounts of ethyl alcohol have no effect on the stomach's emptying rate, but that evacuation is

inhibited by high concentrations of ethanol. A dose dependent effect has also been demonstrated by Harichaux et al. (184). However, their results indicate that low doses of alcohol stimulate gastric emptying, and that ingestion of larger quantities inhibits this process. It has been postulated that stomach emptying is affected by the calorogenic characteristics of ethanol rather than by any property exclusive to alcohols or similar compounds (185).

Varga (186) demonstrated that chloroquine, when administered orally, retards gastric emptying. The magnitude of this effect is dose dependent, as well as due to the route of administration. Following subcutaneous administration of the drug, the stomach's emptying rate remains normal (i.e., similar to controls). Effects on emptying were noted when the drug was in direct contact with stomach tissues and, hence, it was theorized that chloroquine may produce a surface anesthesia of the gastric mucosa, thereby depressing the stomach's response to local emptying stimuli (186).

There is indirect evidence that gastric emptying is also prolonged by phenytoin. Patients receiving long-term anticonvulsant therapy show a slower than normal, or less pronounced, diuretic response to furosemide (187). This drug interaction may reflect delayed absorption of the diuretic due to a phenytoin-induced hinderance of its passage from the stomach into the small bowel (188). The mechanism through which this impairment may occur is unknown. However, investigators also postulate that, rather than modifying absorption, phenytoin may decrease renal tubular sensitivity to furosemide (189).

Caerulein has recently been used in the treatment of paralytic ileus and biliary colic. This gastrointestinal peptide has specific, local effects on stomach motility. The pylorus is contracted by caerulein, whereas tone in the stomach body and fundus is reduced by this compound. The result of these two actions is a delay in the emptying of gastric contents (190). It is not immediately clear, however, if these effects are mediated by neuronal or hormonal mechanisms.

The remarkable ability of the stomach to selectively empty solids and liquids at different rates has been referred to as the solid-liquid discrimination (191). This phenomenon has been explained by the functional sieving action of the contracting terminal antrum and the pylorus, which allows the rapid passage of liquid from the stomach to the duodenum while solids are retained. Certain drugs can affect this solid-liquid discrimination.

Gastric retention in diabetes contributes to poor control of the disease due to unpredictable absorption of food, which compromises the effects of exogenous insulin and oral hypoglycemic drugs and adds to the "brittleness" of the disease itself in patients. Erythromycin has recently been shown to have a motilin-like effect on gastrointestinal muscles. In a study by Urbain et al. (192), the effect of erythromycin in patients with diabetic gastroparesis (and delayed gastric emptying), was studied using a dual radionuclide technique (Tc-99m sulfur colloid scrambled eggs and In-111 DTPA in water). In their patient population (as well as in controls), intravenous erythromycin dramatically accelerated gastric emptying of both solids and liquids which were emptied at the same rate. After chronic oral administration, solid and liquid

emptying remained significantly accelerated. Erythromycin appears to be a very potent gastrokinetic drug that induces post-cibal motor activity in the stomach. The complete abolition of the solid-liquid discrimination in this instance likely corresponds to the abolition of the sieving action of the distal stomach, and reflects induction of powerful contractions which squeeze the distal stomach contents into the duodenum through the pylorus (192). It is quite possible that other compounds can be developed that will have motilin-agonist effects, and allow for the hormonal treatment of delayed gastric emptying. Radionuclide techniques can be extremely useful as a means of monitoring such drug development and therapy.

Chaudhuri et al. (199) reported the effect of Librium, Quarzan and Librax on gastric emptying. Following administration of Librax, mean gastric half-emptying time was significantly prolonged (67 minutes compared to 55.1 minutes for placebo, and 55.2 and 59.2 minutes when Librium and Quarzan, were given, respectively).

The effect of gastrointestinal hormones on gastric motility may be either physiological or pharmacological in nature (200). Secretin, CCK and gastrin slow gastric emptying, but the mechanism of their respective actions differ. For example, CCK and gastrin increase antral motility and delay gastric emptying. Secretin decreases antral motility but increases pyloric pressure; however inhibition of gastric motility only occurs at pharmacological doses. Both CCK and secretin decrease duodenogastric reflux by increasing pyloric pressure.

ENTEROGASTRIC REFLUX

Rationale for Use of Procedure

It is widely recognized that enterogastric reflux may be an important factor in the pathogenesis of several upper GI disorders such as gastric ulcer, reflux esophagitis, gastritis, gallstone dyspepsia, and postgastrectomy discomfort syndromes (202-207). To what extent such reflux is a primary cause rather than a consequence of disease is not immediately clear at this time (208). Several investigators have suggested that bile salts, alone or in combination with pancreatic enzymes, may be harmful or serve as an irritant to the gastric mucosa (209,210). Regardless, it is important to be able to diagnose and quantitate the reflux, if present.

Traditionally, the diagnosis of enterogastric reflux has been made by gastroduodenal intubation, installation of phenol red indicator into the duodenum, and measurement of reflux into the stomach (16). Tolin et al. measured enterogastric reflux using a dual-tracer technique, employing a 5 mCi intravenous injection of Tc-99m HIDA in order to label the bile, followed 45 minutes later by administration of a standard test meal labeled with In-111 DTPA (211). Reflux of the Tc-99m HIDA was then determined and the reflux index calculated as a percentage of activity refluxed into stomach; the results obtained compared well with those derived with the phenol red indicator measurements.

Imaging Technique

In addition to this radionuclide approach, other investigators have proposed techniques that can be used in conjunction with biliary excretion scintigraphy in order to detect enterogastric reflux, without having to resort to the need for intubation (212, 213). However, the detection of the radiotracer in the stomach is largely dependent on it reaching the proximal part of the stomach where the resultant images can be used to help differentiate it from other bile-containing viscera (i.e., activity in the antral regions of the stomach as compared to that in the duodenum, distal common bile duct or proximal jejunum). Additionally, it must be remembered that enterogastric reflux is usually most marked in the early post-prandial period, at a time when the pylorus is opening to allow gastric contents to be evacuated, and when meal-stimulated gallbladder contraction maximizes the duodenal bile available for reflux (214). To help overcome such problems, Mackie et al. (214) have developed a technique in which patients are scanned in a standing position following the ingestion of a meal, which causes the gallbladder to empty. The bile secreted tends to float on the administered meal. These investigators chose milk as the test meal in the presence of Tc-99m-EHIDA, because it was a physiological stimulus, and it is convenient and inexpensive.

In most previously reported enterogastric reflux studies using a biliary radiopharmaceutical, patients have been examined only in a fasting state, or else gallbladder evacuation was provoked pharmacologically by the administration of exogenous cholecystokinin (35). While ingestion of a meal certainly promotes reflux in most afflicted patients, it cannot be presumed that gallbladder emptying, as induced by the use of exogenous cholecystokinin, was the sole explanation for this tendency, since the use of the drug in this manner would be regarded as unphysiological. According to Rhodes et al. (215), patients studied with non-functioning gallbladders or previous cholecystectomy still had evidence of reflux. It seems probable that the tendency to demonstrate enterogastric reflux may be greater if patients are in the erect versus the supine position.

Borsato et al. (216) describe yet another noninvasive technique using Tc-99m HIDA as a means for detecting enterogastric (or duodenogastric) reflux. Patients were required to fast overnight after which they were given a cholecystokinetic composed of dried egg yolk (4 g) and sorbitol (10 g), at least 20 minutes before intravenous administration of the radiopharmaceutical. The patient was placed in a supine position under the gamma camera fixed with a low-energy, general purpose collimator. A series of 60, one-minute images were acquired with the liver and gastric regions appearing in the lower portions of the camera's field of view. At 60 minutes into the study, the patient was asked to drink, in a single swallow, 10 ml of a solution containing Tc-99m DTPA, with a new set of images being acquired (120 images at 0.5 seconds each). Upon completion of this second stage of the study, patients were asked to drink another 200 ml of water to help facilitate exact gastric localization, and a series of 1-second images was acquired for up to 2 minutes during which time the patients underwent a series of Valsalva maneuvers to induce gastroesophageal reflux. Within their

patient population, Borsato et al. (216) showed that scintigraphic evidence compared well (15 out of 25 patients) with 24-hour gastric pH monitoring for the evidence of enterogastric reflux. There was no correlation found with endoscopic findings. The rationale for their methodology is based on pathophysiologic evidence that damage to gastric and/or esophageal mucosa is mainly related to the prolonged contact time with duodenal contents. While this technique seems to allow for a complete functional evaluation of the duodenal-gastric-esophageal tract, without causing any additional discomfort to the patient, the fact that there was still 40% of the patients who showed negative results for reflux may indicate that there may be many differences in the etiology of gastritis.

Quantitation of enterogastric reflux is a formidable task, and at present there is no good single test methodology that can be used with confidence to assist clinicians in the choice of treatment for patients suffering with this anomaly. However, continued improvements in the development and validation of diagnostic testing procedures may help in better understanding the pathophysiology of this disease and in treating symptomatic patients.

SMALL BOWEL TRANSIT STUDIES

In the past, small bowel transit measurements have been achieved by determination of the time taken for recovery of hydrogen from the breath after the ingestion of lactulose by mouth or following oroduodenal intubation (217). This test essentially depends upon the lactulose being broken down by lactobacilli in the colon. It provides a means to assess the arrival of the first portion or head of a meal, in an area of the gut that contains lactobacilli. Similarly, other methods were developed that depend on the bacterial metabolism of a nonabsorbable substrate and the detection of a metabolite in plasma. This includes the acetyl azosulfapyridine method with detection of sulfapyridine in plasma (218). Whereas these methods have the advantage of simplicity and low cost, they are less applicable in patients with motility disturbances of the gut, in whom bacterial overgrowth may occur in the small intestine and may, thus, erroneously underestimate the time taken for the marker substance to reach the colon (218).

