Gastric Emptying and Intragastric Distribution of Lipids in Man

A New Scintigraphic Method of Study

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We measured gastric emptying of fat and water from a solid–liquid meal in healthy volunteers using a tubeless scintigraphic method. Selenium-75 glycerol triether, incorporated in butter, was the lipid-phase marker, and technetium-99m, ingested with 250 ml water, the non-lipid-phase marker. In seven of these subjects we also measured the gastric emptying of solids and liquids with technetium-99m bound to cooked egg whites as the solid-phase marker and indium-111 ingested with 250 ml water as the marker of the solid and aqueous phases. Emptying and intragastric repartition of each marker were measured by detection of radioactivity changes over the abdominal area using a gamma-camera. The stability and the specificity of the labeling was checked for each marker. Mean gastric emptying rate (expressed as percentage ingested marker emptied per hr) of lipids (17.4 ± 2.4) was much lower than that of the rest of the meal (34.2 ± 1.8) and slightly, but significantly, lower than that of solids (22.8 ± 1.8). An intragastric layering of fat above nonlipids was observed only after the first postprandial hour and remained moderate. Thus, lipids are emptied more slowly than any other component of an ordinary meal, and this is not due only to layering of fat above water.

During the last few years, new methods of investigation using scintigraphic detection of isotopically labeled food (1) or intubation with gastric and duodenal perfusions of nonabsorbable markers (2) have allowed the study of "ordinary" meals, that is mixtures of liquids and solids, and lipids and nonlipids. Thus, discrimination between gastric emptying of solids and liquids ingested with the same meal has been well established and quantified (2–5). However, the specific behavior of the lipid phase of the meal remains poorly defined. Studies using intubation techniques (6–10) have given variable results, depending on differences in the nature of the meal tested, and no direct measurements have been made of the reciprocal rate at which lipids and solids leave the stomach. The mechanism by which a possible discrimination could occur between emptying of lipids and nonlipids is unknown. It has been assumed, but only for liquid meals that fat floats on the aqueous phase because of its lower specific gravity (9, 10) and thus is retained in stomach. The new availability of selenium-75 glycerol triether ([^{75}Se]GTE), a gamma-emitting nonabsorbable lipid marker, allowed us to approach these problems using a scintigraphic technique. This noninvasive method obviates some of the experimental errors of the intubation technique and allows studies in comfortable and strictly physiological conditions. Furthermore it gives information on the intragastric distribution of lipids.

Manuscript received July 6, 1981; revised manuscript received September 9, 1981; accepted November 3, 1981.

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The authors thank Dr. DeJong of the Byk-Mallinckrodt Laboratories for kindly supplying us with [^{75}Se]GTE, and Dr. Chavaudra for assistance in radiation exposure determination.

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0163-2116/82/0800-0705$03.00/1

The present study was designed to develop a scintigraphic method to measure gastric emptying of the lipid phase of an ordinary meal and to compare the emptying rate and the intragastric repartition of lipids with those of nonlipid phases of the meal.

MATERIALS AND METHODS

Ten normal subjects (8 males and 2 females, between 23 and 54 years old) gave informed consent to participate in the experiment, which was approved by a local human research committee. In each of these subjects the emptying of the lipid phase of a meal and that of the nonlipid (solid + aqueous) phase were studied (L + NL experiments). In seven of these subjects, using a similar ordinary meal, the emptying of the solid phase and that of the nonlipid (solid + aqueous) phase were studied (S + NL experiments) at another occasion in a randomized order.

Markers and Test Meals

L + NL Experiments (N = 10). The lipid phase was labeled with [^{75}Se]GTE and the nonlipid phase with technetium-99m (^{99m}Tc) sulfur colloid. The [^{75}Se]GTE (1-butylselenyl-2,3-dioctanecycloxypropane) was synthesized as described by Hoving et al (11) and obtained from Byk-Mallinckrodt, Petten, Holland. Its radiochemical purity was 98.5% as determined by thin-layer chromatography (specific activity: 3 μCi/mg). An aqueous solution of ^{99m}Tc sulfur colloid was prepared from a commercial kit (TcKl, CEA Saclay, France; bound ^{99m}Tc greater than 95%). The test meal was prepared with 90 g coarsely ground lean steak, 40 g bread, 10 g butter, 10 g sucrose, 200 ml skimmed milk (total caloric value 438 calories distributed as 38% carbohydrate, 36% fat, 26% protein); 150 ml of water was drunk during the ingestion of the meal. The [^{75}Se]GTE (150 μCi) was mixed thoroughly with the warmed butter and then spread on the bread. The ^{99m}Tc sulfur colloid (800 μCi) was added to the 150 ml water.

