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MOVEMENT OF DISCRETE PARTICLES IN THE 100- TO 200-MICRON DIAMETER RANGE THROUGH THE GASTROINTESTINAL TRACT OF LABORATORY ANIMALS AND MAN*

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Estimates of the radiation dose incurred from small radioactive particles passing through the gastrointestinal (GI) tract depend on many biological and physical factors. Among the former is included the time spent by the particle during passage through the GI tract [hereafter referred to as gross transit time (*GTT*)]. Estimates of *GTT* for small (100- to 200-μ diameter size range) high-density particles have been purely speculative. Entrapment between villi or failure to overcome gravity (e.g., to move up the ascending colon or out from the gastric fundus) has been suggested as mechanisms that might result in long retention times within the GI tract. Clearly, prolonged retention of a similar radioactive particle increases the relative biological hazard. In addition, for refinements of dose estimate to different portions of the tract, something must be known regarding differential transit time (*DTT*), that is, residence times for different portions of the GI tract, such as the stomach or large intestine.

Because of the large variability among people in dietary and toilet habits, there exists little quantitative information on the average time required for any material to pass through the gut. It is not surprising, therefore, that practically no information is available on *GTT* for small high-density particles. As an example, recent work indicates that extremely small insoluble crystals (of the order of 1 μ and smaller) can be removed from the lumen of the gut by phagocytic action and subsequently deposited elsewhere in the body.[1]

This study was designed to measure *GTT* for small high-density particles in man. Another goal was to estimate *DTT* for man on the basis of experiments in laboratory animals. We should point out that results obtained apply only to small high-density particles that are essentially nonradioactive. The presence of a high radiation field around the particle might complicate the problem significantly.

MATERIALS AND METHODS

Particles

Several kinds of spherical particles were used. Ceramic microspheres, containing either ^{54}Mn or ^{46}Sc, were obtained from a commercial supplier.† Size distributions were reported by the manufacturer to be 150 ± 25 μ diameter. Uranium carbide fuel cores,‡ consisting of $^{235}UC_2$ in roughly the same size range as the ceramic spheres, were also used. Density of the ceramic microspheres (3.0 g/cm^3) was similar to the carbon-clad UC_2 fuel cores used in some

* Work performed under the auspices of the U. S. Atomic Energy Commission.

† 3-M Company, St. Paul, Minnesota.

‡ UHTREX (*U*ltra *H*igh *T*emperature *R*eactor *EX*periment) fuel cores obtained from Group CMB-8 Los Alamos Scientific Laboratory.

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nuclear propulsion reactor configurations. The density of the nonclad UC_2 particles used in this study was 10.8 g/cm^3.

Particle diameters were measured with an image-splitting eyepiece* attached to a microscope. Calibration was achieved by use of a 100-μ graticule divided into 2-μ intervals. An average diameter was obtained for each particle based on six observations; the particle was removed and repositioned between each reading to minimize errors resulting from deviations from sphericity.

Particle Detection

Radionuclides were measured by gamma-ray spectroscopy. The dual-crystal detectors (each 8 in. diameter by 4 in. thickness) were covered by 0.005 in. of aluminum to enhance sensitivity at low energies. A 7-in. thick steel shield surrounded the detectors.

One ^{54}Mn-labeled sphere is easily detectable in a fecal sample when measured for 30 min. The net count rate, measured between 750 and 950 keV, is approximately 1 count/min-pCi with a crystal separation of 1 in. Manganese-54 presents little radiologic hazard to man, as decay is by gamma-ray and positron emission. On the average, 150 pCi ^{54}Mn was incorporated within the ceramic matrix of the sphere; this activity was insoluble.

Rodent Studies

Ninety-six female mice of the RF strain and 96 male rats of the Sprague–Dawley strain were used. Single ^{54}Mn-labeled spheres were placed on the back of the tongue of each unanesthetized animal. Twelve animals of each species were sacrificed at hourly intervals for 8 hr, and portions of the GI tract were removed and radioassayed. Portions of the GI tract removed were esophagus, stomach, small intestine, cecum, and large intestine; the small intestine was further subdivided into 4 equal lengths.

Dog Studies

Adult beagle hounds of both sexes were used. Even though the animals were well adjusted to confinement in metabolism cages, a minimum acclimation period of 14 days was observed prior to any experiment. In some experiments, to facilitate subsequent detection in fecal samples by gamma-ray spectrometry, $^{235}UC_2$ fuel cores were irradiated prior to feeding. Irradiations were done in the thermal column of the Los Alamos Water Boiler Reactor at a flux of 2.0×10^{11} neutrons/cm^2-sec for variable times. In other experiments, nonfissioned $^{235}UC_2$ fuel cores were used. Food and water were available *ad libitum*.