Imaging Technique

Small bowel transit studies have been performed with several radiolabeled markers. During the past decade, I-131 labeled fiber has been used (219), as well as In-111 and Tc-99m labeled ion exchange resin pellets (217). These substrates have the advantage of being nondigestible in the small intestine; thus, the same marker that is used to evaluate gastric emptying can be used to assess small bowel transit. Equally important, these alternate techniques yield results that are similar to the hydrogen breath technique (217). Investigators have shown that changes in small bowel transit can occur independent of changes in gastric emptying (220). Ileal cecal transit times have been investigated by Trotman and Price (221) using a radiolabeled meal consisting of Tc-99m labeled bran. Small bowel transit time is calculated by subtracting the time taken for 50% of the marker to empty from the stomach,

from the time taken for that same 50% of the marker to arrive in the colon (220).

Prolonged mouth-to-cecum transit time have been shown in patients with gastroparesis or antral hypomotility, intestinal pseudo-obstruction, or intestinal dysmotility, each of which contributes to a selective delay in the transit of radiolabeled solids in the stomach or small bowel (218). Additionally, some investigators have demonstrated that the emptying of the distal ileum into the colon does not occur linearly in normal subjects, but rather is associated with a series of bolus transfers (218,219) that are significant, particularly in those disease processes that affect the smooth muscle rather than the nerve control mechanisms of small bowel motility.

It has been shown that the presence of a variety of fat emulsions and, to a lesser extent, protein hydrolysate in the ileum will contribute to a slowing of small bowel transit and gastric emptying (222). This may actually constitute a potent feedback mechanism, whereby unabsorbed food in the ileum enhances absorption by prolonging the exposure of the meal to the absorptive epithelium of the GI tract. This mechanism, which has been referred to as "ileal brake," does not appear to be mediated by peptides, neurotensin and enterogastrin (223).

Infusion of fat into the ileum has been shown to 1) slow the transit of a liquid meal through the stomach, 2) delay the arrival of the liquid meal in the ileum and increase its residence time in the upper small intestine, 3) reduce the average flow of digesta through the upper small intestine and alter the pattern of flow, 4) reduce the volume of the meal entering the ileum, and 5) reduce the degree of carbohydrate absorption in the upper small intestine (223). Consequently, the presence of fat in the ileum may have a profound influence on the digestion and absorption of a meal in patients.

Some investigators have examined the effect of various drugs on the small bowel transit studies, such as lactulose (40 g), metoclopramide (20 mg tid), or magnesium sulfate (0.1g/kg of body weight) with concomitant analysis of the ileostomy effluent via chemical means (220).

Lactulose is a nonabsorbable disaccharide, which retains fluid in the intestinal lumen by its osmotic activity, increasing the luminal bulk, and stimulating peristalsis (16). Metoclopramide stimulates small intestinal propulsion by a direct action on small muscle (16). Magnesium sulfate probably accelerates small bowel transit via the release of cholecystokinin as well as by the osmotic effect of the unabsorbed sulfate (16). All three agents significantly reduce the time needed for the meal residues to be voided. In the case of these three agents, the observed effect was due to an acceleration in the passage of food through the small intestines. Overall, gastric emptying in the presence of lactulose and metoclopramide was unaffected, whereas, magnesium sulfate actually slowed the passage of food. All three drugs significantly reduced the time taken for the meal to empty from the ileum. This was also associated with a reduction in the absorption of fat, carbohydrate, protein, water, and electrolytes in the case of lactulose and magnesium sulfate (16). Although metoclopramide reduced transit time to the same degree as the other agents, its effect on absorption of fat, fluid, and electrolytes was much less, and absorption of

protein and carbohydrates was unaffected (16).

Efforts have been taken to better understand the concept of "ileal brake" and its relationship to gastric emptying. Gastric emptying of a liquid meal has been noted to be slowed following infusion of Intralipid in patients. In a study by Jian et al., half-emptying times were significantly prolonged, and the percentage of the meal emptied in the first 30 minutes was greatly reduced (222). In this study, patients were given intravenous infusions of either naloxone in isotonic saline or isotonic saline alone, with accompanying ileal infusions of either isotonic saline or an isotonic solution of Intralipid. When saline was infused intravenously, ileal infusion of Intralipid delayed small bowel transit in all subjects (249 minutes for ileal Intralipid versus 44 minutes for ileal saline). With a longer duration of Intralipid infusion, a greater delay in gastric emptying rate was noted (222). This delay in transit was abolished in 5 of 7 subjects following an i.v. infusion of naloxone. During the infusions of naloxone the average small bowel transit time following ileal Intralipid was not that much different from that seen when ileal infusions of saline were given (89 minutes for ileal Intralipid versus 46 minutes for ileal saline) (222). Finally, i.v. infusion of naloxone had no effect on small bowel transit time when saline was infused into the ileum (46 minutes for i.v. naloxone versus 44 minutes for i.v. saline). These results indicate that naloxone could abolish the delay in small bowel transit induced by ileal Intralipid, although no corresponding effect was seen when saline was infused into the ileum. Therefore, it is strongly suggested that endogenous opiates are involved in the slowing of small bowel transit by ileal fat (serving as modulators rather than mediators), although a more detailed mechanistic explanation has yet to be validated.

ECTOPIC GASTRIC MUCOSA

MECKEL'S DIVERTICULUM

Rationale for Use of Procedure

Ectopic gastric mucosa has been noted to line the Meckel's diverticula lesions in more than half the patients with this disease. The use of Tc-99m pertechnetate to image the Meckel's-related ectopic gastric mucosa has generated great interest because of the possibility of making a specific diagnosis (224). Meckel's diverticulum is the most frequent congenital malformation of the GI tract, which occurs commonly in up to 3% of the general population, becoming clinically manifest in less than 25% overall, though the diagnosis remains one that is difficult to make using radiographic techniques (225).

The difficulty in diagnosing Meckel's diverticula with conventional radiologic methods, and the frequent presence of gastric mucosa appearing in test results, lead to the use of Tc-99m pertechnetate as the agent of choice for scintigraphic test approaches. This is a logical choice because the radiopharmaceutical concentrates in the mucous cells of the gastric mucosa (226). The use of Tc-99m pertechnetate has demonstrated a sensitivity of 85% and a specificity of 95% in cases surgically proven to be Meckel's diverticula with ectopic gastric mucosa (227,228).

The diverticulum is usually situated 30 to 90 cm proximal to the ileocecal valve; it may vary in size up to about 30 cm in length, although it is usually only 3 to 5 cm in size (229). It is a true diverticulum containing all layers of the bowel wall (mucosal, serosal and muscle layer), although about 50% of the diverticula contain gastric or duodenal mucosa or pancreatic tissue (229). The most common symptom of Meckel's diverticulum is rectal bleeding that results from peptic ulceration of the bowel by acid secreted from the gastric mucosa in the diverticulum (230). The cases that will materialize usually do so by the age of 2 years.

Since Tc-99m pertechnetate uptake parallels gastric mucus secretion, maneuvers that enhance gastric secretion may be helpful. Perchlorate, in most cases, diminishes gastric uptake of Tc-99m pertechnetate (231,232). Logically, maneuvers that increase serum gastrin levels or stimulate the basal, cephalic, gastric, and intestinal phases of gastric secretion, after the patient has been fasting, may be of significant benefit (232). For example, placing the patient into a pleasant environment, or the hinting of a favorite kind of food (either via mere discussion or actual physical sight, smell or taste), may be effective in stimulating gastric secretion of Tc-99m pertechnetate, as is the administration of pentagastrin (6 ug/kg) (1,233,234). Glucagon (500 ug/kg) has been successfully used to diminish bowel peristalsis, and thus delay removal of radiotracer from the site of bleeding. Similarly, other methods can be employed that seek to prevent dissipation of trapped Tc-99m pertechnetate, such as cimetidine (300 mg/day orally), given for up to 1 or 2 days prior to the start of testing in order to delay secretion of Tc-99m pertechnetate (235) into the bowel lumen.

Imaging Technique

Patients undergoing testing for Meckel's diverticulum should be fasted for several hours prior to the start of the study. Following intravenous injection of 30-100 uCi/kg of Tc-99m pertechnetate, serial anterior (5 second) images, with the patient's right side tilted upwards about 30 degrees (in order to help sequester gastric secretions), are obtained during the bolus arrival and dissipation, followed by additional anterior views at 5-10 minute intervals (228). Lateral and oblique views may also be obtained in order to visualize sites of activity suspected of being intra- or extraperitoneal in nature. Having the patient void, or placing a lead shield over selected areas of accumulation, may help bring out other small focal areas of activity that otherwise might go unnoticed. In most situations, ectopic gastric mucosa in a Meckel's diverticulum appears as a single, discrete, focal area of activity that parallels gastric activity appearing intraperitoneally in 10-20 minutes following radiopharmaceutical administration. Activity should appear in the right lower quadrant and may change positions with any number of maneuvers that shift the gut (228). This approach helps serve to differentiate ectopic gastric mucosa from inflammatory causes, which tend to accumulate the radioactivity later into the study.

Positive scans generally show a persistent area of uptake in the mid-abdomen, usually between the stomach and the bladder. More specifically, true positive characteristics of the scan results can be described in the following fashion:

1) localization appearing simultaneously with the stomach, 2) localization of activity in the right lower quadrant of the abdomen, 3) anterior versus posterior localization within the abdomen, 4) persistence of localization on muscle images, 5) discrete separation of localization from other bowel loops, and 6) evidence of a small, round, locus of radioactivity (1).

Ryan and Sepahdari (236) have described a case whereby the use of Tc-99m sulfur colloid was helpful in identifying a site of active lower intestinal bleeding from a Meckel's diverticulum, in a 10 month old patient.

The false-negative rate is low, though in reality there may be some underestimation of this. False-negative scan results may occur due to any number of factors/conditions, such as 1) profuse bleeding may dilute the secreted radiotracer and wash it away, 2) mucosal necrosis may prevent localization of the radionuclide, 3) a Meckel's diverticulum may rarely appear as an intussusception which compromises blood supply, preventing radiotracer localization, and 4) an insufficient amount of gastric mucosa may be present to overcome body activity (1,35,237). To avoid these situations, excessive time delay between radiopharmaceutical injection and scanning must not occur. Gastric emptying of secreted Tc-99m pertechnetate can be quite rapid, and scintiphoto images may become unreadable due to the presence of activity in the small bowel as soon as 25 minutes after administration of the radiopharmaceutical. In fact, imaging after one hour can be misleading since passage of the radionuclide into the distal bowel may simulate ectopic localization of the radionuclide. Should this occur, it is advised that the scans for Meckel's diverticulum be repeated with nasogastric aspiration (232).

