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Report

Gastrointestinal Transit of a Solid Indigestible Capsule as Measured by Radiotelemetry and Dual Gamma Scintigraphy[1]

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The objectives of the present study were to evaluate gastric and small bowel transit times of an indigestible solid matrix and to characterize the specific changes in intraluminal pH as a function of transit time through the gastrointestinal tract. Particular attention was paid to the lag time at the ileocecal junction. A Heidelberg capsule (HC), labeled with 10 μCi Indium-111, was given orally to six healthy male subjects 15 min after oral ingestion of 100 μCi of ^{99m}Tc-sulfur colloid as a liquid fatty meal (4 ml/kg). Intraluminal pH was monitored continuously via the HC. Gastric and small bowel transit of the radionuclides was monitored via external scintigraphy at 0.5-hr intervals. Gastric residence times (GRT) of the HC ranged from 2.8 to 4.8 hr, with a mean (±SD) of 3.6 ± 0.8 hr. These values were independent of the individual's weight, height, or body surface area. Small bowel transit times of the HC ranged from 2.8 to >5.5 hr, which were consistent with the reported values of 3 to 5 hr. The lag times of the HC at ileocecal junction ranged from 0.8 to >2.5 hr. The presence of the lag times at the ileocecal junction in all subjects confirmed that it acts as a valve or sphincter. Mouth-to-cecum transit times of the HC occurred within 9.0 hr in 50% of the subjects. In general, following a sharp rise upon pyloric passage of HC the pH dropped slightly but then increased linearly throughout the small intestine. The mean duodenal pH was 5.8 ± 0.8 and the pH at the ileocecal junction ranged from 6.5 to 8.5, with a mean of 7.3 ± 0.7. Passage through the ileocecal junction was associated with a 0.5- to 1.0-unit rise in pH in three subjects who exhibited passage of the HC into the large bowel within the study period. The present data may have implications in the designing of more effective dosage forms with specific delivery to proximal or distal small bowel regions.

KEY WORDS: gastric residence time; radiotelemetry; small bowel transit time; dual gamma scintigraphy; Heidelberg capsule; intragastric pH; ileocecal junction; indigestible solid.

INTRODUCTION

Most drugs are given by mouth in solid dosage form. For formulation such as enteric-coated or controlled-release matrix tablets which are indigestible in the acidic environment of the stomach, the rate of gastric emptying is the determining factor in the onset of drug absorption (1–4). Since small intestine (with a combination of 3- to 5-hr average transit time for a typical dosage form and a large surface area) is the major site of drug absorption, it is important to measure transit throughout the intestinal tract (5–7). However, for some drugs such as theophylline (8) and metoprolol (9) there is clinical evidence that suggests colonic absorption for these compounds. Therefore, to evaluate complete oral absorption of a drug from solid matrix with extended drug delivery, it is important to establish not only gastric retention but also small bowel and colonic transit times of such formulations. The use of external scintigraphy in humans has allowed for measurements of gastric emptying time (10–12) and mouth-to-colon transit time of pharmaceutical formulations (13,14). Recently many investigators have reported the successful measurement of gastric emptying times for liquid or solid test meals using a dual gamma-scintigraphic technique (15–18). Dual isotope scintigraphy has provided a tolerable, noninvasive method of defining and quantifying the gastric handling of liquids and solids in various clinical situations. In addition, the influence of factors such as particle size (19,20), density (11,21), calorific values of meals (20,22), specific effects of fats (23), posture, gender, and age (24), emotional state and stress (25) on emptying rates have been well documented. Read *et al.* (26,27) have shown that most often gastric emptying and small bowel transit are independent variables, each being controlled by its own regulatory mechanisms. The overall mouth-to-colon and stomach-to-ileocecal junction transit times of a solid dosage form along with the intraluminal pH of different segments of gas-

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trointestinal (GI) tract have not been studied in detail in healthy volunteers.

A radiotelemetric technique using the Heidelberg capsule (HC) has been successfully applied in the evaluation of the gastric transit time of an indigestible solid (22) and in the measurement of the absorption lag time of an enteric-coated formulation (28). This technique has also been used to investigate small bowel residence times in fasting dogs and humans (29). Due to its large size (7 × 20 mm), the pyloric passage of the HC is dependent on the gastric phase III interdigestive migrating myoelectric complex (IMMC) (30). It has been reported that in canines, when the radiotelemetry HC passes into the cecum (transit through ileocecal junction), the pH was raised abruptly, then fell slowly again, and subsequently fluctuated much less than in the small intestine (31). The goal of the present study was to combine external gamma scintigraphy and radiotelemetry to evaluate the ileocecal transit and to record any changes in intraluminal pH associated with this process. In addition, the possible utility of the HC as a marker of gastric and intestinal transit times of an indigestible solid dosage form was also evaluated.