Gross GI transit times were measured by hand-feeding a single $^{235}UC_2$ fuel core to each dog. Fecal samples were collected at half-hour intervals during the day and measured for fission-product activity by gamma-ray spectrometry.

A chronic feeding experiment designed to measure *DTT* for portions of the GI tract was also conducted. Ceramic spheres labeled with picocurie amounts of ^{46}Sc were fed at a rate of 1/hr for 3 days to each of 4 dogs. The average activity for the group of 72 spheres fed to each dog was known from previous measurements. At sacrifice, portions of the GI tract were removed and measured by gamma-ray spectrometry; fecal samples voided over the 3-day period were also measured. If equilibrium conditions were obtained between intake and output, the time spent by the particles in each segment of the tract should be proportional to the number of particles detected. Particles were dispensed from an electrically powered carrousel-type of feeder which completed 1 revolution each 24 hr. Each hour one particle, contained in a portion of a frankfurter, was dropped through a fixed hole into a metal feeding cup suspended within the cage. The animals were conditioned to this feeding system before the experimental period.

* Vickers, A. E. I., Malden, Massachusetts.

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Human Studies

The experimental protocol for establishing *GTT* in human subjects was as follows. A No. 5 gelatin capsule containing two $^{235}UC_2$ fuel cores and one ^{54}Mn-labeled sphere was measured for 30 min in the twin-crystal spectrometer counting system to verify the presence of peaks at about 180 keV (^{235}U) and 840 keV (^{54}Mn) in the gamma-ray spectrum. Each subject was given a capsule and instructed to collect succeeding fecal samples until the particles were identified. Times of ingestion and sample voiding were recorded by the subject. In most instances, particles were ingested between 9:00 and 10:00 AM. One subject repeated the experiment 10 different times to provide an estimate of variation within the same person. Several others repeated the ingestion at various times of day, on different days, to provide an estimate of the time-of-day variable. Information obtained from 57 individuals represents the history of some 156 individual particles (114 $^{235}UC_2$ fuel cores and 42 labeled ceramic spheres). In some instances, no ceramic spheres were given.

A typical pair of uranium carbide spheres weighed about 25 μg, thus, on the average, a maximum of 25 μg ^{235}U was ingested per dose per person. Because of the low specific activity ($\sim 4.66 \times 10^5$ g ^{235}U per curie), the amount of ^{235}U required to produce one allowable (i.e., as recommended by the ICRP) body burden of 3×10^{-2} μCi, with the kidney as the critical organ, is roughly 1.4×10^{-2} g. Current ICRP recommendations for continuous intake of insoluble ^{235}U, with the lower large intestine as the critical organ, is 3×10^{-4} μCi/ml. For comparison, 25 μg ^{235}U represents about 5.5×10^{-5} μCi and is taken only once.

EXPERIMENTAL RESULTS

Particle Sizes

The mean particle diameter for a sample of 26 ceramic spheres randomly removed from the entire supply was 149 ± 11 μ (SE). This value was in good agreement with the average diameter of 150 μ supplied by the manufacturer; the observed range, however, was larger than that reported. Similar measurements for a sample of 26 $^{235}UC_2$ fuel cores yielded an average diameter of 173 μ, with a standard error of 39 μ.

Rodent Studies

Table 1 shows the deposition of particles as a function of time after ingestion in mice.

TABLE 1

Deposition of ceramic spheres throughout the GI tract of mice following single particle administration*

Segment	Hours after Feeding†							
	1	2	3	4	5	6	7	8
Esophagus	–	–	–	–	–	–		–
Stomach	3	–	–	–	–	–	–	–
Small intestine 1	1	–	–	–	–	–	–	–
Small intestine 2	2	1	–	–	–		–	
Small intestine 3	3	–	1	–	–	–	–	–
Small intestine 4	1	1	–	–	1	1	–	–
Cecum	1	9	3	4	2	2	1	1
Large intestine	1	–	7	5	4	2	4	2
Excreted	–	1	1	3	5	7	7	9

* Diameter 150 microns; density 3.0 g/cm³.
† Twelve mice sacrificed each hour.

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–	–	–
–	–	–
–	–	–
1	–	–
2	1	1
2	4	2
7	7	9

No particles were found anterior to the stomach. At 1 hr after ingestion, one quarter of the particles remained in the stomach; of the remainder, most were found throughout the small intestine. One was found in the cecum; none had been removed from the body. At 2 hr, 1 particle was found in the feces, and 9 of the remaining 11 particles were in the cecum. By 6 hr, half the particles had been passed. At 8 hr, 75 % of the particles had been passed, and the remaining 3 were in the cecum and large intestine. Thus, particles of density 3.0 g/cm³ (about 150 μ diameter) can traverse the GI tract of the mouse in as few as 2 hr.