Hemangiomas may also be visualized due to their increased blood volume (238), and can serve as an example of a false-positive on a Meckel's scan. However, the activity in these lesions usually decrease with time and thus should be distinguishable from ectopic gastric mucosa in which activity generally increases with time (215).

A uterine blush which can be seen on Meckel's scans from regularly menstruating women (or in the secretory phase of the cycle), has also been reported to be a potential cause of false-positive test results (239). In this situation, increased radionuclide activity is thought to be due to either the edema and hyperemia of the secretory phase or to sequestration of the radionuclide within areas of necrosis and hemorrhage during menses itself. In case reports noted by Fink-Bennett (239), no focal radionuclide uptake superior to the bladder was observed in premenstrual girls, menopausal women, or posthysterectomy women. Other possible causes of false positive scans include localized activity in the renal tract from uretic obstruction or hydropelvis (240), presence of bladder activity (which should be emptied prior to scanning in order to avoid confusion) (241), leiomyoma of the terminal ileum (242), ulcerative colitis (241), malignant lymphoma (243), Crohn's disease (244), intestinal duplication (245), duodenal ulcer (240), and Meckelitis with bleeding in the absence of gastric mucosa.

Irritants to the gastrointestinal tract produce inflammation and also stimulate localization of the radionuclide (Tc-99m pertechnetate) within the mucosa. Cathartics, enemas, or other medications should be withheld until after the Meckel's

diverticulum study is completed (246). Barium gastrointestinal studies and proctoscopy should be performed after abdominal imaging. Barium sulfate can attenuate photons and could mask a Meckel's diverticulum (246).

BARRETT'S ESOPHAGUS

Barrett's esophagus is a condition in which the mucosa of the lower esophagus is replaced by columnar epithelium of the gastric type, rather than with normal stratified squamous epithelium (83). The condition is considered to be pre-malignant and early diagnosis is important. The diagnosis is typically made if the patient presents with a history of severe reflux, often with dysphagia and occasional hematemesis, together with the finding on barium esophagography of reflux and esophageal irregularity, such as ulceration or stricture (83). Generally, where endoscopy and biopsy will confirm the diagnosis, esophageal uptake of Tc-99m pertechnetate will be strongly supportive, since the radionuclide is concentrated by gastric columnar epithelium, not by esophageal squamous epithelium (83,84).

Radionuclide testing for Barrett's esophagus is accomplished by administering 5-15 mCi of Tc-99m pertechnetate intravenously to a fasted patient. It is not necessary to administer potassium perchlorate, and the patient should be instructed not to swallow any saliva during actual testing (84). With the patient in an erect position in front of the gamma camera, scintiphotos are acquired (300,000 to 600,000 counts per image) in an anterior, posterior and lateral projection at 20 minutes and 30 minutes post-radiotracer administration (84).

DETECTION OF GASTROINTESTINAL BLEEDING

Rationale for Use of Procedure

Localization of the specific bleeding site in patients presenting with acute gastrointestinal hemorrhage remains a serious clinical problem. Alavi et al. (247) were the first to recognize the significant diagnostic role that GI scintigraphy held in the localizing of bleeding lesions. Evaluation of gastrointestinal bleeding via radionuclide methods now is a routine nuclear medicine procedure.

Initial efforts utilizing Cr-51 labeled red blood cells (RBCs) demonstrated the feasibility of detecting and localizing sites of gastrointestinal hemorrhage (248-250). Iodine-131 labeled albumin has also been used successfully in localizing experimentally-produced bleeding (251), and Tc-99m labeled albumin has also been proposed as a suitable imaging agent in the clinical detection of GI bleeding (252,253). Use of the technetium-99m labeled agent was shown to detect all patients with clinically active bleeding (most within 35 minutes, though heavy bleeders were detected within 5 to 10 minutes), with a sensitivity limit of 2-3 ml/min blood loss.

Successful management of acute GI bleeding usually depends on accurate localization of the bleeding site. In addition to scintigraphic approaches, application of flexible endoscopy and selective arteriography appear to provide clinicians with accurate diagnoses for the majority of patients presenting with upper GI bleeding (35,254). However,

detection of lower GI bleeding sites still remains a challenge. Endoscopy and barium studies are of limited value in studies involving active hemorrhage of the small bowel and colon. Arteriography, despite its apparent successes, also has its limitations (254). Use of angiographic methods is possible only when the injection of the contrast material coincides with active bleeding at a rate greater than 0.5 ml/min; given the fact that lower GI bleeding is often intermittent in nature rather than continuous, a high rate of false-negative test results can occur. Also, given the invasive nature of angiography, use of repeated catheterizations in order to detect bleeding sites is impractical. As a result, radionuclide scintigraphy appears to be the modality of first choice today for localizing bleeding sites in the lower GI tract.

Currently, there is controversy over the selection of which type of radiopharmaceutical should be used to identify sites of GI bleeding. Two basic groups of agents have been proposed, based on whether or not they are extracted rapidly or slowly from the intravascular space.

The two radiopharmaceuticals classified as rapidly extracted agents are Tc-99m sulfur colloid and Tc-99m-labeled heat-treated RBCs (see Table 9) (248). Slowly extracted imaging agents include Tc-99m labeled albumin and non-heat treated Tc-99m labeled RBCs, which can be prepared using either an in vivo or in vitro technique (see Table 9) (248). A comparison of both rapidly and slowly extracted imaging agents is presented in Table 10. Finally, Table 11 lists some of the ideal characteristics that a radiopharmaceutical should possess if it is to be used successfully as a GI bleed imaging agent (248). However, each of the radiopharmaceuticals mentioned have unique problems to overcome, which continues to serve as the basis for the controversy evident today as to which radiopharmaceutical is the agent of choice in GI bleed detection studies.

Table 9. Radiopharmaceuticals Used in the Evaluation of Gastrointestinal Bleeding

Cell-specific Agents

Tc-99m sodium pertechnetate (i.e. Meckel's diverticulum)

Rapidly-Extracted Agents

Tc-99m labeled, heat-damaged red blood cells

Tc-99m sulfur colloid

Slowly-Extracted Agents

In-111 labeled red blood cells

In-113m labeled red blood cells

Tc-99m albumin

Tc-99m labeled red blood cells

(adapted from Waxman AD²⁴⁸)

In upper GI hemorrhage, bleeding above the ligament of Treitz is easily diagnosed and localized in upwards of 90% of patients by use of gastric aspiration and endoscopy (255). The major causes of bleeding in these patients include esophageal varices, esophagitis, gastritis, peptic ulcer, and tumor. In these situations, radionuclide techniques have not been stressed since endoscopy appears to be quite effective.

Table 10. Comparison of Rapidly- Versus Slowly-Extracted Agents for the Detection of Gastrointestinal Bleeding

Rapidly-Extracted Agents - Advantages

- 1) Improved target contrast due to lower background activity (rapid washout)
- 2) Highly specific for GI bleed sites; poor visualization of vascular structures
- 3) When test results are positive, higher accuracy of GI bleed site location
- 4) Testing can be repeated more frequently

Rapidly-Extracted Agents - Disadvantages

- 1) Intermittent bleeding episodes may be missed
- 2) Reduction of target contrast if agent extracted by abdominal organ
- 3) Repeat testing will require additional administrations of the imaging agent

Slowly-Extracted Agents - Advantages

- 1) Can detect intermittent bleeding episodes for extended periods without needing additional radiotracer administrations

Slowly-Extracted Agents - Disadvantages

- 1) Higher background activity results in lower target/background ratios
- 2) Vascular organs (liver, kidney, spleen and major blood vessels) can interfere with interpretation of results/location of GI bleed sites.
- 3) False-positive test results possible due to late dissociation of label
- 4) Obtaining infrequent delayed images may impair identification of GI bleed sites.

(adapted from Waxman AD²⁴⁸)

In lower GI hemorrhage, bleeding can be due to inflammatory bowel disease, Meckel's diverticulum (in young adults and especially pediatric populations), and tumors (255). Sites of lower GI bleeding are, however, very difficult to localize during both pre-operative evaluation and at surgery. Radionuclide techniques may be especially useful for the detection and localization of these lower GI bleeds.

Table 11. Description of an Ideal Radiopharmaceutical for the Evaluation of Gastrointestinal Bleeding Studies

1. Low cost, easily prepared and administered
2. Low radiation burden and nonallergenic to the patient
3. Structures normally visualized do not interfere with test interpretation
4. High target/background ratio (even with small amounts of GI bleeding)
5. No excretion or absorption into GI tract unless due to bleeding
6. Can be re-administered or re-imaged frequently avoiding problems due to intermittent bleeding episodes
7. Available in sufficient quantity to permit detection of GI bleed sites
8. Extraction sites for the radiotracer do not interfere with testing

(adapted from Waxman AD²⁴⁸)

Imaging Technique

1) Rapidly- Versus Slowly-Extracted Radiotracers

Alavi et al. (247) have proposed the use of Tc-99m sulfur colloid as the agent of choice in detecting lower GI bleeding. There are many reasons for this statement. First, when an radioactive agent that is cleared by a specific organ (i.e., liver, spleen) is administered intravenously to a patient with active bleeding, a fraction of the injected activity will be extravasated at the bleeding site and be eliminated from the circulation. This is repeated each time the blood is recirculated, but with a lesser fraction of injected activity being extravasated each time. Because of continued clearance of the radiopharmaceutical in this manner, a contrast is eventually reached between the site of bleeding and surrounding background tissues (35). Maximum contrast occurs upon the completion of the extraction of the intravascular activity by the target organ. In light of this, there is usually a good target-to-background ratio established at the time of imaging. Tc-99m sulfur colloid is cleared from the intravascular space rapidly (blood clearance half-time is 2.5 to 3.5 minutes), and by 12 to 15 minutes post-injection, most of the injected activity has been cleared. This group determined that rates of extravasation as low as 0.05 to 1.0 ml/min were detectable (256). Clinically, a perfusion study is performed following the intravenous injection of 10 mCi of Tc-99m sulfur colloid, with 1-2 minute serial images (including the lower edge of the liver) being acquired. If a bleeding site is seen in early images, additional views will be obtained in order to further clarify the exact site of bleeding as bleeding progresses distally in the bowel lumen (256). If the site is not seen on initial scintiphotos, later images involving upper quadrant areas will be obtained. This may include a LAO view to allow visualization of the splenic flexure area. Images taken at 30 to 45 minutes into the study permit extravasated material in hidden areas to migrate into areas of the bowel that will not be masked by the high hepatic and splenic activity encountered (248).