S + NL Experiments (N = 7). The solid phase was labeled with ^{99m}Tc sulfur colloid bound to solids and the nonlipid (solid + aqueous) phase with indium-111 chloride (^{111}In). The solid marker was obtained as previously described and validated by Kroop et al (12): one egg white (30 ml) was mixed with ^{99m}Tc sulfur colloid (800 μCi) and then fired. The same meal was used as for the L + NL experiments but 20 g meat was replaced by the egg white labeled with ^{99m}Tc sulfur colloid, in order to test identical protein loads on the two study days. The ^{111}In (150 μCi) was added to the 150 ml of water.

In Vitro Experiments

The stability and specificity of the labeling of the different phases of the meal by each marker used was checked. The test meals labeled as described above (by [^{75}Se]GTE + ^{99m}Tc sulfur colloid or by ^{99m}Tc sulfur colloid bound to solids + ^{111}In) were grossly ground, diluted with an equal volume of a 0.2 N HCl solution, and stirred slowly in a beaker at 37° C for 90 min. Four samples were taken at 30, 60, and 90 min. In each sample

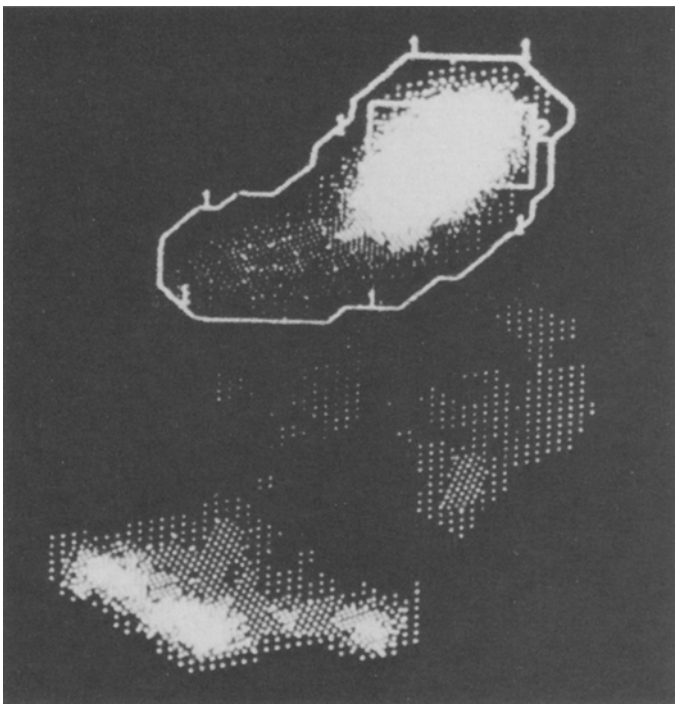

Fig 1. Gastrointestinal scintigraphy in a single subject (^{99m}Tc window). Areas of interest are delineated: 1 = stomach, 2 = upper fundic part.