MATERIALS AND METHODS

Radiotelemetry

The Heidelberg capsule is a pH-sensitive radiofrequency (1.98-MHz) transmitter encased in an inert, indigestible shell, approximately the size of a No. 1 gelatin capsule (22). After oral ingestion, the capsule transmits signals from the gastrointestinal tract to a receiving antenna incorporated in a wide belt worn by a subject. These signals are passed to a receiver, decoded, and displayed as a pH reading. Because pH values change with location within the gut, alterations in pH should be indicative of the movement of the capsule through the different segments. Generally, the capsule functions for 22 hr after activation and provides readings with ±0.5-pH unit accuracy and excellent *in vivo* reproducibility in the pH range of 1 to 8 (32). The Heidelberg radiotelemetry instrument and the Heidelberg capsule were purchased from the Heidelberg International Incorporation (Atlanta, Georgia).

Gamma Scintigraphy

The Heidelberg capsule was labeled away from its pH-sensing end with 10 μCi nonabsorbable Indium-111 (^{111}In) source point (E_{max} = 247 keV, $t_{1/2}$ = 67 hr). The radioactive source (10 μCi/10 μl solution) was placed into a polyethylene tubing 1.2 × 10 mm, PE-60 Clay Adams, Parsippany, N.J.) which was heat sealed at both ends and was physically attached onto the Heidelberg capsule via nondigestible surgical suture. The GI tract was outlined in each volunteer by oral administration of 100 μCi of a solution of technetium-^{99m} (^{99m}Tc)–sulfur colloid (E_{max} = 140 keV, $t_{1/2}$ = 6 hr). The gamma camera was equipped with a medium-energy collimator and two pulse height analyzers, one centered at 104 keV with a 20% window for ^{99m}Tc and the other at 247 keV with a 20% window for indium-111 photons. The exposure radiation dose to the gastrointestinal tract from 50 μCi of oral indium-111 DTPA was calculated to be 0.027, 0.080, 0.14, and 0.325 rad, respectively, to the stomach, small intestine, and proximal and distal large intestine. The exposure dose from 100 μCi of oral ^{99m}Tc–sulfur colloid was calculated to be 0.15, 0.01, and 0.02 rad to the stomach, gonads, and whole body, respectively (33).

Study Protocol

The protocol was approved by the Thomas Jefferson Institutional Review Board. Six healthy male subjects between 23 and 34 years of age (mean ± SD, 28 ± 5 years) and weighing 64 to 90 kg (77 ± 9 kg), with no prior signs or symptoms of ulcer or GI dysfunction volunteered to participate in this study. Following satisfactory completion of the physical examination and signing of the informed consent form, each subject reported to the Nuclear Medicine Department at 8:00 AM following an overnight fast (from 10:00 PM the previous night). Each volunteer ingested 100 μCi ^{99m}Tc–sulfur colloid, a liquid fatty meal (4 kcal/ml/kg body weight) 15 min before oral administration of the radiolabeled Heidelberg capsule (^{111}In-HC). Each volunteer was placed in the supine position under a scintillation camera which was centered over the stomach. Serial images of the ^{111}In-HC and ^{99m}Tc were obtained on radiographic film at 30- to 45-min intervals until the pyloric passage of the capsule was detected. Subsequently, images were obtained at 30-min intervals for 2 hr, followed by images at 15-min intervals until the completion of the study. Intragastric and intestinal pH was monitored continuously via the radiotelemetry technique until the time of passage through ileocecal junction. Subjects remained under moderate physical activities (i.e., standing, short walks) except during the telemetry monitoring and each scintigraphic imaging period. An 800-kcal lunch was served 4 hr after administration of the ^{111}In-HC only if gastric emptying of the HC had been detected prior to that time.

Data Analysis

Following duodenal passage of the capsule, more frequent scintigraphic views of the HC were recorded to characterize intestinal transit of the capsule. Special attention was given to the time of passage of the HC through ileocecal sphincter. Two external source points were used as markers to reproduce the exact position of each volunteer for the repeated scintigraphic measurements. All scintigraphs were interpreted at the completion of each study day by the same investigator. The relationship between the intraluminal pH and the location of the capsule in the GI tract was established in each volunteer.