Proponents of slowly extracted radiotracers have maintained that GI bleeding patterns are typically those of an intermittent nature. Therefore, invasive testing procedures such as angiography and endoscopy are less effective in detecting GI bleeding sites, unless the patient is actively bleeding at the time of actual testing. The most promising of the slowly extracted agents is that of Tc-99m labeled RBCs, because the agent is able to reside in the intravascular pool for longer periods of time than are rapidly extracted agents (248, 257). For example, serial abdominal images are obtained for upwards of 24 hours at a time when the patient is suspected of bleeding, losing on the average 500 to 1800 ml of blood in 24 hours (rate of 0.35 to 1.25 ml/min) (258). This method is reported to be more sensitive than the Tc-99m sulfur colloid and Tc-99m labeled albumin methods which, according to some investigators, can only measure acute bleeding when it is at a rate of 2-3 ml/min (259). This, of course, contradicts earlier reports as to the sensitivity as noted above.

Winzelberg et al. (258), using a modified in vivo technique for labeling RBCs, noticed that upwards of 15% of patients studied showed signs of gastric and/or bladder activity (free

pertechnetate) in their scan images. Nevertheless, out of 32 patients studied who were clinically shown to have active bleeding from a lower GI site, 29 had positive scintigraphic findings. This compared to only 10 of 26 patients who underwent angiography as a means of detecting the bleeding source. Additionally, these investigators established an important relationship between the time of scanning following radiopharmaceutical administration. For example, a majority of patients were shown to be positive for GI bleed within one hour after being given the radiolabeled RBCs. Another 25% of their studied patient population became positive between 1 to 6 hours postinjection, another 13% becoming positive between 6 to 12 hours postinjection, and another 25% showing positive signs of GI bleeding between 12 to 24 hours postinjection (258). The delayed appearance of the radiolabeled RBCs demonstrated the intermittent nature of GI bleeding.

Clinically speaking, many investigators have supported this concept of intermittent bleeding as the dominant feature in most patients with lower GI hemorrhage. Agents with a short blood-pool duration show lower diagnostic sensitivity because they are typically cleared before the onset of the next bleeding episode. For example, angiography (vascular T1/2 less than 30 seconds) proved to be less sensitive than Tc-99m sulfur colloid (vascular T1/2 being close to 3 minutes), which in turn is less sensitive than Tc-99m labeled RBCs (vascular T1/2 being 24 hours or greater) for demonstrating bleeding sites that are often intermittent in nature (260-264). A majority of investigators today feel that better sensitivity exists in detecting GI bleeding episodes by using Tc-99m labeled RBCs (265-268). One report describes a large, multi-institutional prospective study involving 100 patients, in which a sensitivity of 93% for Tc-99m RBCs compared to only 12% for Tc-99m sulfur colloid (with a specificity of 95% and 100% for the two agents, respectively) were noted in detecting and localizing bleeding sites (269). The following conclusions can be drawn from this study which highlight several advantages for using Tc-99m RBCs over that of Tc-99m sulfur colloid: 1) approximately 95% of the injected activity of the in vitro labeled RBCs persists in the vascular compartment beyond 30 minutes (which permits imaging to take place for up to 24 hours postinjection in some patients), 2) radiation dose to the liver and spleen is much less for the radiolabeled RBCs than that received by using Tc-99m sulfur colloid, and 3) upper GI bleeding also could be detected because activity in the liver and spleen was of lesser intensity than that which was seen for Tc-99m sulfur colloid (286,293).

Heyman et al. (270) described a case highlighting a potential diagnostic pitfall that could be encountered if using Tc-99m sulfur colloid for the detection of GI bleeding sites. They noted that while it is usual to observe progression of radioactivity as blood passes through the lumen of the bowel, there may be little movement in situations involving small bleeds. Therefore, these investigators stress that if an abnormal focus fails to alter in shape and position after having acquired sequential images, that this may be due to radiotracer uptake into an accessory spleen (even though the incidence of such is estimated to be only 10% involving regions of the splenic hilum). Bleeding sites can be missed if they lie behind

or adjacent to the liver or spleen, or if they do not show signs of progression through the bowel.

On the other hand, use of Tc-99m labeled RBCs has been found to be particularly useful in elderly patients who present, at the time of study, with various underlying medical problems such as diabetes, renal failure, or peripheral vascular disease (262). A negative radionuclide study in patients of this category, with suspected GI bleed, is good evidence that angiography will not detect the site of hemorrhage.

Alavi et al. (260) describe several potential shortcomings that can be encountered by use of an intravascular indicator to demonstrate sites of hemorrhage. First, the sensitivity of this technique was such that bleeding sites were unable to be localized until 30-60 ml of extravasated blood had accumulated. This lack of sensitivity was due to the fact that there was significant background activity in the vascular system. Using Tc-99m sulfur colloid, bleeding sites were identified within 5-10 minutes postinjection of the radiotracer. According to the authors, to observe abnormal bleeding in the same time frame using an intravascular agent, the bleeding rate would need to exceed 3-6 ml/min. Therefore, it is not as likely that intravascular indicators will demonstrate the site of hemorrhage within the first 5-10 minutes of a given procedure in a majority of patients with GI bleeding. Second, bleeding is only detected with delayed scintiphoto imaging, thus adding to the likelihood that sites of extravasation could be easily misrepresented. Since GI bleeding is thought to be intermittent in nature, and given the fact that it is not practical to keep patients under imaging cameras for extended periods of time, if an intravascular agent fails to show the site of bleeding within the first 10-15 minutes following radiotracer injection, it is likely that the true site of extravasation may not be seen on later scintiphotos. Third, structures with increased vascularity (i.e., varices and arteriovenous malformations), and organs with high vascularity (i.e., liver, kidneys) may interfere with the visualization of the GI bleeding site. Fourth, when in vivo tagged RBCs are used to detect a bleeding site, a large percentage of the administered dose may contain free radiopertchnetate which can localize in stomach, intestines, kidneys and bladder, thus contributing to the possibility of obtaining false-positive scan results. Fifth, when this occurs, the remaining activity of the Tc-99m labeled intravascular agent can be detected up to 48 hours later, which can interfere with the proper use of other radiopharmaceuticals (e.g., Tc-99m sulfur colloid) when the patient is actively bleeding and could benefit from having a repeat examination performed. And sixth, the time needed to perform a GI bleed study using an intravascular agent (including preparation time of the agent) is generally quite long, and can be problematic in patients who are seriously ill.

Several other radiopharmaceuticals that clear rapidly from the circulation have been studied as agents for use in GI bleed studies, but with much less success. Technetium-99m DTPA, Tc-99m pertechnetate and I-131 iodohippurate have been tried and found to demonstrate bleeding sites poorly (271-273). Each of these agents is either cleared by glomerular filtration or tubular secretion (or both), but the low sensitivity is due more to prolonged, higher background activity by diffusion into the extravascular space, thus reducing the amount of

circulating radiotracer for extravasation at GI bleeding sites. Another approach that has been tried involves the use of heat-damaged RBCs that are removed by splenic sequestration, and do not diffuse freely from the vascular compartment (274). Technetium-99m labeled heat-damaged RBCs are cleared more slowly than is Tc-99m sulfur colloid (approximately 10% of the injected dose per minute); use of this agent has resulted in some success in detecting sites of GI bleed with blood loss occurring at a rate as low as 0.12 ml/min (274). The theoretical advantage of using heat-treated Tc-99m RBCs includes the absence of activity in the right upper quadrant, a moderate increase in accumulation at the bleeding site due to prolongation of the half-time to 6-11 minutes, and virtually no marrow activity (274). The major disadvantages encountered with the use of this agent include a high degree of splenic activity which could obscure GI bleeding in the area of splenic flexure and stomach, and the time needed to prepare the imaging agent by qualified personnel (274).

Other blood-pool labels have been studied, but are seldom used today. For example, radiolabeled proteins such as Tc-99m albumin and In-113m transferrin have been able to localize GI bleeding sites, but have not been widely accepted due to problems such as cost, convenience, availability and stability. Miskowiak et al. (252,275) described their experience using Tc-99m labeled albumin in which sites of bleeding were detected only if the total volume of accumulated blood at a given region exceeded 70 ml. In comparing their scintigraphic approach to that of endoscopy, they noted that the radionuclide procedure had a sensitivity of 86% and a specificity of 100%. In half of their patient population studied, the site of bleeding was seen between 2.5-10 minutes into the study, with the bleeding site identified in the remaining patients by 30 minutes into the study.

Similar considerations have been shown for the potential use of In-111 labeled autologous RBCs, since the radionuclide's long half-life permits for the localization of GI bleeding sites that are either very slow or intermittent in nature (276,277). However, problems of cost, convenience, availability and stability have also been raised in conjunction with the use of this imaging agent as well.

2) Methods of RBC Radiolabeling (RBC Labeling Considerations)

Three different methodologies have been used in order to radiolabel RBCs with technetium-99m, namely, the in vivo method, the in vitro method and the modified in vivo method. It should be noted that the third lesson in Volume One of this UNM Nuclear Pharmacy CE Series was entitled "Radiolabeled Red Blood Cells: Methods and Mechanisms," and readers are encouraged to review this publication for a more adequate discussion on RBC labeling.

All three methods of labeling require the addition of a reducing agent, usually stannous ion, to the RBCs prior to labeling with Tc-99m pertechnetate. This process is sometimes referred to as "pre-tinning" the RBCs.