In contrast, Table 2 shows that no particles were passed from the rat until 8 hr after ingestion even though removal from the stomach was complete by the third hr. Particles moved rapidly to the cecum (3 to 4 hr), where they remained for several hr. In most instances, particles could not be found in the large intestine until the seventh hr.

TABLE 2

Deposition of ceramic spheres throughout the GI tract of rats following single particle administration*

Segment	Hours after Feeding†							
	1	2	3	4	5	6	7	8
Esophagus	–	–	–	–	–	–	–	–
Stomach	6	3	–	–	–	–	–	–
Small intestine 1	1	–	–	–	–	–	–	–
Small intestine 2	2	2	–	–	–	–	–	–
Small intestine 3	3	5	3	–	–	–	–	–
Small intestine 4	–	2	9	2	3	–	2	–
Cecum	–	–	–	9	9	12	7	9
Large intestine	–	–	–	1	–	–	3	1
Excreted	–	–	–	–	–	–	–	2

* Diameter 150 microns; density 3.0 g/cm³.
† Twelve rats sacrificed each hour.

Dog Studies

Measurements of *GTT* in beagles were inconclusive because particles were sometimes passed during the night. Four dogs were each given a $^{235}UC_2$ particle at 1430 hr. Three passed the material in the first voiding at approximately 17 hr; the fourth passed its particle at 26 hr in the second fecal sample. Seven others were each given a particle at 1700 hr. Two dogs passed the particles early the following morning, about 15 hr later. Another particle was voided at 24 hr and 2 others between 24 and 39 hr after feeding. The sixth was passed at 44.5 hr and the last at about 63 hr. These data were obtained with fissioned $^{235}UC_2$ particles. Similar results were obtained when nonfissioned $^{235}UC_2$ was used; all particles were recovered. A reasonable estimate of *GTT* for dogs would be about 1 day.

Table 3 summarizes the results of the chronic feeding study. Dog 23 passed no particles during the 72-hr feeding period. Over 90 % of the particles were in the cecum (10 %) or in the large intestine (80 %). For the other 3 dogs, 19–34 % of the particles were passed before sacrifice. The contents of the large intestine accounted for 54–67 % of the ingested particles. Only animal 26 had an appreciable amount, about 13 %, in the cecum. Passage through the four segments of the small intestine was rapid, as evidenced by the paucity of particles retained. Holdup in the stomach was only transitory. These data clearly indicate a rapid movement of the particles from the stomach to the cecum. After a slight holdup, particles passed into the large intestine where residence time was of the order of 9–12 hr.

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TABLE 3

*Distribution of scandium-46 labeled microspheres in the GI tract of beagles following intake of one sphere per hour for 72 hours**

Location	Animal Number			
	20	23	26	27
Esophagus	–	–	–	–
Stomach	3	1	6	4
Small intestine 1	–	1	1	–
Small intestine 2	1	1	–	–
Small intestine 3	–	1	–	–
Small intestine 4	–	2	3	1
Cecum	1	8	9	–
Large intestine	48	57	37	42
Feces	19	–	13	24

* The numbers in the columns represent the activity measured in a given segment divided by the activity previously determined for the 72 spheres fed to that dog.

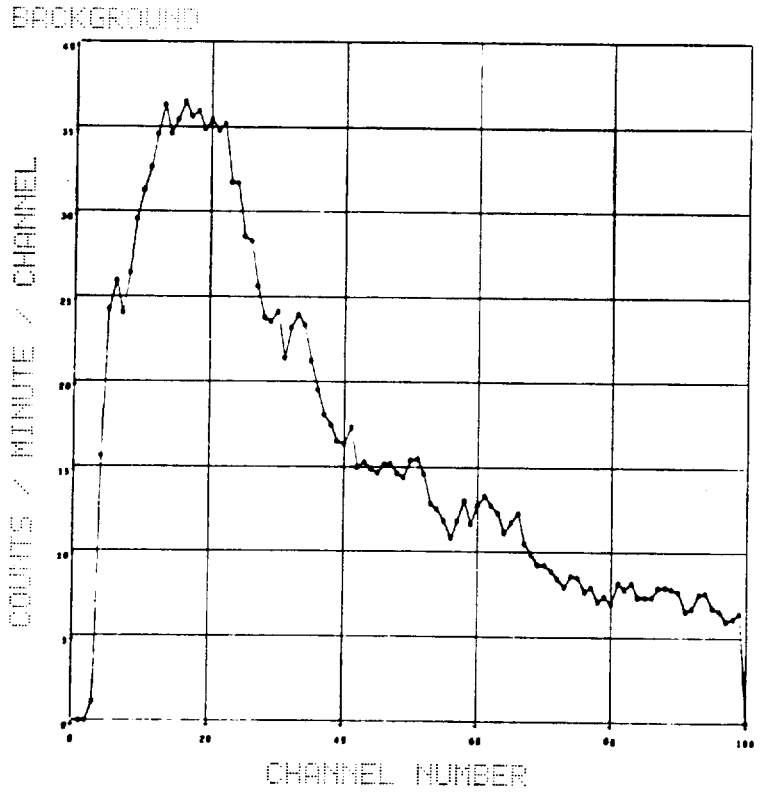

Fig. 1—Background spectrum measured for 30 min in spectrometer (30- to 1000-keV energy interval).

