Detection of Ectopic Gastric Mucosa in Meckel's Diverticulum and in Other Aberrations by Scintigraphy: I. Pathophysiology and 10-Year Clinical Experience

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Ten years of clinical experience with pertechnetate (Tc-99m) scintigraphy has proven its validity for the diagnosis of ectopic gastric mucosa in bleeding Meckel's diverticulum and other congenital anomalies. Careful patient preparation and a standardized technique based on sequential gamma imaging has resulted in an overall sensitivity of 85%. Experience in differentiating "nonspecific" accumulations of pertechnetate from true ectopic gastric mucosa has increased the specificity to 95%. When we consider all the studies reported (954) with a surgical or clinical diagnosis, the accuracy of the method is calculated at 98%. When only surgically proven cases are analyzed, the calculated accuracy is 90%. Pertechnetate excretion by the mucoid cells of gastric mucosa is the basis of this test. The effect of drugs and hormones on the test has been studied in animals and in patients. The findings suggest that an improvement can be achieved by the use of cimetidine, pentagastrin, or glucagon.

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Since the clinical introduction of the pertechnetate anion ($^{99m}TcO_4^-$) (*1*), it has been known to concentrate in the gastric mucosa (*1-3*). In 1967, Harden et al. (*3*) proposed the use of this radioindicator for the noninvasive diagnosis of Meckel's diverticulum with ectopic gastric mucosa. In 1970, the method was introduced into clinical practice by Duszynski et al. (*4-6*). Many reports followed about the method (*7-26*) or the clinical significance (*27-66*). Experimental studies in animals were also performed (*67-82*), and the method was utilized to diagnose Barrett's esophagus (*83-86*).

Abdominal imaging with pertechnetate has become an established routine procedure in children and adults. Ten years after the initial publications, the pathophysiologic mechanisms involved have been revealed, significant clinical experience has been accumulated, the merits of this approach have been evaluated, and clinical indications and methods have been standardized, but further research is still needed to improve its sensitivity.

The pathophysiology and the past clinical experience on pertechnetate abdominal imaging are described in this paper. The current knowledge on indications, patient preparation, imaging techniques, principles of interpretation, and dosimetry will be the subjects of a future publication.

PATHOPHYSIOLOGY

The clinical suspicion of bleeding ectopic gastric mucosa in a Meckel's diverticulum is the principal indication for pertechnetate abdominal imaging, since this condition is nearly always missed by roentgenologic methods, including angiography (*15,90-92*).

Meckel's diverticulum is a congenital outpouching usually located in the distal 100 cm of the ileum, a remnant of the omphalomesenteric duct of the embryo (Fig. 1). It occurs in 1-3% (*11*) of the general population, but only 25-40% are symptomatic (*17*). Of the symp-

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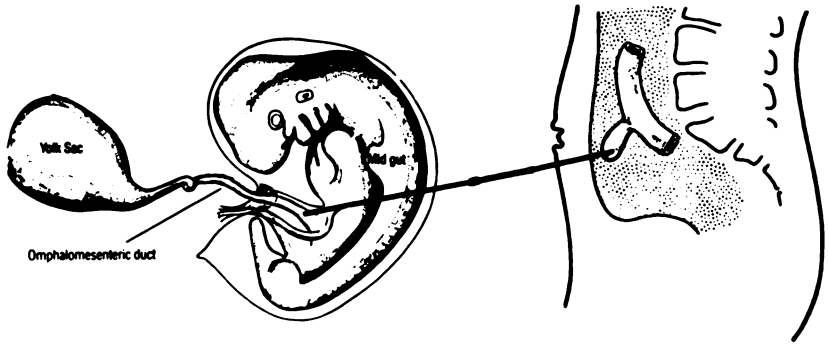

FIG. 1. Omphalomesenteric duct and Meckel's diverticulum.

tomatic Meckel's diverticula, 57% contain ectopic gastric mucosa. Significant acid-peptic secretion may lead to complications because of ulceration of the unprotected adjacent intestinal mucosa and severe bleeding; less commonly there is perforation, obstruction, and occasionally pain (*87*). Bleeding, as well as other complications from a Meckel's diverticulum, are much more common in early life: more than 50% occur by the age of 2 yr (*87*). Diverticulitis, enteroliths (*88,89*), and intestinal obstruction complicating Meckel's diverticulum are usually unrelated to ectopic gastric mucosa, which may be present incidentally (*87*).