The simplest of the three methods is that of in vivo labeling, and while applicable for use in GI bleed detection, it is probably most often used for cardiac blood-pool scintigraphy. In this approach, the patient first receives an

intravenous injection of "cold" stannous pyrophosphate. After 10-15 minutes, the patient is given another intravenous injection of Tc-99m pertechnetate (usually 20-25 mCi, given via the antecubital vein in the arm opposite the one in which the cold stannous pyrophosphate was given). In this manner, approximately 80-85% of the injected radionuclide enters the cells and binds to hemoglobin, with the remaining activity being in the form of free pertechnetate which enters several body compartments from the circulation, including the salivary glands, gastric mucosa and possibly the colon (sites where activity can either mask or mimic bleeding) (278).

The *in vitro* method allows for an overall improvement in RBC labeling efficiency (usually greater than 95%). With this method a small volume of the patient's blood is drawn into a syringe and the RBCs tagged with Tc-99m pertechnetate. The patient is then reinjected with the tagged RBCs. Although subsequent reinjection of RBCs after radiolabeling them outside the patient's body could conceivably lead to identity problems, this procedure is able to achieve lower background levels due to higher labeling efficiency.

The modified *in vivo* method utilizes observations derived from the other two methods, most notably that the incorporation of Tc-99m pertechnetate into human RBCs *in vivo* proceeds at a measurable rate (279). Therefore, an isolated incubation period of 10-20 minutes, preceded by the use of anticoagulation and pretinning, results in good labeling efficiency with minimal free pertechnetate. For anticoagulation, ACD solution is preferred over heparin because it decreases renal and bladder activity related to excretion of Tc-99m-heparin complexes (280). Patients with low hematocrits seem to require longer incubation times than that normally used for the modified *in vivo* method.

The manner in which scintiphotos of potential GI bleed sites are obtained is as important as the manner by which RBCs are radiolabeled with Tc-99m. A scintigraphic approach must be employed that overcomes the problems of localization due, in part, from intermittent luminal bleeding and bidirectional movement of blood activity in the bowel lumen. According to Lull and Morris (255), this is best accomplished by either continuous dynamic imaging or by using frequent serial images. In most instances, imaging should begin at the time of radiopharmaceutical injection in order to assure correct localization of early bleeding. If initial images are not acquired until 15-20 minutes postinjection, the potential for missing a bleeding episode that occurs at 5-15 minute intervals can be appreciable.

When bleeding is not visualized during early continuous imaging, the acquisition of delayed images should be considered at reasonable time intervals; in some cases, imaging may be required for as long as 24-hours postinjection. Both Benedetto and Nusynowitz (281), and Jacobson (282) note that if intraluminal activity is seen in delayed images, then sequential imaging should be restarted over the next 10-15 minutes with use of either the same dose or a new dose (second injection) of Tc-99m labeled RBCs in order to confirm the correct location of the bleeding site.

During the course of testing for the presence of GI bleeding sites, there are several normal variations and common artifacts that can be confused with actual sites of bleeding,

some of which are presented in Table 12. Each of these situations offer certain identifiable characteristics which should make their identification from bleeding sites possible. For example, vascular lesions present themselves as showing no change in location or relative intensity over time (255). On the other hand, artifacts that are caused by urinary excretion are readily identifiable in most instances, usually by obtaining pre- and post-voiding views (255).

Table 12. Gastrointestinal Bleed Imaging Artifacts Using Tc-99m Labeled RBCs

Blood-pool Activity Artifacts

Abdominal tumor blood flow
Aneurysm
Mesenteric varices
Penile blood flow
Uterine blood flow

Urine Activity Artifacts

Bladder artifact
Foley catheter pattern
Renal outflow (dilation/obstruction)

(adapted from Lull RJ²⁵⁵)

Other techniques can be utilized when trying to ascertain the exact nature or location of a GI bleeding site. For instance, if it is unclear whether a bleeding site is located in the small bowel or colon, these structures can be outlined scintigraphically by administering either an intravenous dose of Tc-99m DISIDA or an oral dose of Tc-99m sulfur colloid in order to help visualize the small bowel, or a Tc-99m DTPA enema for visualization of the colon (255).

3) Interventional Techniques

Theoretically, certain drug interventional maneuvers have the potential for enhancing the outcome of GI bleed testing using Tc-99m-labeled RBCs. For example, glucagon (0.1-1.0 units IV) can be administered to the patient in order to slow rapid bowel transit (inhibit gastrointestinal peristalsis) and thereby permit more time for the radiotracer to accumulate at the bleeding site(s) (256). On the other hand, cholecystokinin could be used in order to stimulate bowel peristalsis when movement of a bleeding focus might enable a more accurate definition of its location (255). Recently, some investigators have advocated the use of employing measures that would stimulate renewed bleeding during sequential imaging. While this can be achieved by merely raising the patients blood pressure (via the use of fluid replacement and/or pressor agents), another form of provocation calls for the administration of heparin (10,000 units given at a rate of 1000 units/hr) to patients with chronic bleeding (283).

The use of radionuclide approaches in detection of gastrointestinal bleeding sites can also be used for monitoring the course of patient therapy, along with angiography and endoscopy. Surgery, it seems, is used today as a last resort in order to stop GI bleeding in patients in whom other

approaches have proved unsuccessful. As noted previously, endoscopy is being used to monitor treatment in patients with upper GI hemorrhage. Both vasopressin and epinephrine have been used to control bleeding, with vasopressin often being called upon in order to avoid the problems of tachyphylaxis and rebound hyperemia seen with epinephrine (284, 285). Vasopressin infusion at rates of 0.2-0.4 units/minute has been regarded as being safe and unlikely to cause organ infarction. Systemic infusion of low-dose vasopressin has become the standard first line approach for treatment of variceal bleeding, and can be given intravenously at the same dosage levels as those that have been used for intra-arterial therapy (286). Animal studies involving the use of prostaglandin indicate that this agent may be superior to vasopressin via a dose-dependent vasoconstriction of visceral vessels without concomitant effect on systemic blood pressure or cardiac output (287). Tyden et al. (288) have described a situation in which the intravenous administration of somatostatin resulted in the successful management of patients with variceal bleeding. Embolic therapy involving the use of autogenous clots, gelfoam and Ivalon, had been reserved for patients who failed to respond to control of GI bleeding using vasoconstrictive agents (289). However, this approach is being used more today as a primary hemostatic modality, aimed at the stoppage of bleeding in gastric and duodenal lesions as well as the distant bowel.

GASTROINTESTINAL MALABSORPTION STUDIES

In pancreatic disease, insufficiency of enzyme production may lead to diminished gastrointestinal absorption of proteins, fats, and other nutrients. Other disease states, generally referred to as the protein-losing gastroenteropathies, can lead to hypoproteinemia through excess loss of plasma proteins, primarily albumin, from the blood into the GI tract (290).

A major class of nonimaging nuclear medicine tests are available for the evaluation of gastrointestinal absorption, and because of their relevance to the general nature of this current discussion, will be briefly addressed here.

Many of these tests were initially developed by gastroenterologists, and include tests for vitamin absorption (i.e., the Schilling test); fat, carbohydrate, and bile acid absorption (the CO₂ breath test); and tests for mineral absorption (i.e., calcium and iron studies) (291).

Fat Absorption

The daily diet of an American adult consists of an average of 140 grams of fat, mainly as triglycerides. This constitutes almost 50% of their caloric intake and ingested nutrients, and can be most difficult to absorb (291). The absorption of triglycerides includes a number of different processes such as emulsification (both mechanical and chemical), hydrolysis, solubilization, and mucosal cell transport followed by chylomicron transport (291). Short chain fatty acids (less than 10 carbon atoms) are directly absorbed into the portal blood. Long chain fatty acids (more than 16 carbon atoms), along with lower glycerides, are resynthesized within the intestinal cells into newer forms of triglycerides (coated with beta lipoproteins to form chylomicrons) that finally pass into the lymph and are then ultimately delivered to the liver (292).

Pancreatic enzymes (e.g., lipase), bicarbonate ions, and bile salts digest the fats in the duodenum into soluble products which are further altered, at the level of the microvillus membrane of the intestinal cell, into free fatty acids and glycerol, with subsequent passage into the intestinal cell. Following absorption, a portion of the fat is oxidized (via the citric acid cycle pathways) by tissues to yield energy, carbon dioxide and water. It is by the measurement of the expired radiolabeled carbon dioxide that fat metabolism and absorption can be measured.

The inability of the gastrointestinal tract to absorb fat, proteins, vitamins and minerals often is reflected as steatorrhea (large, bulky, fatty stools). Steatorrhea may result from many conditions, some of which are listed in Table 13. This condition can be diagnosed via inspection of stool samples by means of microscopic inspection, or by a more accurate approach involving the chemical determination of the fecal fat (291). The most accurate method for detection of fat malabsorption is the measurement of a three to five day fecal fat excretion. However, the test is unpopular with patients and the medical staff due to the unpleasantness of the collection, storage, homogenization, sampling and analysis of the stool samples (293). Additionally, there can be doubt about the completeness of sample collection and the amount of dietary fat intake.

Table 13. Malabsorption Syndromes Contributing to Steatorrhea in Patients

<u>Absorption Defects</u>	<u>Condition</u>
1. Alterations in intestinal flora	Antimicrobial therapy Blind loop syndrome Jejunal diverticulitis
2. Anatomic alterations	Enterogastric fistulas Stenosis Surgical resection
3. Biochemical lesions	Celiac disease
4. Intestinal wall lesions	Amyloidosis Bacterial or viral enteritis Radiation or vascular enteritis Scleroderma
5. Lymphatic lesions	Intestinal tuberculosis Lymphoma
6. Miscellaneous	Carcinoid syndrome Diabetes mellitus Mesenteric insufficiency
<u>Digestive Defects</u>	<u>Condition</u>
1. Biliary insufficiency	Biliary fistula Biliary obstruction Liver disease Surgery
2. Intestinal lesions	Total gastrectomy Zollinger-Ellison syndrome
3. Pancreatic insufficiency	Pancreatic cancer Pancreatic fibrosis Pancreatitis

(adapted from Harbert J¹⁶)

To avoid the technical difficulties of fecal fat determination by chemical methods, as well as the time-consuming

process involved with metabolic balance studies, radionuclide techniques have been developed. Historically, labeled fats such as I-131 triolein and C-14 tripalmitate, as well as labeled fatty acids (i.e., I-131 oleic acid), have been utilized in such testing methodologies. I-131 labeled triolein had been available commercially for many years, but the test was not very popular because of its poor reliability and the necessity to collect and process multiple stool samples, and is no longer available today. The I-131 oleic acid test came into being because it was believed that steatorrhea, caused from lack of lipase secretion by the pancreas, could be differentiated from that resulting from small bowel disease. This did not prove to be the case and, thus, this testing approach is no longer a clinical option. Recently, the use of exhaled $^{14}\text{CO}_2$ following C-14-triolein, for example, has been reported to have high sensitivity and specificity in the evaluation of patients with steatorrhea (293).