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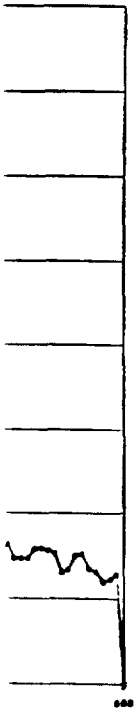

00-keV energy interval).

Human Studies

Figure 1 shows the spectrum obtained for a 30-min background measurement between 0 to 1000 keV. Background rates were of the order of 1684 counts per min (cpm), with a standard deviation (σ) of 7.5 cpm. About 40 % of the total rate occurred within the 100- to 300-keV energy interval, where the ^{235}U gamma ray (180 keV) is detected. The rate and standard deviation for this interval are 693 $\pm$ 5 cpm. Using the 3σ criterion,[2] at least 15 cpm from ^{235}U are required for statistical significance. The background count rate ($\pm$ σ) for the 750- to 950-keV interval is 161 $\pm$ 3 cpm; a minimum of 9 cpm from ^{54}Mn (840-keV photopeak) is required for statistical significance.

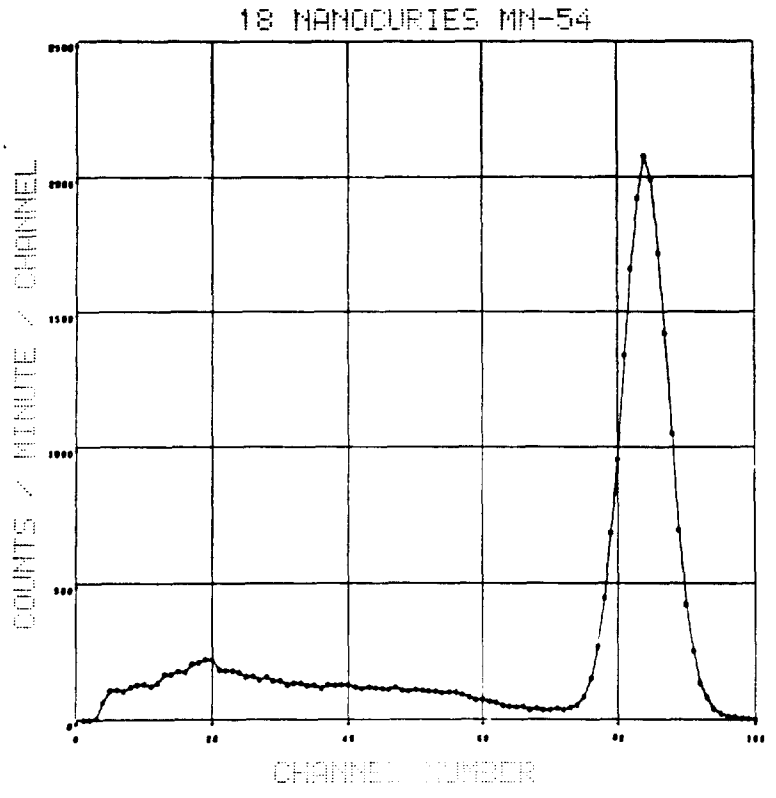

Fig. 2—Net spectrum obtained from point source containing 18 nCi ^{54}Mn (30- to 1000-keV energy interval).

Figure 2 shows the spectrum obtained from 18 nCi ^{54}Mn. Photopeak resolution (full width at half-maximum) is about 9.5 %. The Compton edge can be seen at about 644 keV and the backscatter peak at 200 keV. Twenty percent of the count rate for the 750- to 950-keV energy interval is measured between 100–300 keV (i.e., in the ^{235}U region). When both ^{235}U and ^{54}Mn are present, the spectrum in the 100- to 300-keV energy interval must be corrected for ^{54}Mn backscatter. Sensitivity is about 1 cpm per pCi ^{54}Mn. The average ceramic sphere ingested by human subjects contained 150 pCi ^{54}Mn.