RESULTS

Table I demonstrates the combined gamma scintigraphy and radiotelemetry data in six healthy volunteers. Demographic data, gastric and intestinal transit time, and gastroduodenal (pH at GRT) and ileocecal pH's are shown for all subjects in Table II.

Gastric residence time of the HC as indicated by the pyloric transition of the capsule was associated with a sustained rise in pH. The passage of the HC into the large bowel (transition through the ileocecal junction) was observed in three of six subjects within the 9.0-hr study period (see Table I). GRT of the HC ranged from 2.8 to 4.8 hr, with a mean

Table I. Heidelberg Capsule Location Confirmed by External Gamma Scintigraphy and (GI pH Measured by Radiotelemetry) in Six Healthy Male Volunteers[a]

Time (hr)	Subject No. 1	2	3	4	5	6
0.08	PSt (4.5)	PSt (5.0)	PSt (3.0)	PSt (4.5)	PSt (4.7)	PSt (4.5)
1.0	PSt (4.0)	PSt (5.5)	DSt (2.8)	DSt (3.0)	St (2.0)	St (2.6)
2.0	St (1.5)	St (4.5)	DSt (1.0)	DSt (1.5)	DSt (1.0)	DSt (1.5)
3.0	DSt (1.0)	DSt (2.2)	DSt (3.9)	PSB (4.7)	PSB (5.8)	PSB (5.4)
3.5	DSt (1.5)	DSt (1.3)	D (5.6)	PSB (5.0)	PSB (5.4)	PSB (5.0)
4.0	—	DSt (1.0)	PSB (5.0)	SB (4.9)	SB (4.9)	SB (5.0)
4.5	DSt (2.0)	PSB (7.0)	PSB (6.1)	SB (5.2)	SB (5.2)	DSB (5.1)
5.0	D (6.3)	SB (7.1)	SI (6.2)	DSB (5.8)	SB (5.2)	DSB (5.5)
5.5	PSB (6.0)	SB (6.5)	SI (6.5)	DSB (6.1)	SB (5.8)	IJ (6.1)
6.0	SB (7.0)	SB (6.8)	DSB (6.8)	DSB (6.5)	DSB (5.9)	IJ (6.3)
6.5	IL (7.0)	SB (7.0)	DSB (6.7)	DSB (6.4)	DSB (6.1)	IJ (6.4)
7.0	IL (7.0)	DI (8.1)	DSB (6.8)	DI (6.4)	IJ (6.4)	IJ (6.4)
7.5	IJ (8.0)	DI (7.7)	IJ (6.8)	IJ (6.4)	IJ (6.8)	IJ (6.5)
8.0	IJ (8.0)	DI (8.5)	IJ (6.8)	IJ (6.5)	IJ (6.9)	IJ (6.4)
8.5	LB (8.5)	LB (9.2)	IJ (6.8)	IJ (6.8)	LB (7.9)	IJ (6.6)
9.0	—	LB (9.3)	—	IJ (6.8)	LB (8.0)	—

[a] ST—stomach; C—cecum; D—duodenum; IJ—ileocecal junction; LB—large bowel; PSt—proximal stomach; PSB—proximal small bowel; DSB—distal small bowel; IL—ileum; DSt—distal stomach; DI—distal ileum.

(±SD) of 3.5 ± 0.8 hr. These values were independent of weight, height, or body surface area. The lag time of the HC at ileocecal junction ranged from 0.8 to >2.5 hr and the small bowel transit time ranged from 2.8 to >5.5 hr (see Table II). Mouth-to-cecum transit time of the solid capsule occurred within 9.0 hr in 50% of the subjects.

The pH at the ileocecal junction ranged from 6.5 to 8.5, with a mean of 7.3 ± 0.7 as shown in Table II. Duodenal pH (pH at GRT) ranged from 5.0 to 7.0, with a mean of 5.8 ± 0.8 (see Table II). Transition from the small bowel to the large bowel was associated with a 0.5-, 0.7-, or 1.0-unit increases in pH as observed in subjects 1, 2, and 5 (see Table I). Figures 1 and 2 show two examples of pH vs time profiles in subject 5, who had a small bowel transit time of 5.0 hr (Fig. 2), and subject 6, who had a small bowel transit time of >5.5 hr (Fig. 1). In this subject transition to the large bowel was not observed within the study period.