Ectopic gastric mucosa can also be found in gastrogenic cysts (*14*), enteric duplications (*41,51,58,66*), duplication cysts (*42,52*), in an otherwise normal small bowel (*29,46*), or in the esophagus (Barrett's esophagus) (*86*). Identical complications may occur through acid-peptic secretion of the ectopic tissue.

Obstructed loops of bowel (*27*), intussusception (*4,5,27*), inflammatory lesions (*27,47,58,65*), arteriovenous malformations (*29,30,50*), ulcers (*58*), and some tumors of the bowel (*34,57*)—along with urinary-tract abnormalities—have been related to pertechnetate abdominal imaging because of positive findings due to nonspecific accumulation of the pertechnetate.

The pertechnetate anion (TcO_4^-) is selectively accumulated and subsequently excreted into the bowel lumen by the mucoid surface cells of the gastric mucosa (*1,46,67,68,73,75,77,79,85*). These cells excrete an alkaline juice, approximate in ionic composition to an ultrafiltrate of plasma to which mucus has been added. The mucus as a gel entraps the alkaline fluid, and the resulting juice has a pH of 7.67. It forms a mucous film that protects the mucosa from the high acidity of the gastric fluid. The secretion of the alkaline fluid is spontaneous, but mechanical, neural, and hormonal stimuli influence its rate (*93,94*). Histologically identical cells are present in the mucosa of the intestine, but they are less abundant and their excretory rate is much lower than that of the gastric mucosa. Although a histologic diagnosis of ectopic gastric mucosa is based upon the finding of parietal cells, these may be absent and the pertechnetate study positive if mucoid surface cells are present. Parietal cells do not specifically accumulate $^{99m}TcO_4^-$, so are not essential for imaging purposes (*85*). There are similarities between the uptake of pertechnetate in the salivary glands and gastric mucosa.

The pertechnetate anion is therefore accumulated, probably actively, and secreted by the gastric mucosa and also, to a lesser degree, by the upper small intestine, whereas the distal ileum and the large bowel do not significantly accumulate pertechnetate (*76*) unless inflamed or stimulated by food or drugs (*72*). Forward propulsion of the radioactive secretions takes place at different rates from the stomach, through the duodenum, and into the small bowel, adding to the visualization of these hollow organs (*24,80,81*).

Ectopic gastric mucosa accumulating pertechnetate can be detected by imaging because it contrasts against the relatively low background radioactivity of the abdomen or the chest. Ectopic gastric mucosa can be either simulated or obscured (*21*) by the images of normal organs or various abnormalities that appear on the scintigram. Duodenal and jejunal accumulation of pertechnetate is a common phenomenon, and so are renal parenchyma, renal pelvic, ureteral, and bladder accumulations. Thus, these organs can normally be seen to a varying degree, and they may be distinct and confusing if enhancing conditions exist, such as active secretion in the intestine (digestion, drug action, inflammation, or obstruction, including intussusception) or obstructive urinary-tract disease. Preparation of the patient, and familiarity with the anatomy of these normal or abnormal organs, help in their differentiation. Lesions with an increased blood pool, such as arteriovenous malformations, hemangiomas, and other tumors, may show up, but if they do not accumulate pertechnetate, they appear early (flow study, first 10 min) and then fade, whereas gastric mucosa generally becomes more prominent with time. Finally, some lesions, particularly neurogenic tumors, may localize the pertechnetate anion and produce images suggesting the presence of ectopic gastric mucosa. Any structures with reduced or absent blood pool will appear on the scan as photon-deficient regions. They can be physiologic (bowel content before accumulating radioactive secretions, urinary tract containing urine before arrival of pertechnetate) or pathologic (obstructed regions of bowel, hydronephrosis especially early in the study, cysts, and cystic or necrotic lesions).

It is logical that a Meckel's diverticulum without ec-

topic gastric or distal esophageal epithelial metaplasia without gastric mucoid cells will not accumulate pertechnetate. Barrett's esophagus by definition presents ectopic gastric mucosa with or without parietal cells, and therefore would accumulate pertechnetate, but metaplasia of the esophageal mucosa due to acid injury may not be seen unless it is lined by mucoid cells.