Figure 3 is a net spectrum obtained from a fecal sample containing only ^{54}Mn. The photopeak at 840 keV is easily distinguishable and significant (91 $\pm$ 4 cpm). Between 100 to 300

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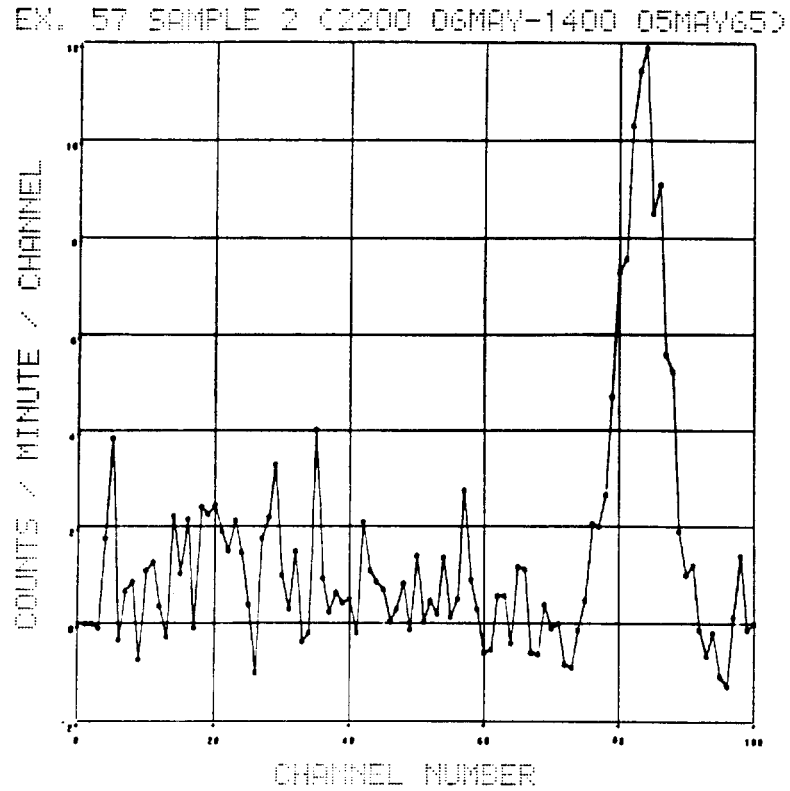

Fig. 3—Net spectrum obtained from 30-min measurement of fecal sample containing ^{54}Mn (30- to 1000-keV energy interval).

keV the count rate is 30 ± 7 cpm. Of this amount, 18 cpm arises from ^{54}Mn backscatter. The remaining 12 cpm falls within 3σ (15 cpm) for background and cannot be attributed to ^{235}U.

The spectrum shown in Fig. 4 shows the presence of only ^{235}U in the fecal sample. For the 100- to 300-keV energy interval a count rate of 116 ± 7 cpm indicates the presence of ^{235}U. At greater energies (750 to 950 keV), the 10 ± 3 cpm is not significantly different from 9 cpm (3σ) obtained for background. A spectrum containing both ^{235}U and ^{54}Mn is shown in Fig. 5; both the 180- and 840-keV gamma rays are prominent.

Table 4 lists individual *GTT* values and the number of the fecal sample containing the particles for each of the 52 subjects. On the average, particles were passed in the second fecal sample following ingestion. The observed range was from 1–4. Subjects included in Table 4 passed particles of both densities in the same sample. Table 5 summarizes this information. The arithmetic average *GTT* is 34.5 hr, with a standard deviation of 16.6 hr.

Fig. 4—Net spectrum obtained from 30-min measurement of fecal sample containing ^{235}U (30- to 1000-keV energy interval).

Fig. 5—Net spectrum obtained from 30-min measurement of fecal sample containing both ^{235}U and ^{54}Mn (30- to 1000-keV energy interval).

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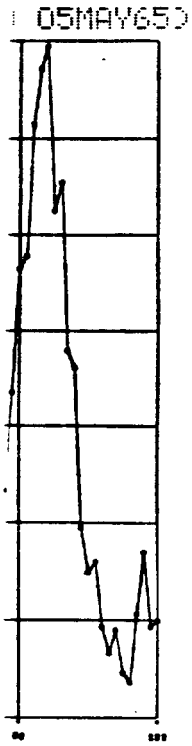