There was a clear distinction between the location/transition of the liquid (^{99m}Tc–sulfur colloid) and the radioactive solid capsule (^{111}In-HC) in all subjects. Liquid radioactivity moved faster and ahead of the HC in all subjects to the proximal transverse and descending colon by 8 to 9 hr after administration. Sequential gamma scintigraphic frames for both ^{99m}Tc–sulfur colloid and ^{111}In-HC at 0, 1, 2, 3, 6, 8, and 8.5 hr after administration are shown in subject 5 in Fig. 3. The position of each radionuclide and the combined image are shown at each time interval.

DISCUSSION

The absorption process is a complex phenomenon. It is generally believed that for the majority of the drugs, little, if any, absorption occurs from the stomach. The small intestine, with a combination of a larger surface area and longer

Table II. Demographic Data, Gastric Residence Time (GRT), Small Bowel Transit Time, and pH of Gastroduodenal and Ileocecal Junctions in Six Healthy Male Volunteers Measured by Radiotelemetry and Dual Gamma Scintigraphy

Subject No.	Wt. (kg)	Ht. (cm)	Age (years)	BSA[a] (m^2)	GRT (hr)	pH at GRT	Ileocecal lag time (hr)	Small bowel transit time (hr)	Ileocecal pH	pH of transition[b]	Mouth to cecum (hr)
1	80	188	32	2.06	4.75	6.3	0.75	2.75	8.0	8.5	7.50
2	90	180	34	2.10	4.25	7.0	~1.0	4.0	8.5	9.2	8.25
3	72	175	23	1.87	3.50	5.0	>1.5 hr	>4.0[c]	6.8	Last pH (6.8)	>7.5
4	83	188	26	2.09	3.00	5.0	>2.5 hr	>3.5	6.8	Last pH (6.8)	>6.5
5	75	183	29	1.96	3.00	5.8	1.0 hr	5.0	6.9	7.9	8.0
6	64	175	23	1.78	2.75	5.4	>2.25	>5.5	6.5	Last pH (6.6)	>8.25
Mean	77	182	28	1.98	3.5	5.8	—	—	7.3	—	—
(SD)	(9)	(6)	(5)	(0.1)	(0.8)	(0.8)			(0.7)		

[a] Body surface area.
[b] pH of transition from small bowel to large bowel.
[c] Did not pass to LB by 9.0 hr.

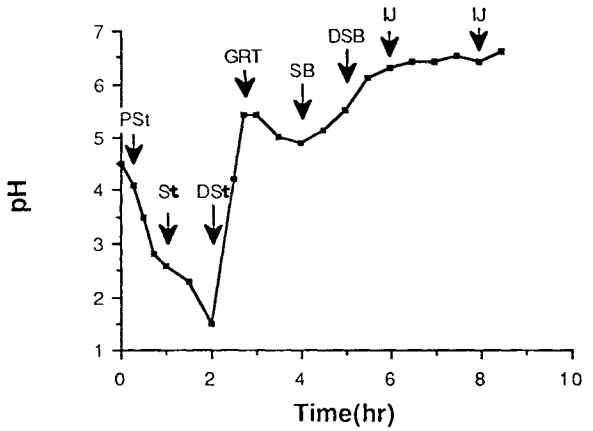

Fig. 1. Gastrointestinal pH vs time profile measured by the radiotelemetry technique in a healthy volunteer (subject 6). The intraluminal location of the radiotelemetry capsule is shown by the arrows at the appropriate time point (see Table I, footnote *a*, for the abbreviations). This subject showed a 2.8-hr GRT with a >2.3-hr delay at the ileocecal junction. Transition to the large bowel was not observed in this subject within the 9.0-hr study period.

transit time, is the major site of drug absorption in the GI tract. Therefore drug molecules which are released in the proximal small bowel may be efficiently bioavailable, while the release of drug after the passage into the large bowel may not contribute to therapy. However, colonic absorption of some drugs has been reported (8,9). Furthermore, the rate and extent of drug absorption are dependent upon many factors such as (a) physical and chemical properties of the drug, i.e., solubility, ionization, permeability, etc., (b) the physiology of the GI tract, i.e., pH, surfacea area, blood flow, food, bacteria, etc., (c) the nature of the formulation, i.e., solution, suspension, single- or multiparticular unit, disintegrating or nondigestible, size, shape, specific gravity, etc.,