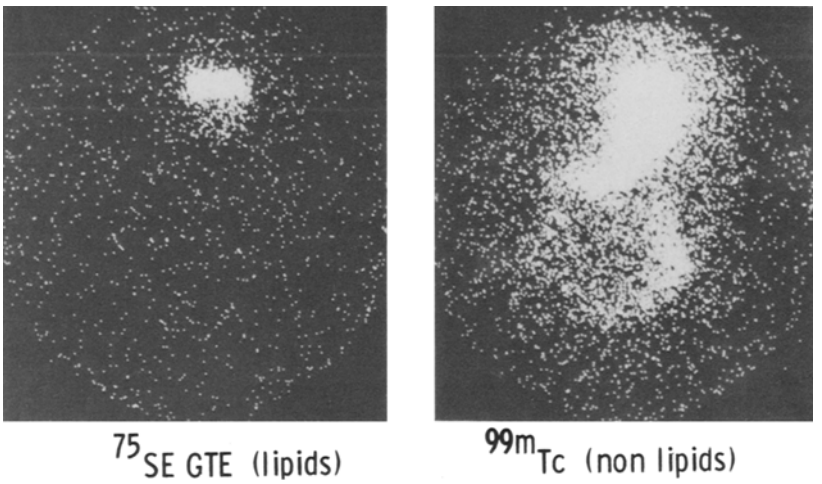

Fig 2. Gastrointestinal scintigraphs taken, 30 min after meal ingestion during a preliminary experiment, in the [^{75}Se]GTE window (lipid-phase marker) and the ^{99m}Tc window (non-lipid-phase marker). In the particular conditions of this experiment a layering of lipids above nonlipids occurred and was correctly detected.

lipids were extracted with toluene–ethanol (6), and then the extract (containing at least 90% of the lipids of the sample) and the aqueous and the solid phases were separated by centrifugation (1000*g* for 15 min) and counted for each marker on specific channels of a gamma-spectrometer (CG 4000, Kontron-Intertechnique, Velizy, France). After correction of cross-channel activities, the distribution of each marker between the three phases of each samples was calculated.

Design of *In Vivo* Studies

The same protocol was used for all *in vivo* studies. Volunteers who had fasted for at least 7 hr were seated erect in front of a gamma-camera (gamma-camera large field, Philips, Holland). The 340 keV parallel collimator was positioned over the stomach and the whole intestine, with the aid of an oscilloscope display. The labeled meal was eaten within 8–12 min and immediately afterwards both markers (^{75}Se + ^{99m}Tc or ^{99m}Tc + ^{111}In) were detected separately using specific windows (270 keV ± 10% for ^{75}Se, 140 keV ± 5% for ^{99m}Tc, 171 keV ± 5% for ^{111}In). The two marker counts were recorded for 2-min periods at 5-min intervals for 90 min, stored on disks, and processed by a digital computer (Informateck, Orsay, France) which was used for all the following operations: (1) The areas of interest corresponding to the stomach and its upper fundic part were outlined (Figure 1). The stomach area was identified by the location of activity immediately after the ingestion of the meal. (2) Radioactivity was counted on each acquisition (ie, every 5 min during 90 min for each marker) and on each area of interest. (3) All counts were corrected for background, for scatter of ^{75}Se (or ^{111}In) Campton activity into the ^{99m}Tc window using phantom sources of known activities, and for physical decay of the markers. (4) All counts were expressed as fraction of ingested activity, this latter was given by the gastric activity measured just after the ingestion of the meal (time zero). Slopes of individual emptying curves were determined by linear regression analysis. All results are given as means ± SEM; analysis of linear regression and Student's paired-*t* test were used in the statistical evaluation of the data.

To test the adequacy of our experimental design to detect a layering of lipids above nonlipid nutrients, we performed a preliminary experiment in modified conditions in order to provoke or exaggerate the lipid layering: an identical meal was ingested but the lipid marker was mixed with 10 ml of olive oil instead of butter and was given at the end of the meal. As expected, a layering of fat occurred in these conditions at the end of the meal; it was correctly detected on each scintigraphic acquisition (Figure 2). The percentages of the gastric activity detected in the upper fundic part (calculated as described above) were 84% for the lipid marker and 61% for the nonlipid marker (values obtained 30 min after the meal ingestion).

Radiation Dosimetry

Using the data of the Medical International Radiation Dose Committee (13), and considering the nonabsorbability of the markers used by the gastrointestinal tract to any appreciable extent (12, 14, 15), we have estimated

Table 1. RADIATION DOSIMETRY*

	Radiation doses (rads)	
Isotopes used	*Total body*†	*Critical organ (lower large intestine)*‡
^{75}Se (0.15 mCi) + ^{99m}Tc (0.8 mCi)	0.037	0.966
^{111}In (0.15 mCi) + ^{99m}Tc (0.8 mCi)	0.034	1.045

*Estimated using the MIRD data (13).
†Assuming a retention time of 31 hr in the digestive tract.
‡Assuming a retention time of 18 hr in the lower large intestine.