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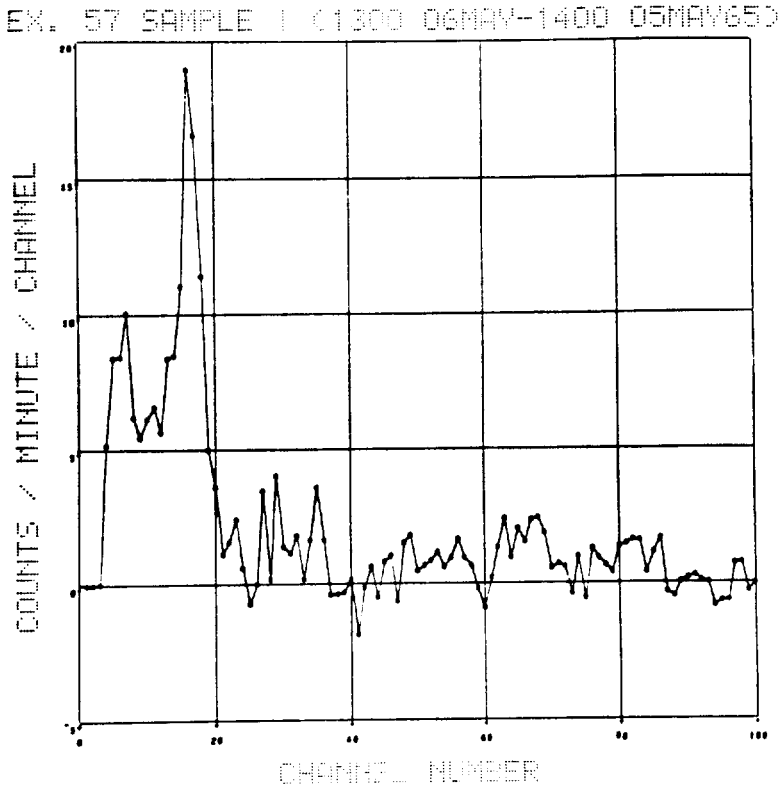

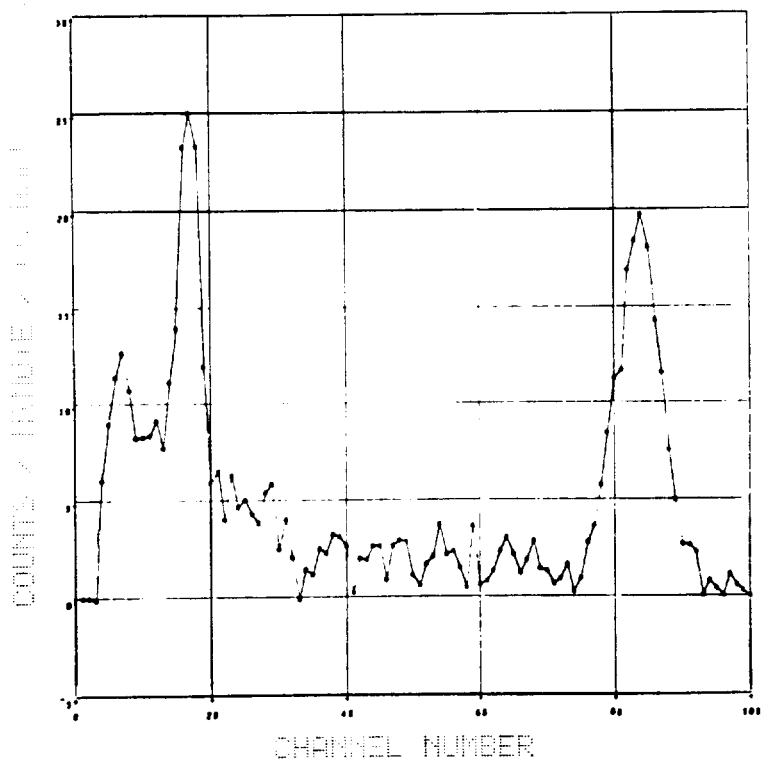

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TABLE 4

GTT for small particles of different densities in 52 subjects

Subject Number	*GTT*, hours	Sample Number	Subject Number	*GTT*, hours	Sample Number
1	31.40	2	27	53.30	1
2	15.50	1	28	45.30	2
3	27.55	2	29	71.45	3
4	22.31	1	30	23.00	1
5	39.45	2	31	71.30	3
6	14.00	3	32	31.15	4
7	29.30	2	33	46.00	3
8	26.08	1	34	43.40	1
9	61.30	3	35	17.15	1
10	58.00	3	36	49.25	3
11	55.05	3	37	22.23	2
12	35.30	3	38	68.20	3
13	23.25	1	39	16.20	1
14	27.35	3	40	22.45	2
15	41.00	2	41	28.05	2
16	17.40	1	42	20.30	1
17	33.30	2	43	56.30	2
18	24.45	1	44	18.40	1
19	38.00	2	45	18.45	1
20	48.00	1	46	35.00	2
21	34.30	2	47	17.50	1
22	41.30	2	48	27.28	2
23	72.00	4	49	41.00	2
24	22.40	2	50	24.58	2
25	22.50	1	51	25.75	2
26	20.40	2	52	24.33	2

TABLE 5

GTT for small particles of different densities in 52 subjects

	Interval, hours			
	0–24	24–48	48–72	0–72
GTT, hours	19.6	34.0	61.6	34.5
Range	14.0–23.3	24.3–48.0	49.3–72.0	14.0–72.0
σ_i*	3.6	7.5	8.5	16.6
n	17	25	10	52

* $\sigma_i = \pm \left[\frac{\Sigma (x - \bar{x})^2}{n - 1}\right]^{1/2}$.