Drugs and hormones influence the localization of pertechnetate in the gastric mucosa (*2,3,78*), and in situ or ectopic (*23,37,69*). Perchlorate anion suppresses the localization (*2,3,37,69,70,95*), pentagastrin enhances it (*23,71,78,96*), and cimetidine (*24*) and glucagon (*80,82*) indirectly increase the concentration. Most probably cimetidine, a potent histamine H_2-receptor antagonist, inhibits the intraluminal release of pertechnetate (*81*); glucagon, an intestinal antiperistaltic (*97,98*), enhances the image by suppressing "wash-away" and dilution of the intraluminal activity, which thus accumulates at the site of gastric mucosa (*80*). Therefore, perchlorate is not given before the study, and pentagastrin (*23*) and cimetidine (*24*) have been used to optimize imaging of ectopic gastric mucosa in patients. Glucagon, or a combination of glucagon and pentagastrin, improved the imaging of experimental ectopic gastric mucosa in dogs (*80,82*). Histalog slightly stimulates (*68,78*), atropine blocks (*2*), and secretin has no effect on pertechnetate localization in the gastric mucosa (*78*). Finally, in one patient, intravenously injected pertechnetate failed to leave the intravascular space when hyperaluminemia was present (plasma aluminum levels 65 μg/l, as opposed to 5.8 μg/l in pooled plasma) and the stomach or bladder was not seen. The normal pattern returned 2 mo after discontinuation of the 7.2 g per day of aluminum hydroxide medication (*20*).

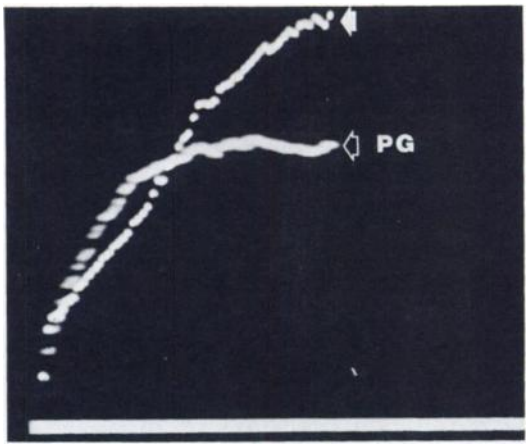

FIG. 3. Gastric activity from dog as detected by sequential 1-min computer acquisition of abdominal images after 2 mCi of pertechnetate i.v. Solid arrow indicates curve from study without hormone. Pretreatment with pentagastrin (PG), initially increases both uptake and wash-away, so that activity levels off.

In experiments in dogs, full-thickness, viable, ectopic patches of gastric mucosa larger than 1.8 cm^2 were reported to be required for visualization with the gamma camera (*68*). It was recently determined, however, that 1-cm^2 lesions were clearly visualized (Fig. 2) using a gamma camera with 11-in. crystal, 19 photomultiplier tubes, and high-resolution collimation (*80,82*), which is in accord with studies on retained gastric antrum (*99*). In dogs, the peak target-to-nontarget ratio is achieved

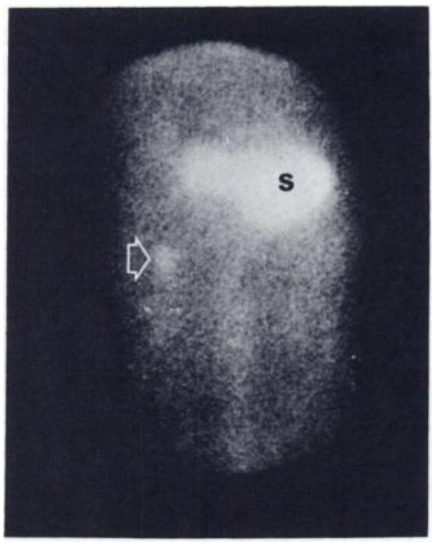

FIG. 2. Abdominal scintigram in dog with experimental ectopic gastric mucosa in RLQ, 40 min after 2 mCi of pertechnetate i.v. Experimental patch of gastric wall measured 1 cm^2 at autopsy. Arrow indicates increased activity at site of lesion. S = stomach.