TABLE 2. DISTRIBUTION OF MARKERS BETWEEN THREE PHASES OF THE MEAL*

	[^{75}Se]GTE (lipids)			^{99m}Tc (nonlipids)			^{111}In (nonlipids)			^{99m}Tc-s (solids)		
	30 min	60 min	90 min	30 min	60 min	90 min	30 min	60 min	90 min	30 min	60 min	90 min
Lipids	85 ± 5	85 ± 6	84 ± 4	1 ± 1	1 ± 0	2 ± 1	3 ± 4	2 ± 1	3 ± 2	1 ± 1	4 ± 1	3 ± 1
Water	6 ± 1	4 ± 4	4 ± 2	36 ± 6	38 ± 2	37 ± 3	35 ± 3	43 ± 5	34 ± 8	12 ± 6	13 ± 1	11 ± 2
Solids	9 ± 5	11 ± 3	13 ± 6	63 ± 5	62 ± 2	62 ± 1	63 ± 5	55 ± 4	65 ± 6	87 ± 7	84 ± 2	87 ± 4

*Expressed as percentages (mean ± SEM) of total counts recovered in each phase of samples collected 30, 60, and 90 min after *in vitro* incubation of the homogeneized test meals diluted and acidified; lipid, solid, and aqueous phases were separated, in each sample, by lipid extraction and centrifugation.

radiation dose for our scintigraphic studies as shown in Table 1.

RESULTS

***In Vitro* Studies.** The distribution of the markers between the three phases of the test meals was stable for 90 min (the duration of the *in vivo* studies), and a good specificity of labeling was achieved: 85% of the lipid marker ([^{75}Se]GTE) was recovered in the lipid phase, 86% of the solid marker (^{99m}Tc sulfur colloid bound to solids) was recovered in the solid phase, and more than 97% of the nonlipid markers (^{99m}Tc sulfur colloid and ^{111}In) were recovered in the nonlipid phase, with a similar distribution ratio between solid and aqueous phases (Table 2).

Emptying Rates of Lipid, Nonlipid, and Solid Phases of the Meal. A marked difference was seen during each L + NL experiment between gastric emptying of the lipid and the nonlipid markers (Figures 3 and 4). Analysis of the composite results confirmed these findings: the mean emptying rate of the lipid marker (17.4 ± 2.4%/hr) was definitely lower ($P < 0.001$) than that of the nonlipid marker (34.2 ± 1.8%/hr). Results obtained in subjects who underwent the two study days (L + NL and S + NL experiments) showed that the mean emptying rate of lipids (14.4 ± 3%/hr) is also slightly lower ($P < 0.05$) than that of solids (22.8 ± 1.8%/hr).

The mean emptying rate of the solid marker (22.8 ± 1.8%/hr) was definitely lower ($P < 0.01$) than that of the nonlipid (solid + aqueous) phase marker. Finally emptying rates of the two nonlipid markers labeling the same components of the meal (solid + aqueous phases) were closely related (34.2 ± 1.8%/hr for ^{99m}Tc and 33.6 ± 3%/hr for ^{111}In).

Intragastric Distribution of Lipids. In most subjects, no intragastric separation of lipid and nonlipid markers was imaged. The comparison of the mean retention of these two markers in the upper fundic part of the stomach showed that the layering of lipids above the rest of the meal was slight and occurred only after the first postprandial hour (Figure 5).

DISCUSSION

Gamma-camera recording of radioactive isotopes was used in the present study to measure the emptying of lipids and to compare it with that of nonlipids and solids simultaneously ingested.