The large error is indicative of the wide range in *GTT*, as individuals ranged from a minimum of 14 hr to a maximum of 72 hr. The minimum was obtained for a normal stool and did not represent a diarrheal condition. Twenty-five of the 52 subjects passed the particles between the 24th and 48th hr after ingestion. About one-third of the subjects passed the materials before 24 hr.

In only 5 of the 57 trials was a separation of particles observed. Three subjects passed the

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TABLE 6

GTT for small particles of different densities in 5 subjects

Subject Number	^{54}Mn Ceramic Spheres		$^{235}UC_2$ Spheres	
	GTT, hours	Sample Number	*GTT*, hours	Sample Number
53	28.5	3	51.8	4
54	21.5	2	51.5	3
55	70.9	3	47.1	2
56	74.5	4	95.6	5
57	32.0	2	23.5	1

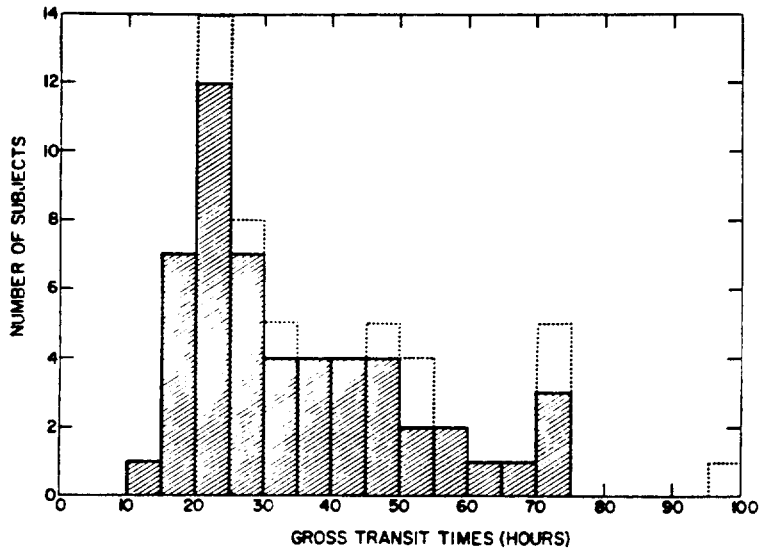

Fig. 6—Frequency distribution of *GTT* for 62 subjects for 5-hr intervals between 10 and 100 hr.

lower-density ceramic spheres first, whereas 2 passed the higher-density UC_2 first. Table 6 presents the data, representing about 9 % of the total sample, for the 5 subjects. All *GTT* values are within the range observed for the 52 subjects listed in Table 4, except for 74.5 and 95.6 hr recorded for subject 56. Figure 6 shows the frequency distribution of *GTT* values for all 62 subjects; a 5-hr interval is used between 10 and 100 hr. The dashed portions represent the data given in Table 6 (treated as 10 subjects); the area bounded by solid lines corresponds to the 52 subjects presented in Table 4.

Figure 7 shows the relation between GTT and time of day that particles were ingested for 3 subjects. Time of ingestion and number of the fecal sample containing the particles are shown in parentheses. The steady decrease in *GTT* noted in the first 4 trials (subject A) represents decreasing times between particle ingestion and early morning bowel emptying. However, trial 5 in the same subject indicates that particles ingested at 1700 hr were not lost the following morning but rather on the second morning after ingestion. Subject B shows a similar pattern for 3 trials spaced at 6-hr intervals. Subject C, representing 10 trials, is more

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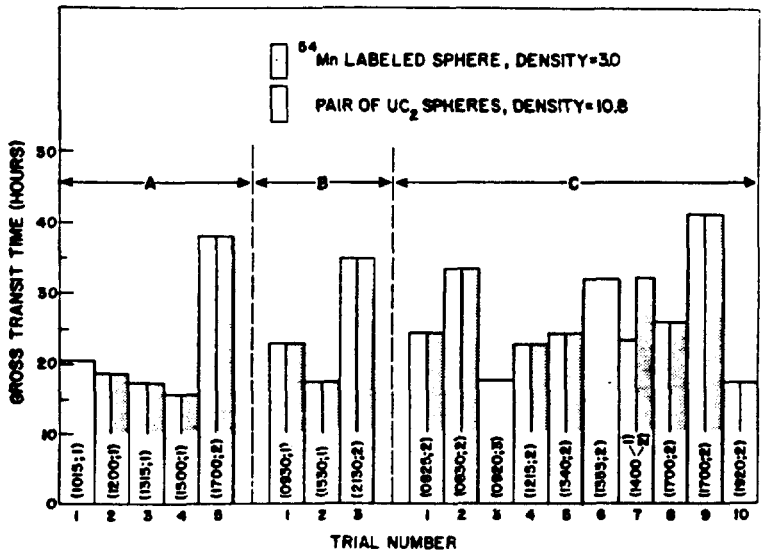

Fig. 7—*GTT* in man in relation to time of day particles were ingested.

typical of a person with nonregular bowel habits. Despite the dispersion of the data, most values fall within a factor of 2 and, in most cases, the particles were identified in the second sample.