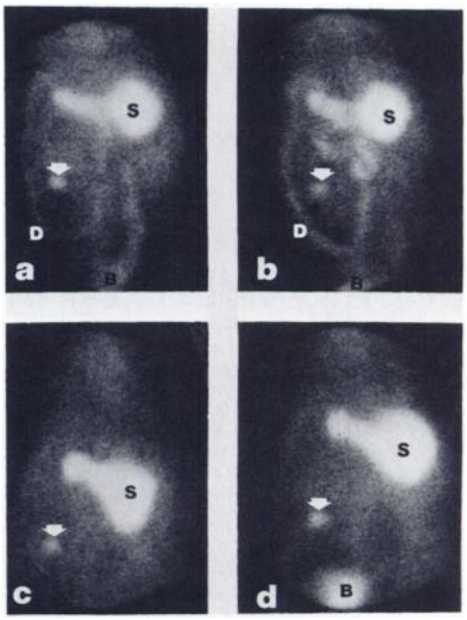

FIG. 4. Abdominal scintigrams from dog with experimental ectopic gastric mucosa, 60 min after 1 mCi of pertechnetate i.v. Visualization of intestine and decreased lesion activity resulted from "wash-away" of activity in control (a) or after pentagastrin (b), but these were blocked by glucagon, used alone (c) or with pentagastrin (d). Arrows show lesion. S = stomach; D = duodenum; B = urinary bladder.

at 60 min after injection, when the study was terminated, and it probably occurs even later (Fig. 3). "Wash-away" of the activity from the site of the lesion has been observed to occur automatically or after using pentagastrin. It can be prevented by glucagon (Fig. 4) or cimetidine (*24*).

PAST CLINICAL EXPERIENCE

Pertechnetate (Tc-99m) abdominal imaging was proposed initially as a method to study the stomach (*2,3*), and as such it has found limited clinical application in assessing gastric function and in detecting residual gastric tissue following gastrectomy (*99*), although clearly the test is not directly related to the pepsin-acid secretion of the gastric mucosa.

For those miscellaneous abdominal diseases for which it was originally proposed (*4,6,27*) (intussusception,

TABLE 1. REVIEW OF PAPERS REGARDING CLINICAL EXPERIENCE WITH PERTECHNETATE SCINTIGRAPHY

First author and reference	Presenting symptoms*	Instrumentation, technique, premedication†	No. of patients studied‡	Reported Results: Total scintigrams	Reported Results: Abnormal studies	Reported Results: Normal studies	Reported Results: Equivocal or uninterpretable	Correlation with surgery: True positives for EGM¶	True negatives for EGM	False positives for any lesions	False negatives for EGM	Excluded studies: Reported abnormal studies without EGM: Other surgical lesions (atypical positives)	Excluded studies: Reported abnormal studies without EGM: Technique or misinterpretation	Excluded studies: Reported negative for EGM studies due to technique or misinterpretation
Duszynski (*4, 6, 27*)	RB, AP, An, Ob, Mis.	RS (0.5, 4, 24 hr) perchlorate originally	50 C	52	27	23	2	3	7	0	1	§		
Rosenthal (*28*)	RB, AP, An Ob, Mis.	GC	45 C	45	4	41		4	8	0	4			
Leonidas (*33*)	RB, AP	GC	13 C	13	4	9		2	1	0	1	1		
Berquist (*46*)	RB, Ap, An, Ob, Mis.	RS (15, 45 min)	22 C 78 A	111	8	102	1	8	23	0	1			
Kilburn (*19*)	RB, AP	GC	170 C	170	14	156		11	1	1	1		2	
Gelfand (*56*)	RB, AP	GC (prone or R decubitus)	58 C	58	6	45	7	6	6	0	2			
Sfakianakis (*22*)	RB, AP, An	RS (57 pts)	57 C	57	7	50		5	6	0	1		2	3
		GC (63 pts)	63 C	66	8	57	1	7	5	0	0			1
Ho (*41, 58*)	RB, AP	GC	83 C	83	7‖	64		6	0	1	1			
Musse (*54*)	RB, AP	RS, GC	5 C	7	2	5		2	2	0	0			
Schussheim *10, 55*)	RB	GC-videotape	70 C	70	5	65		5	1	0	0			
Yamaguchi (*59*)	RB, Mis.		15, C,A	18	12	6		9	3	0	3			
Seitz (*60*)	RB: (42 pts)		42 C,A	42	11	21	10	6	21	1	0	4		
	Mis. No-RB (98 pts)	GC-videotape	98 C,A	98	0	98								
Petrokubi (*24*)	RB, AP	GC, cimetidine	4 C,A	8	4	4		2	0	0	0			
Feggi (*25*)		GC (nasogastric aspiration)	12 C	16	4	12		1	0	0	0			
Singh (*21*)	RB, An	GC (nasograstric aspiration)	4 C,A	6	1	2	3	1	1	0	0			
Case reports (*7, 13, 16, 23, 29, 30, 32,* 34–38, 42, 43 45, 50–53, 57, 61–66, 68)	RB, AP, An	RS, GC nasogastric aspir. (16) perchlorate (7, 13, 66) perchlorate with/ without (37, 53) pentagastrin (23)	28 C,A	34	24	7	3	16	6	2	1	2	4	1
Total			917	954	148‖	767	27	94	91	5	16	7§	8	5