This method has obvious advantages; it is simple, noninvasive, conforms well to physiological conditions and gives quantitative information on the intragastric distribution of the different phases of the meal. However, several difficulties have been pointed out concerning this technique: The first

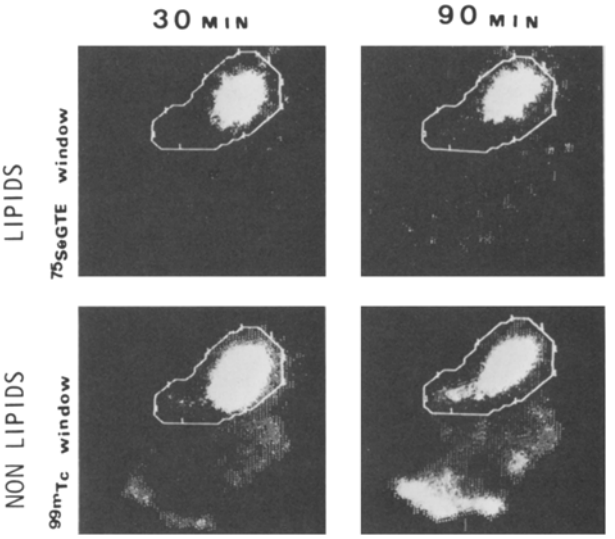

Fig 3. Gastrointestinal scintigraphs in a normal single subject 30 min and 90 min after meal ingestion in [^{75}Se]GTE window (lipid-phase marker) and ^{99m}Tc window (non-lipid-phase marker). Differences between emptying rates of the two markers are evidenced by activity in stomach and small bowel.

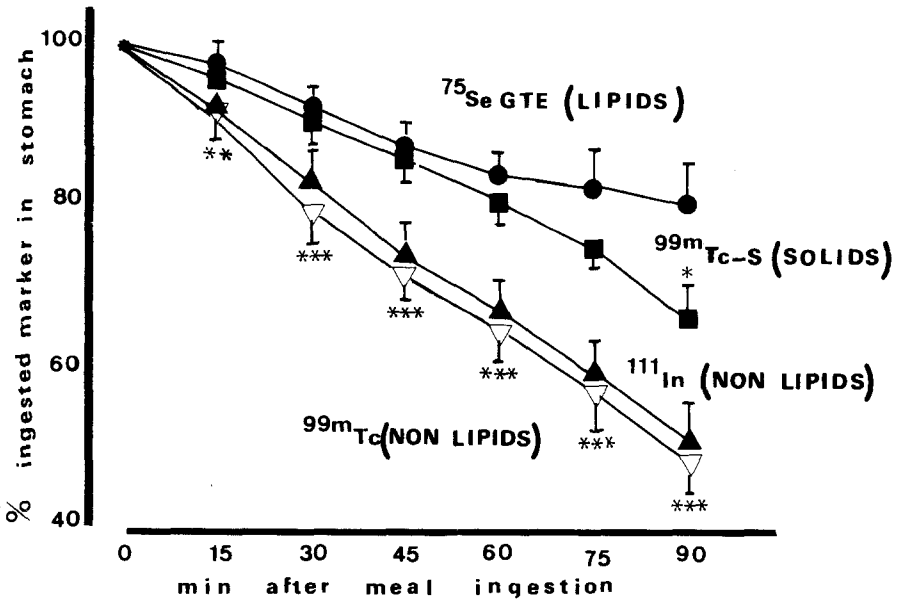

Fig 4. Gastric emptying of the different phases of the same meal. Lipids were labeled by the [^{75}Se]GTE (day l), solids by the ^{99m}Tc sulfur colloid bound to egg white (day 2), and nonlipids (aqueous + solid phases) by ^{99m}Tc sulfur colloid (day 1) or ^{111}In (day 2). Emptying of lipids was compared with that of solids and nonlipids (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