Breath Tests

Newcomer et al. (294) have compared the sensitivity and specificity of three different C-14 labeled fats, namely, triolein, tripalmitin, and triolein, in patients with steatorrhea, as well as those who had diarrhea but without steatorrhea (alias, irritable bowel syndrome). Basing their analysis on peak $^{14}\text{CO}_2$ percent of administered dose per hour, the breath $^{14}\text{CO}_2$ curves were higher after triolein and showed better separation from normal patients. They found that C-14 triolein was superior to the other two agents. When 3.4% of the dose per hour was defined as the lower limit of the normal peak, the test had a sensitivity of 100% and a specificity of 96% (normal range is described as 3.43-6.3% and malabsorption as 0%-3.43% of the dose per hour).

The analysis of $^{14}\text{CO}_2$ breath exhalation after the oral administration of C-14 labeled fats is probably the most definitive isotopic test of fat absorption currently in use today. Because the breath test reflects the rate of fat absorption and oxidation per unit of time, its reported high sensitivity is likely due to the fact that patients with mild steatorrhea are included as positive test results (295). However, it has been noted that there is not a good correlation between the results achieved using the breath test technique and the quantitative determination of fecal fat. Thus, in using the breath test technique, it is not possible to distinguish between varying degrees of severity of fat malabsorption (291).

Clinically, breath analysis techniques using radioactive carbon tracers have been used successfully for more than 20 years to evaluate patients suspected of having a number of specific gastrointestinal disorders. In general, these tests are noninvasive, simple, reliable and safe; they are based on similar and fundamental biochemical principles and all require the use of the same type of instrumentation (296). For example, since the terminal step of oxidative metabolism of carbohydrates, lipids and other organic substrates results in the production of CO_2 and H_2O , the rate limiting step in the production of these metabolic end products, following oral administration, is intestinal absorption. Therefore, $^{14}\text{CO}_2$ breath analysis of orally administered C14-labeled compounds provides information about the rate and amount of absorption of that compound. Using this technique, if a radiolabeled fat

is administered to a patient and less than normal amounts of $^{14}\text{CO}_2$ are detected, then there may be some defect in intestinal fat absorption. On the other hand, if the administered compound is not absorbed but metabolized by intestinal bacteria, the measurement of $^{14}\text{CO}_2$ output may be such to suggest that the compound is exposed to excessive numbers of intestinal bacteria (291). Various metabolic diseases that result in a disturbance of the rate of fatty acid conversion to CO_2 can lead to confusion in the analysis of test results. Such a problematic situation can occur in patients who, at the time of testing, are known to have diabetes mellitus, hyperthyroidism, liver disease and the febrile state (291).

As eluded to previously, fat absorption breath tests have been shown to be an effective approach for the diagnostic evaluation of steatorrhea. The technique closely approaches the sensitivity and specificity of the "gold standard" (fecal fat excretion) and is markedly superior to the serum carotene test (291,297). Various methods have been devised for assessing fat absorption indirectly by measuring the metabolism of labeled lipids. Other breath analysis tests have been devised which measure parameters related to gastrointestinal absorption of various factors, and/or assess various anomalies of the GI tract (see Table 14).

Table 14. Examples of Clinical Breath Analysis Tests

<u>Clinical Application</u>	<u>Test Substrate</u>	<u>End Product</u>
1. Bacterial overgrowth	14C-glycocholate	$^{14}\text{CO}_2$
	14C-xylose	$^{14}\text{CO}_2$
2. Ileal dysfunction	14C-glycocholate	$^{14}\text{CO}_2$
3. Lactase deficiency	14C-lactose	$^{14}\text{CO}_2$
4. Small bowel transit time	14C-lactulose	$^{14}\text{CO}_2$
5. Steatorrhea	14C-triolein	$^{14}\text{CO}_2$

(adapted from Reba RC²⁹¹)

Bacterial Overgrowth and Ileal Dysfunction

Cholesterol is metabolized in the liver, yielding two polar primary bile acids. Most conjugated bile acids are not absorbed until they reach the distal ileum, where reabsorption via active transport mechanisms occurs, usually in a highly efficient manner (298). Deconjugation of bile acids by bacterial flora in the gastrointestinal tract occurs predominately in the colon and ileum. The free bile acids produced by this process are partially reabsorbed in the colon (291). This process of bile acid recycling, otherwise known as the enterohepatic circulation, remains fairly constant with the amount of fecal loss being offset by the amount derived by hepatic synthesis.

Reba and Salkeld (291) state that there are three clinically significant events which can lead to a disturbance within the enterohepatic circulation resulting in steatorrhea and/or diarrhea due to an increased rate of bile acid deconjugation. First, malabsorption of bile acids as a result of ileal dysfunction can lead to an increase in the amount of free bile acids reaching and being acted upon by colonic bacteria. Second, the anomaly can be due to an increased growth of deconjugating anaerobic bacteria within the intestines (perhaps

in a stagnant loop area). Finally, the third possible problem is related to an increased rate of enterohepatic recycling in patients lacking gallbladders.

Hepner et al. (299) noted that bile acid deconjugation could be assessed by measuring the excretion of $^{14}\text{CO}_2$ following the administration of a small dose of radioglycine labeled cholic acid. The normal enterohepatic circulation was found to have little effect on this compound. However, if the deconjugated, liberated, radiolabeled glycine compound is oxidized by intestinal bacteria (or intestinal mucosa, or the liver), the $^{14}\text{CO}_2$ that is produced appears in the exhaled breath of the patient. Using this technique, these investigators reported that following a dose of 1-2 uCi of the radiolabeled compound, the normal mean 24 hour excretion of $^{14}\text{CO}_2$ is approximately 26 % of the administered dose (with indications of abnormality being percentage values less than 26 %) (299).

In patients with uncomplicated ileal malabsorption receiving antibiotic therapy at the time of breath test testing, normalization of an otherwise abnormal bile acid breath test has been reported (291). Antibiotics could lead to a significant reduction in bile acid deconjugation and CO_2 production via their action on normal colonic bacteria. Similarly, it has been mentioned that false-negative bile salt breath tests can occur in patients with gastric retention, which causes a delay in the delivery of the substrate to the small bowel (300). It is also possible that there could be false-positive test results in situations where bacterial overgrowth is not confined to the proximal GI tract, but also appears in the stomach, esophagus and mouth, or if the stock solution of the substrate becomes contaminated in some way with bacteria (300). It has been suggested that C-14 labeled xylose (xylose being a carbohydrate that is only partially absorbed by the mucosa of the proximal small bowel, and is a sugar that is not metabolized in man), would be a better agent to use to gauge bacterial overgrowth rather than the bile acid breath test (300,301).

Gastrointestinal Protein Loss

Protein loss through the gastrointestinal tract has been associated with more than 85 different disease states, a few of which are listed in Table 15. The radionuclide techniques used to assess GI protein loss involve the intravenous administration of a radiolabeled plasma-protein tracer with subsequent measurement of activity that appears in the feces. In order for any of these techniques to work, they require the use of a tracer that is not reabsorbed by the GI tract as a result of its being broken down in the bowel due to fermentation or bacterial action (16).

Initially, I-131 or I-125 labeled albumin was utilized with the expectation that plasma turnover rates might be measured at the same time as gastrointestinal loss (302,303). Radioiodine-labeled compounds proved to be unacceptable for use because iodine, while excreted by the salivary glands and the gut, is also reabsorbed in the intestines. Waldmann (303) elected to use Cr-51 labeled albumin because chromate is not reabsorbed by the intestine; he showed that recovered tracer in the stools, following oral administration, ranged from 93 % to 100 % in his patient population. However, while this agent may be an excellent tracer for measuring gastrointestinal

protein loss, it does not lend itself to the study of albumin kinetics because the labeling process alters the albumin itself and changes its biologic half-life significantly (304). Despite this shortcoming, Cr-51 labeled albumin serves quite nicely as a tracer for assessing gastrointestinal protein loss since it does maintain its physical characteristics (i.e., molecular size, form, etc.). Knowing this, Waldmann (305) stated that a complete analysis of albumin kinetics, including gastrointestinal protein loss, requires the use of both I-131 and Cr-51 labeled albumin in the same patient.

Table 15. Conditions Which Contribute to Gastrointestinal (GI) Protein Loss

1.	<u>Lymphatic disorders</u>	
	Congestive heart failure	Peritonitis
	Granulomatous diseases	Retroperitoneal fibrosis
	Lymphomas	Whipple's disease
2.	<u>GI tract ulcerations</u>	
	GI neoplasms	Regional enteritis
	Infectious enteritis	Ulcerative colitis or gastritis
3.	<u>Diseases with unknown mechanisms for protein loss</u>	
	Abdominal irradiation	Hookworm infection
	Acute gastritis	Immune enteropathies
	Amyloidosis	Kwashiorkor
	Blind loop syndrome	Megacolon
	Celiac disease	Nephrotic syndrome
	Chronic pancreatitis	Parasitoses (various types)
	Cystic fibrosis	Postgastroectomy syndrome
	Diverticulitis/diverticulosis	Scleroderma
	Infectious mononucleosis	Toxic enteritis
	Hepatic cirrhosis	Zollinger-Ellison syndrome

(adapted from Harbert J¹⁶)

The techniques that have been proposed by various authors for determining gastrointestinal protein loss vary considerably. Most emphasize that a dose of 1 to 1.5 uCi/kg of $^{51}\text{CrCl}_3$ be administered intravenously to patients without the need for any other prior patient preparation (305). However, others have mentioned that due to the difficulty in obtaining $^{51}\text{CrCl}_3$, it is hoped that $^{111}\text{InCl}_3$ will soon be validated as a suitable alternative in procedures determining GI protein loss (291), especially since use of this radiotracer would lead to improved counting statistics and lower patient radiation dose.