* RB = rectal bleeding; AP = abdominal pain; An = anemia; Ob = obstruction; Mis = miscellaneous.

† RS = rectilinear scan; GC = gamma camera; pts = patients.

‡ C = children; A = adults.

¶ EMG = ectopic gastric mucosa.

§ A number of studies, not clearly specified, had atypical, positive results due to other surgical or medical diseases.

‖ Twelve studies were reported "positive" for gastroduodenal ulcer and were excluded.

obstruction, localized or generalized inflammation, including infection), subsequent reports (*28,46*) documented poor sensitivity and specificity and, therefore, that clinical application was abandoned. Lack of specificity and sensitivity precludes its use for detection of tumors and arteriovenous malformations (*46*). The diagnosis of gastroduodenal ulcer has been proposed as a potential application of pertechnetate imaging (*41,58*), but no further work was done and certainly more efficient and specific tests are available for this problem. Meckel's diverticulum without ectopic gastric mucosa, manifested clinically by obstruction and related problems (*87*), has given consistently negative pertechnetate images, as would be expected (*28,60*).

Encouraging results, however, appeared in the literature from the application of pertechnetate abdominal imaging in the nonoperative evaluation of the child or adult with acute massive rectal bleeding (hematochezia), and less commonly in patients with melena or chronic intermittent or low-grade rectal bleeding (Table 1). This test could indicate reliably the existence of ectopic gastric mucosa, which is usually located within a Meckel's diverticulum. Associated anemia, and occasionally abdominal pain, were present in those patients as a result of the bleeding from, or inflammatory reaction around, the acid-peptic ulcer. Unlike pertechnetate imaging, other radiological studies, including angiography, are usually negative or noncontributory for the diagnosis of bleeding ectopic gastric mucosa in a Meckel's diverticulum (*15*).

Endoscopy locates the bleeding in more than 95% of the patients with hemorrhage from the esophagus, stomach, or duodenum, and radiological contrast studies may also be positive. Active bleeding from the jejunum, ileum, or large intestine as a result of tumors or polyps can also be detected with contrast radiological studies, but the majority of patients with intestinal bleeding, particularly children, remain without a specific diagnosis, and usually the hemorrhage is not recurrent. Although Meckel's diverticulum is an uncommon cause of rectal bleeding, pertechnetate imaging is a specific and noninvasive method to diagnose ectopic gastric mucosa. Before its introduction, the diagnosis was made at laparotomy in approximately 60% of the patients who presented with clinically suggestive symptoms and laboratory findings (*10,60*). With the introduction of the gamma camera, the standardization of the technique, and the recognition of other conditions producing positive scans, the accuracy has improved. An analysis of data compiled from the literature of 5 yr ago indicates that the accuracy of the radionuclide technique for detecting surgically proven ectopic gastric mucosa in Meckel's diverticulum was "at least 78%" (*48*). The specificity of the method was found to be 79%, with false-positive interpretations resulting from suboptimal techniques—such as rectilinear imaging or delayed imaging, and the positive images of normal organs or different types of intra-abdominal lesions. The sensitivity of the method was found to be 75%, with false negatives resulting from suboptimal techniques, from use of perchlorate (*6*), from insufficient or destroyed gastric tissue, or from downstream wash of the pertechnetate by active bleeding or excessive secretions and/or motility.