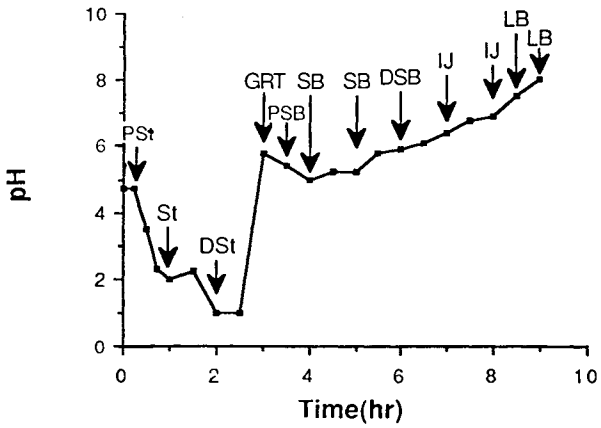

Fig. 2. Gastrointestinal pH vs time profile measured via the radiotelemetry Heidelberg capsule in a healthy male volunteer (subject 5). The luminal location of the telemetry capsule is shown by the arrows at each time point (refer to Table I, footnote *a*, for abbreviations). This subject showed a GRT of 3.0 hr followed by an ileocecal lag time of 1.0 hr. Passage through the ileocecal junction was observed in this subject 8.0 hr after the administration of the Heidelberg capsule. Small bowel transit time was about 5.0 hr as measured by external gamma scintigraphy.

and (d) the interaction between all of these factors. In order to understand the oral absorption process, there is a need to define both the location of the dosage form and its transit time through the gut. The combined gamma scintigraphy and radiotelemetry generate this type of information for a solid dosage formulation in a single experiment.

In the present study, external gamma scintigraphy and radiotelemetry have been combined to evaluate the GRT and small bowel transit time of a solid nondigestible capsule in healthy volunteers in a noninvasive manner. The excellent reproducibility and good acceptance of both radiotelemetry (32) and dual isotope scintigraphy methods allowed for precise evaluation of the GI transit of the indigestible capsule (34). Our results on small bowel transit times of the HC (2.8 to >5.5 hr) are in agreement with the work of Davis *et al.* (35,36), who reported a mean transit time of about 3.0 ± 1.0 hr for various matrix tablets and osmotic pumps. Our results are also consistent with the recent study by Hardy *et al.* (37), who showed small intestinal transit times ranging from 2.3 to 4.9 hr, with a mean (±SD) of 3.4 ± 1.1 hr in a group of six patients with ulcerative colitis.

Radiotelemetry data revealed that in most subjects, following a sharp rise in pH upon pyloric passage of the capsule (mean, 5.8 ± 0.8), the pH dropped slightly, and thereafter, the pH increased in a roughly linear fashion throughout the small bowel (Figures 1 and 2). The ileocecal lag time behavior of a nondisintegrating matrix is poorly understood. The existence of a measurable lag time (0.8 to >2.5 hr) at the ileocecal valve in all subjects suggested that, as in the gastroesophageal and gastroduodenal junctions, it also acts as a junction. The observed variability in both small bowel transit and ileocecal lag times may be explained by variability in motility of the jejunum and terminal ileum in healthy volunteers. Kerlin and Phillips (38) reported marked inter- and intraindividual variability in the rate, duration, and intensity of phase III of the migrating motor complex throughout the human small intestine including the terminal ileum.

The results of the present study combined with the data from our previous work (30,34,39) confirm the utility of this radiotelemetry capsule as a noninvasive marker of phase III gastric IMMC in both healthy subjects (30) and the diseased state (39). In addition, these data indicate that the HC may mimic the intestinal transit and ileocecal passage characteristic of a solid, matrix dosage form. Finally, with a clear understanding of factors controlling drug absorption and intraluminal transit time, one may design a suitable controlled-release formulation with specific delivery to various areas of the small intestine or large bowel. The present information on the mouth-to-cecum transit time in healthy subjects indicates that a controlled-release dosage form with a release duration of 8 to 10 hr may allow for uniform drug delivery over the jejunum, ileum, and cecum. Such a formulation will prevent unacceptable accumulation of drug in individuals with slow ileal or colonic motility.