To date, Cr-51 labeled albumin remains the agent of choice, and the test to measure GI protein loss can be performed in two parts over a period of four (4) days. The first part of the test involves the intravenous administration of 75 uCi of Cr-51 labeled albumin, and the patient is instructed to collect all stools (hopefully free of any potential urine contamination) for 96-hours, in 24-hour increments (290). A standard that contains 10% of the administered dose, in the same volume and geometry, is retained for use at a later time into the study (305). Daily blood samples are obtained and appropriate test samples of the plasma prepared for counting. At the end of the collection period, the stools are homogenized

and aliquots of each 24-hour sample are counted. The amount of administered dose recovered in the stool is determined using the following equation:

$$\% \text{ recovery} = \frac{\text{Net cpm (counts per minute) of all stool samples} \times 100}{\text{Net cpm of injected standard} \times \text{dilution factor}}$$

Normal subjects excrete less than 2% of the administered dose (generally in the range of 0.1% to 0.7%) during the 4-day recovery period of stool collection, whereas patients with protein-losing disorders will excrete 2% to 40% of the dose (246,261). The second part of the test involves the determination of the amount of plasma that is lost per day from the gastrointestinal tract. This value is derived using the following equation:

$$\text{Plasma lost(ml)} = \frac{\text{Net cpm in 24-hour stool collection}}{\text{Net cpm per ml of plasma on day preceding collection period}}$$

In normal patients, the value obtained can range from 5 to 35 ml per day (246).

Vitamin B₁₂ Deficiency

Megaloblastic anemia may be due to vitamin B₁₂ or folic acid deficiency, and radionuclide methods exist for the measurement of both of these vitamins.

The Schilling test is useful when malabsorption of vitamin B₁₂ is suspected. In this test, the patient is given 0.5 uCi of ⁵⁷Co-B₁₂ orally, following an overnight fast. This is followed by an intramuscular injection of 1 mg of nonradioactive cyanocobalamin (vitamin B₁₂) within a 2 hour period. The patient is asked to collect all his/her urine for a 24 hour period (hopefully free of any potential fecal contamination), after which it is measured for Co-57 content (1,3,16). Under normal situations, the radiolabeled vitamin B₁₂ links with intrinsic factor from the stomach and is then absorbed by the terminal ileum, and normal patients will yield values indicating that 8% or more of the administered radiotracer was excreted in the urine (306). Excretion of radioactive Vitamin B₁₂ in patients with impaired absorption is usually less than in patients with megaloblastic anemia, and the values are typically less than 3% if the patients have pernicious anemia (306). Patients suffering from renal failure will yield falsely low test results, as will those patients whose urine collection was incomplete. In patients suspected of having inadequate intrinsic factor, the Schilling test can be repeated with concomitant administration of intrinsic factor.

Bell and Lee (307) described a modification of the Schilling test involving a dual radionuclide approach, which has come to be known as the Dicopac test. This test permits one to distinguish malabsorption of vitamin B₁₂ due to lack of intrinsic factor (i.e., as a result of atrophic gastritis, pernicious anemia, or gastrectomy), and that due to a lesion of the small intestine (i.e., Crohn's disease) (3,307). Performance of the Dicopac test involves the simultaneous oral administration to the fasting patient of ⁵⁸Co-B₁₂ and ⁵⁷Co-B₁₂ attached to intrinsic factor, followed by an intramuscular injection of Vitamin B₁₂. As in the Schilling test, the patient collects his/her urine for the next 24 hours after which both the Co-57 and Co-58

content is determined and compared to prepared standards. The equation for determining the ratio of each radiolabeled vitamin B₁₂ is as follows:

$$\frac{{}^{57}\text{Co-B}_{12} + \text{intrinsic factor}}{{}^{58}\text{Co-B}_{12}}$$

In patients with a low serum B₁₂, if the ratio between isotopes is greater than 1.8, then the lack of intrinsic factor present is due to pernicious anemia, otherwise a small bowel lesion should be suspected (3). In this testing approach, should the patient not obtain complete urine collection during the prescribed 24 hour period, the outcome of the test itself will not be altered.

COLONIC TRANSIT STUDIES

Colonic transit scintigraphy is a method of quantifying the colonic transit of a radiolabeled marker from cecal installation to defecation. The transit of solid and liquid food through the upper GI tract has been generally well studied, but the movement of these same substances through the large intestine has received little investigative attention over the years. Several different techniques have been proposed for the studying of colonic transit such as direct observation (308), radiographic visualization of radiopaque markers (309), manometric and myoelectric measurement (310,311), and scintigraphic approaches (312,313).

Imaging Technique

Radiographic techniques for evaluating colonic motility have involved essentially two different approaches, one using radiopaque markers and the other using radionuclides. Several investigators have advocated the use of radiopaque granules which, as a marker, are given to the patient along with a meal; serial radiographs are then taken as the meal/marker passes through various segments of the intestines and the transit time for each segment is calculated (314,315). The major drawbacks in this approach are that data points are established at relatively infrequent intervals, and exact intracolonic localization of the marker (based from film readings) is difficult because of bony landmarks and gaseous outlines along anatomical borders of the colon (316).

Various approaches have been tried in terms of the scintigraphic evaluation of colonic motility. Ileal cecal transit times have been measured using Tc-99m labeled bran (221). Whole bowel transit times have been determined following administration of Tc-99m and/or In-111 labeled resin bead (318), as well as a combination of Cr-51 chromium chloride along with Tc-99m sulfur colloid (319). Each of these techniques is primarily investigative in nature, but they nevertheless yield important information concerning the small bowel, colonic transit and the pathophysiology of irritable bowel syndrome (including the various causes of diarrhea and constipation) (103).

Many of the scintigraphic techniques that have been described in the literature involve an invasive aspect to them.

For example, Krevsky et al. (313) employed a methodology that called for the insertion of a 4.5 meter long, 3mm diameter tube into the patients cecum in order to control the release of the radionuclide (50 uCi of In-111 DTPA). Patients were then fed a meal after which serial scintigrams were obtained over a 48 hour period using geometric analysis of predetermined regions of interest. Following the ingestion of a balanced diet (containing approximately 20 gm of dietary fiber), the study is complete after 3 days. It was reported that the cecum and ascending colon emptied quite rapidly with a half-emptying time of approximately 88 minutes. Activity in the rectum and sigmoid colon increased within 20-30 hours, while activity in the transverse colon declined (313).

Scintigraphic methods involving radiolabeled fiber (320,321) and cation exchange resin beads (322) have recently been proposed as acceptable approaches for the measurement of colonic motility in patients. Despite apparent misgivings about the potential solid-liquid discrimination factors that must be considered as the test substances move through various parts of the intestines, it has been shown that large intestinal transit of encapsulated radionuclide materials can be very reproducible within both individual patients or groups of patients. This is true, at least, when there is strict adherence to dietary considerations and imaging schedules during the course of testing.

For example, Stubbs et al. (323) employed the use of 100 uCi of In-111 encapsulated in 2 cm nondigestible capsules, which were administered to patients following a 6 hour fasting period. Additionally, 250 uCi of Tc-99m sulfur colloid was also administered in order to facilitate outlining of the gastrointestinal tract. Images of preset regions of the colon were acquired at 4-hour intervals until all the administered capsules were excreted.

Other investigators (321,324,325) have described the use of I-131 labeled cellulose, however, the full scope of how this approach can be relied upon in the assessment of colonic transit is not yet fully appreciated. For example, constipation is a common problem in patients, but most only seek medical attention when it becomes severe. McLean et al. (326) studied the use I-131 labeled cellulose in both normals and patients suffering from constipation. Following dosing with the radiotracer, patients were imaged at pre-set time points for up to 96 hours. These investigators found that there are clear differences between normal and constipated patients, in terms of the total percent of retention at all time intervals, as well as in all intestinal segments examined at 48 and 72 hours. The three-day urinary excretion of radioiodine was minimal (only 2.4% in constipated patients and 3.1% in normals, with approximately 75% of radioiodine excretion taking place within the first 24 hours).

There are several reasons why the use of I-131 labeled cellulose has not received more attention, but the technique itself remains a promising one (327). First, the preparation of the radiolabeled fiber is rather time consuming and it requires the use of specialized personnel. However, given the long half-life of the radioiodine itself, it may be possible to prepare a monthly supply of material at one time. Because there is a small dissociation of the radionuclide from the cellulose, patients should be pretreated with Lugol's solution to prevent

thyroid accumulation of the radioiodine. Second, technical allowance must be made for the fact that while most of the colon is situated anteriorly in the abdomen, the rectum is positioned more posteriorly. Therefore, calculated activity in this region can be underestimated due to attenuation. Also, when acquiring anterior images of the abdomen, it may be desirable to do so utilizing smaller segmental regions of interest in order to maximize precision and reproducibility. For example, depending on where regions of interest are established, retention results may vary from patient to patient for a particular segment, although the total percent retention may be unaltered.

MISCELLANEOUS PROCEDURES

Rectal Emptying Studies

Rectal emptying studies are principally used only as a research tool today. When the desire arises to evaluate problems of defecation in patients involving constipation or severe diarrhea, various techniques are available such as anorectal manometry, recto-anal inhibitory reflex measurements, defecating proctogram using barium and use of a radiolabeled stool analogue (103). The radionuclide approach enables investigators to quantitate the rate of emptying and the percentage emptying of the radiolabeled stool analogue (103).

Gastric and Duodenal Ulcer Detection

Technetium-99m sucralfate has been used in the detection of gastric and duodenal ulcers because it adheres to the site of mucosal ulceration (328,329). Others have proposed the use of this radiopharmaceutical as a means for detecting oral microlesions, since the use of unlabeled sucralfate is effective in preventing chemotherapy- and radiotherapy-induced oral mucositis (330). Bonazza et al. (331) noted that in patients who swished a 2 ml suspension of Tc-99m sucralfate (1.5 mCi) in their mouths without swallowing the material, no focal uptake (except for slight, persistent activity in the mouth) was seen in control patients. In all cases with macroscopic lesions, however, a relatively larger uptake of the labeled sucralfate was seen. Based on the scintigraphic observation that there was adherence to minimal lesions in control patients, it has been suggested that the material will adhere to microscopic lesions and a prophylactic effect could result from therapeutically preventing the deterioration of such lesions (331).