A comparative analysis of earlier and more recent studies from one institution (Table 1, Sfakianakis) demonstrates that newer techniques and clinical expe-

TABLE 2. 10-YR REPORTED EXPERIENCE ON PERTECHNETATE IMAGING

Total no. of studies	954
Reported normal	767
Reported abnormal	148
Uninterpretable or equivocal	27
Excluded (ulcer disease?)	12
Patients with Surgically Proven Diagnosis	
Total no. of studies	226
Ectopic gastric mucosa:	
True positive	94
True negative	91
False positive	5
False negative	16
Other surgical lesions:	
Atypical positive studies	7
Poor technique or misinterpretations:	
Reported as positive	8
Reported as negative	5

TABLE 3. CLINICAL USEFULNESS OF PERTECHNETATE IMAGING

A. Correlation with surgically proven diagnosis	
Total Number of studies	226
(excluded	20)
For ectopic gastric mucosa:	
Sensitivity $\left(\frac{TP}{TP + FN}\right)$	85%
Specificity $\left(\frac{TN}{TN + FP}\right)$	95%
Accuracy $\left(\frac{TP + TN}{TP + TN + FP + FN}\right)$	90%
B. Correlation with surgical and clinical diagnosis or no recurrence of bleeding	
Accuracy	98%

TP = true positive; TN = true negative; FP = false positive; FN = false-negative studies.

rience have improved the accuracy of the method to a point that, in two groups of about 60 patients each, the false-negative rate was reduced from 8 to 2% and the false positive from 4 to 0%, based on combined surgical and clinical data (*22*).

In the literature available to us, we found series and case reports to total 917 patients with 954 studies, of which 148 were reported as abnormal and 767 as normal (Table 2). Twenty-seven (2.8%) studies were reported as equivocal or uninterpretable, and several cases were interpreted as showing other abnormalities (ulcers, etc.). There were 226 studies with a surgically proven diagnosis of which 94 were true positive (TP) and 91 true negative (TN) (Table 3). Five cases are excluded as technically poor or as misinterpretations (according to the authors), resulting in 16 false negatives (FN). Of the 20 studies reported "positive" without ectopic gastric mucosa at surgery, seven had other surgical lesions (these are considered "atypical positive cases"), and eight were misinterpretations or technically poor studies, leaving five cases as false positive (FP). The sensitivity (TP/TP+FN) for diagnosis of ectopic gastric mucosa (accepting comments of authors excluding "atypical" cases) was found to be 85%, and the specificity (TP/TP+FP) for ectopic gastric mucosa 95%. On the basis of "tissue diagnosis" alone (surgery or biopsy), the accuracy of the method—(TP+TN)/total surgical cases—is 90%. When considering all the negative studies in patients with either a different clinical diagnosis or no recurrence of bleeding, we calculate a 98% accuracy.

Obviously, the results of this 10-yr experience have proven the validity of the method. Lesions other than those with ectopic gastric mucosa can result in "atypical" positive scans. The sensitivity of the method (85%) is good but not excellent. There is hope, however, that the false-negative studies may be reduced following the clinical application of hormonal (pentagastrin and/or glucagon) or H_2-receptor-blocking agents.

A site of active bleeding at >0.1 ml/min can be located by imaging with Tc-99m sulfur colloid (*100*). This method has not been applied to a significant degree in children. If radiological and pertechnetate studies are negative, Tc-99m SC can be used to locate the bleeding site when laparotomy is contemplated, although 1 or 2 days would be required for the pertechnetate activity to decay before this method could be applied. It is certainly possible to perform successively a Tc-99m sulfur colloid study and a pertechnetate study. The merit of this approach has to be evaluated, in terms of the benefit of the potential discovery of a bleeding site, the additional radiation exposure to the patient, and the possible masking by the liver image of some Meckel's diverticula located above the level of the umbilicus.

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