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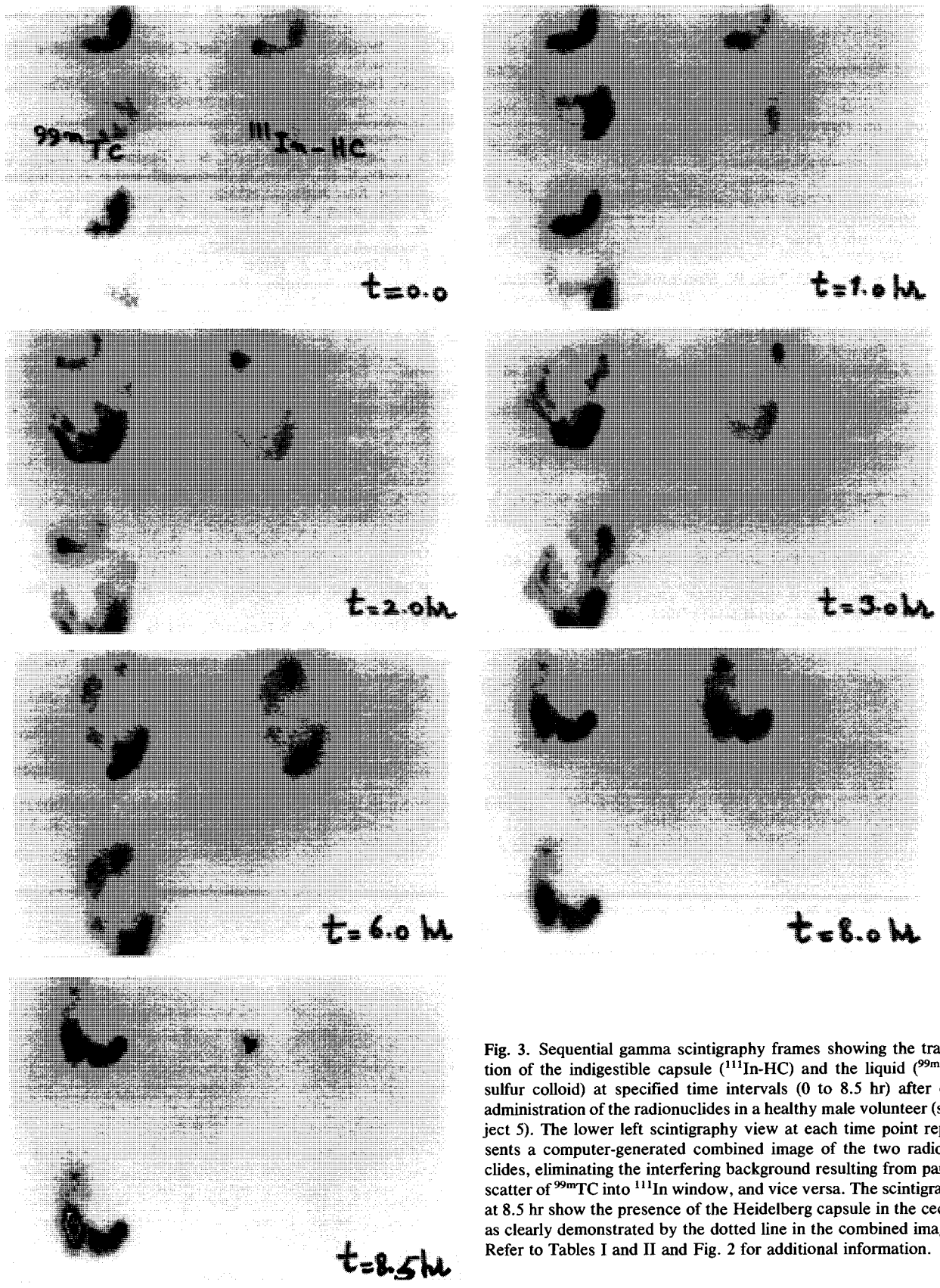

Fig. 3. Sequential gamma scintigraphy frames showing the transition of the indigestible capsule (^{111}In-HC) and the liquid (^{99m}Tc–sulfur colloid) at specified time intervals (0 to 8.5 hr) after oral administration of the radionuclides in a healthy male volunteer (subject 5). The lower left scintigraphy view at each time point represents a computer-generated combined image of the two radionuclides, eliminating the interfering background resulting from partial scatter of ^{99m}TC into ^{111}In window, and vice versa. The scintigraphs at 8.5 hr show the presence of the Heidelberg capsule in the cecum as clearly demonstrated by the dotted line in the combined images. Refer to Tables I and II and Fig. 2 for additional information.

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