CONCLUSIONS

Manganese-54 labeled ceramic spheres and $^{235}UC_2$ fuel cores in the 100- to 200-μ diameter size range are not preferentially retained in the GI tracts of experimental animals, including man, because of small size. Ceramic spheres (density 3.0 g/cm^3) can move through the GI tract of mice with a *GTT* as short as 2 hr. Passage to the cecum and large intestine is essentially complete by the 3rd hr after ingestion. By the 6th hr, half the mice had passed the spheres; by the 8th hr, only one-quarter of the mice retained the spheres.

In the rat, no spheres were passed until the 8th hr after ingestion. Movement to the cecum and large intestine required 4–6 hr.

Dogs fed $^{235}UC_2$ fuel cores showed variable *GTT* values with an estimated average of roughly 15–20 hr. A chronic feeding experiment demonstrated rapid movement of particles through the GI tract to the cecum and large intestine.

Information accrued on 57 individuals represents *GTT* values for some 156 individual particles (114 $^{235}UC_2$- and 42 ^{54}Mn-labeled ceramic spheres). Distribution of values does not correspond to a normal distribution, as a peak occurs in frequency distribution (5-hr intervals) at 20–24 hr, with secondary peaks at 45–50 and 70–75 hr. The arithmetic average of 34.5 hr, however, agrees well with the value of 31 hr recommended for the standard man by Committee II of the ICRP.[3] LeRoy *et al.*[4] recently suggested a revision to 49 hr based on studies with particulate materials in humans. Leaching of label might have complicated the interpretation of these results. *GTT* is partially dependent on time of ingestion. Up to a point, spheres ingested at different times of the day are lost the following morning. Spheres ingested late in the day, however, will not be passed until the second morning. This applies to persons with regular bowel habits.

Density does not affect *GTT* in man. Low-density (3.0 g/cm^3) ceramic spheres behaved

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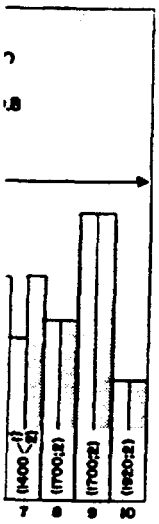

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This applies to persons

ramic spheres behaved

much the same as higher-density (10.8 g/cm^3) materials. Recent work from another laboratory[5] suggests that small high-density particles might be preferentially retained in the gut (of the pig) if the particles are highly radioactive. Particles were found more than 14 days after ingestion in the posterior ileum at the junction with the cecum, embedded within crypts of lymphoid tissue, and surrounded by small amounts of necrotic tissue. The fraction held up was well less than 1 %. This condition obviously increases the radiation hazard and must be studied in more detail. Regardless, we can say with some confidence that small size and high density are not in themselves parameters which complicate estimations of radiation dose for discrete particles traversing the GI tract. The model currently used by the ICRP for retention of food in different portions of the GI tract is adequate in view of other related dosimetric problems (e.g., where the particle is within a particular segment).

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DISCUSSION

Smyth: I would like to raise a small question of terminology. Some earlier paper this afternoon talked about transit time, meaning the time taken to pass along the intestinal length. Now transit time, if we have the analogy of the kidney, should mean the time it takes to cross the epithelial cell. Perhaps we should sort out what words we are going to use.

Richmond: You might notice I'm smiling, because originally we thought of this in terms of transport time. We did not talk about transport for this very reason. But I agree with you, I think that there is a problem in terminology.

Smyth: Sooner or later we must, as physiologists, get a proper terminology for all of the things that happen in the alimentary tract so that we all use the same words for the same thing. At present we use different words for the same thing, or the same words for different things.

Sullivan: I'm certainly pleased to hear Dr. Smyth bring that point up because I made myself quite unpopular at Hanford by pushing for some uniformity. Our cell kinetic people speak about transit time in the mucosal cell.

Smyth: Yes, that's another use of the word.

Friedman: Do you observe in your patients any difference with respect to the shape of the stomach or body habitas? You know, that the "fish-hook" type of stomach and the "steer-horn" type have different evacuation rates.

Richmond: No. Now let me emphasize another point. It is extremely difficult to get even 57 of your best friends, if anyone might have that many, to do this type of experiment. I purposely did not go into the lengthy problems of dosimetry but this required long measurements for each fecal sample, repeated four or five times for some subjects. We have done no other work as far as trying to measure other variables.

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REPORT OF A SYMPOSIUM
HELD AT RICHLAND, WASH., U.S.A.
ON SEPTEMBER 25-28, 1966

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