Nuclear Enema and GI Bleed Detection

Mentioned briefly under the discussion for gastrointestinal bleed detection, Bunker et al. (332) have described a procedure involving the use of Tc-99m DTPA in what they refer to as a "nuclear enema," a technique for scintigraphically demonstrating colonic activity. When dealing with situations of gastrointestinal bleeding, the configuration of extravasated radiotracer can be misleading, and the differentiation of colon from the small bowel is sometimes quite impossible. These investigators showed how a standard radiographic enema bag, designed for air-contrast examination, was modified slightly and filled with 1500 ml of warm tap water and elevated about

one meter above the plane of the supine patient. Approximately 300 ml of water was released from the reservoir after injection of 3 mCi of Tc-99m DTPA from a tuberculin syringe. A larger syringe containing 10 ml of water was used to flush the tubing system. Controlled volumes of water from the reservoir were subsequently released and the progress of the radionuclide activity through the colon monitored using the persistence oscilloscope of the standard gamma camera. Extravasated blood pool activity in the gastrointestinal tract that remains extracolonic after the administration of the Tc-99m DTPA enema can be assumed to represent upper gastrointestinal tract hemorrhage. Conversely, extravasated blood-pool activity corresponding to that of the radiotracer in the colon confirms a colonic source of hemorrhage.

Intraabdominal Blood Flow

Various techniques to study intraabdominal distribution of blood, detection of ischemic bowel and lesions characterized by pooling or extravasation of blood have been described by several authors (333-340). Although not all of these techniques are currently being utilized for diagnosis, they are important because of the basic methodology involved. Most of these techniques are noninvasive and can be repeated in short intervals for evaluation of a given parameter that, if desired, can be changed with pharmacologic intervention. Most of these techniques involve the rectal administration of radiotracers (i.e., Na-24, I-131 sodium iodide, Tl-201 thallous chloride, N-13 ammonia and Tc-99m pertechnetate) in order to study the portal circulation.

Diffusible inert gases like xenon can be injected into the intestinal mucosa, and the rate of radiotracer disappearance serves as a measure of intestinal blood flow (with activity reaching the liver at a rate proportionate to the rate of removal from the intestines) (341).

Arönsen et al. (342) have performed studies utilizing Tc-99m pyrophosphate (PYP) in an attempt to scintigraphically demonstrate an ischemic loop of bowel in newborns with necrotizing enterocolitis. The maximum injected dose was 500 uCi of Tc-99m PYP, and the most common finding was that of diffuse abdominal uptake, which either preceded or accompanied liver uptake of the radiotracer. The explanation for the liver uptake was not clear, but the activity was limited to the hepatic parenchyma and the spleen was never visualized (342). It was theorized that the radiotracer interacts with the necrotic debris in the intestines and forms aggregates that drain into the portal system and the liver, or the radiotracer may be present in peritoneal fluid and following the formation of aggregates with debris, peritoneal macrophages then carry the resultant complexes to the liver.

Finally, scintigraphy using Tc-99m labeled RBCs provides for an excellent demonstration of the intraabdominal distribution of blood. Portal hypertension with collateral circulation has a characteristic scintigraphic appearance, with the liver appearing as a hypoactive area contrasting with other normal imaging studies where the liver displays uniform activity. Such a pattern can create confusion when searching for sites of gastrointestinal bleeding.

CONCLUSION

In this CE lesson, we have taken a glimpse of the multifaceted subject of radionuclide scintigraphy of the gastrointestinal tract.

While some aspects of this topic seem to be popular in terms of routine applications in nuclear medicine practice (i.e., detection of GI bleeding and Meckel's diverticulum imaging), a majority of the imaging procedures discussed here remain underutilized by the medical community in favor of diagnostic information that can be obtained from other imaging/testing procedures. Some studies are, in fact, still of an investigational nature, for the most part.

Nonetheless, it is hoped that a greater appreciation for the full range of studies that can be performed in GI tract scintigraphy has been obtained, and that the reader will take the time to try and further expand his/her interests in this subject.

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Self-Assessment Questions

1. Increased concentration of Tc-99m sodium pertechnetate in the salivary glands occurs in which of the following?
 - a) Carcinoma
 - b) Lymphoma
 - c) Mixed tumors
 - d) Oncocytomas
2. Which of the following is not considered to be a primary motor disturbance of the esophagus?
 - a) Achalasia
 - b) Amyloidosis
 - c) Scleroderma
 - d) Spasm
3. In normal patients, the transit time of a liquid bolus from the pharyngoesophageal junction to the cardia is approximately:
 - a) 10 seconds
 - b) 20 seconds
 - c) 30 seconds
 - d) 60 seconds
4. Which of the following diagnostic modalities can be considered as a "standard" to which scintigraphic test results for evaluation of gastroesophageal reflux can be compared?
 - a) Acid reflux test
 - b) Barium esophagography
 - c) Endoscopy
 - d) Esophageal manometry
5. Gastroesophageal reflux scintigraphy can be used as a tool for evaluating a patient's response to therapy. Which of the following is not a therapeutic approach used for gastroesophageal reflux?
 - a) Atropine sulfate
 - b) Bethanecol
 - c) Gaviscon
 - d) Surgery
6. Gastric emptying in patients can be influenced by all of the following parameters of a meal except:
 - a) Chemical composition
 - b) Osmolality
 - c) pH
 - d) Volume
7. Which of the following pharmacologically promotes an increase in the rate of gastric emptying in patients?
 - a) Cholecystokinin
 - b) Insulin
 - c) Secretin
 - d) Somatostatin
8. Which of the following radiopharmaceuticals has not been used as a radionuclidic marker in conjunction with meals in gastric emptying studies?
 - a) Cr-51 sodium chromate
 - b) In-111 DTPA
 - c) I-123 sodium iodide
 - d) Tc-99m albumin colloid
9. Which of the following drugs can have a pharmacologic effect of accelerating the rate of gastric emptying in patients?
 - a) Bethanecol
 - b) Chloroquine
 - c) Dopamine
 - d) Morphine
10. Which of the following conditions can contribute to a false-positive interpretation in the evaluation of Meckel's diverticulum?
 - a) Duodenal ulcer
 - b) Hemangiomas
 - c) Malignant lymphoma
 - d) Renal tract activity due to hydropelvis
11. Which of the following is not a valid reason for selecting Tc-99m labeled RBCs over Tc-99m sulfur colloid for the evaluation of gastrointestinal (GI) bleed?
 - a) Imaging up to 24 hours post-injection possible in some patients
 - b) Lower radiation dose to the liver and spleen
 - c) Agent can be used for detection of upper GI bleeding
 - d) Specificity of 100%
12. Which of the following can not be used as an interventional maneuver to enhance testing outcomes for the detection of GI bleed site(s)?
 - a) Cholecystokinin
 - b) Glucagon
 - c) Heparin
 - d) Vasopressin
13. Which of the following is not a technique used for the assessment of gastric emptying in patients?
 - a) Barium burger
 - b) Installation of phenol red indicator
 - c) Saline load test
 - d) Serial intubation and aspiration
14. Which of the following drugs does not contribute to a prolongation in the rate of gastric emptying in patients?
 - a) Domperidone
 - b) Hexamethonium
 - c) Librax
 - d) Phenytoin

15. Which of the following can be described as a rapidly extracted imaging agent for use in gastrointestinal bleed studies?
- In-111 labeled red blood cells
 - Tc-99m albumin
 - Tc-99m labeled, heat-damaged red blood cells
 - Tc-99m sodium pertechnetate
16. Which of the following is not considered a disadvantage when using Tc-99m labeled RBCs for the evaluation of GI bleed episodes?
- Liver and kidney activity can interfere with interpretation of test results
 - Dissociation of the label can occur in vivo
 - Detects intermittent bleeding episodes without the need for repeat injections
 - Obtaining delayed images may impair identification of GI bleed site(s)
17. The test substrate for use in the clinical evaluation of ileal dysfunction is:
- C-14 xylose
 - C-14 glycocholate
 - C-14 lactulose
 - C-14 triolein
18. Which of the following is not a factor in contributing to gastrointestinal protein loss in patients?
- Amyloidosis
 - Congestive heart failure
 - Cystic fibrosis
 - Diabetes mellitus
19. Which of the following is a factor in contributing to steatorrhea in patients?
- Diverticulitis
 - Hookworm infection
 - Kwashiorkor
 - Pancreatic fibrosis
20. Which of the following is not used as an interventional technique during the course of salivary gland imaging?
- Ascorbic acid
 - Atropine sulfate
 - Lemon drop
 - Potassium perchlorate
21. Which of the following is not considered to be a clinical manifestation of severe gastroesophageal reflux in children?
- Intermittent wheezing
 - Tonsillitis
 - Aspiration pneumonia
 - Nocturnal cough
22. Which of the following is not a true statement concerning the quantitation of gastric emptying studies?
- Radionuclide markers must remain stable in vivo during testing
 - Standardized meals (in terms of their size and composition) should be used
 - Patient position and posture can vary during testing when data analysis by means of geometric mean is employed
 - Allowance should be made for photon interference when more than one radionuclide marker is used
23. Which of the following conditions can contribute to an acceleration in gastric emptying rates in patients?
- Cigarette smoking
 - Hypothyroidism
 - Obesity
 - Trauma
24. Which of the following conditions can contribute to a prolongation in gastric emptying rates in patients?
- Duodenal ulcer
 - Electrolyte imbalance
 - Surgery (pyloroplasty)
 - Zollinger-Ellison syndrome
25. Which of the following statements is not true as it pertains to the behavior of liquid or solid meals in gastric emptying?
- Liquid meal emptying alone approximates a monoexponential curve
 - Liquids emptying faster than solids in normal patients
 - In mixed liquid-solid meal studies, the liquid component empties in a biphasic fashion
 - Solid meal emptying alone exhibits zero-order