potential error concerns the inaccuracy of the detection linked to depth variations; estimations of these errors have given conflicting results, depending on the nature of the meal, the isotope, and the technique of detection used (16–18). However, our results are not based on absolute values but on differences in emptying rates between two markers; in fact when two markers (^{111}In and ^{99m}Tc) labeling the same phase (nonlipids) were used, we obtained identical emptying rates. Another critical point is to know exactly what the markers are labeling. The new gamma isotope used in this study as a lipid phase marker, [^{75}Se]GTE, identifies lipids accurately. Hoving et al (19) have shown that in iterative postprandial sampling of gastric contents in man, the triglycerides/[^{75}Se]GTE ratio remains constant and identical to the initial ratio in the meal ingested. In rats after administration of [^{75}Se]GTE, the radioactivity is almost completely recovered in the lipid phase of stools (11), and in our *in vitro* experiments radioactivity of [^{75}Se]GTE remains in the lipid phase. Likewise, ^{99m}Tc sulfur colloid bound to cooked egg white identifies solids accurately: our *in vitro* experiments and those of Kroop et al (12) have demonstrated that such a binding is sufficient to prevent elution of the isotope during peptic-acid digestion in man. So, a good specificity of labeling was achieved with our lipid and solid markers. However, they identify essentially one component of each phase (ie, butter for the lipid marker and egg white for the solid marker) and not necessarily the other constituants of this phase (ie, extra butter fat for lipid marker, bread for solid marker). The two isotopes ingested with water (^{99m}Tc sulfur colloid and ^{111}In) are good markers of the nonlipid phase of the meal, but our *in vitro* experiments showed that these two markers label both aqueous and solid phases of the meal, a result in agreement with previous reports (4, 20). In a recent study, ^{111}In was found to be a very specific aqueous-phase marker (16); differences in experimental conditions (use of indium DTPA instead of indium chloride, very thorough mechanical blending of the meal) may explain this discrepancy.

Our results show that lipids leave the stomach more slowly than solids. In the absence of a marker specific for the aqueous phase, we cannot compare directly gastric emptying of lipid and aqueous phases, as done by others (6, 7, 9). Yet we can strongly suggest that lipids leave the stomach more slowly than water since our data clearly show that lipids are emptied slower than solids and solids themselves are emptied markedly slower than ^{111}In which labeled both solids and water. This is the first

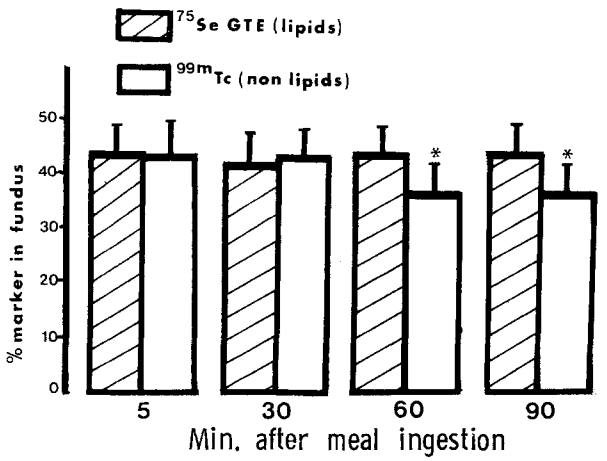

Fig 5. Fraction of marker in fundus, expressed as percentage of total intragastric counts (mean values ± SEM, $N = 10$); differences between lipids and nonlipids are depicted (*$P < 0.01$).

demonstration that among the three main components of a meal (ie, lipids, solids, and water), fats are emptied at the lowest rate.

The mechanism of discrimination between emptying of lipids and of nonlipids is unknown. It was assumed that lipids float on the aqueous phase because of differences in specific gravity, so that fat is emptied after water (9, 10). However, this point was assessed indirectly and with artificial liquid test meals. During the emptying of our solid–liquid meal, we found some layering of lipids above the rest of the meal, but this cannot be the only mechanism by which lipids are retained in the stomach since a significant intragastric retention of lipids was observed in the absence of layering during the first postprandial hour and even at its maximum, the magnitude of layering is insufficient to account for the differences observed between the emptying rates of lipids and nonlipids. Another factor could be that lipids were physically attached to solid particules and were thus retained in stomach with them. However, some discrimination also occurred between emptying of solids and lipids. It remains possible that adhesion to solids and layering act simultaneously or consecutively; indeed, it appears from our results (Figures 4 and 5) that lipid layering begins at the time when lipid and solid emptying rates diverge.

The scintigraphic detection of the [^{75}Se]GTE lipid marker, together with that of other phases of an ordinary meal, may provide an accurate, simple, and useful tool for further studies. It could be used, for instance, to investigate the specific control of emptying rates for each phase ingested with a meal and pathological conditions in which lipid emptying may be specifically altered.

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