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Gastrointestinal transit of pellets in rats: effect of size and density

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Abstract

Gastrointestinal distribution kinetics of a large amount (0.5–1 g) of three types of non-disintegrating pellets which had the same size (S1, 710–1000 μm) but different densities (D1, 0.9 and D2, 1.5 g cm^{-3}), or which had the same density (D1) but different diameters (S1 and S2, 1250–1600 μm) were examined in fed rats. The percentage of pellets remaining in the stomach, small gut, caecum and colon was measured at suitable intervals. Whatever the size of the pellets, the heavier the density, the longer the gastric emptying (2.1 h for D2–S1 instead of 1.3 h for D1–S1 and 0.7 h for D1–S2). The small gut transit time was not influenced by density but was slightly prolonged by size: 3.3 h for D1–S2 instead of 2.6 h for D1–S1 and D2–S1. Conversely, the gastrocolonic transit time was widely influenced by density (13.5 h for D2–S1) and somewhat by size (8.2 h for D1–S2 and 4.5 h for D1–S1). This delays were proportional to caecal residence time in the large, sacculated and derivated caecum of rats. In order to use the rat as an experimental model for pharmaceutical pellets, those results should have implication for the design of dosage forms, particularly those for controlled or timed release or those for targeted release at specific positions in the gastrointestinal tract.

Keywords: Gastrointestinal transit; Pellet; Density; Pellet size; Rats

1. Introduction

Large animals are usually used to assess absorption from formulation such as tablets or pel-

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lets. Therefore, many studies have concerned the gastrointestinal transit of pellets in dogs (Itoh et al., 1986; Heinamaki et al., 1988). Experiments have also been performed in humans (Coupe et al., 1991; Clarke et al., 1993). Smaller animals like rats or mice are commonly considered most suitable for determining the mechanism of drug absorption and bioavailability values from powder or solution formulations (Kararli, 1995). But, transit of pellets in the rat is poorly documented, mainly on gastrointestinal transit of small amounts of pellets (Ch'ng et al., 1985; Mori et al., 1989), or is documented for smaller sizes like micro or nano particles (Palin et al., 1982; Jani et al., 1990). Nevertheless, small animals, more than the ease of use and the cost, allow one to study transit with precision in each compartment of the gastrointestinal tract by animal sacrifices, as radiography or gammascintigraphy on small animals are not suitable methods compared with large animals. Thus, the aim of this work was to provide data about various gastrointestinal distribution kinetics of a large amount of three types of non-disintegrating pellet, which had the same diameter but different densities, or which had the same density but different diameters, in fed rats.

2. Material and methods

2.1. Animals and diets

Conventional adult (3 months at least) female rats ($n = 34$) from the Fischer 344 strain were used.

Rats were given a fibre-free diet (casein, 20%; saccharose, 20%; corn starch, 50%; vegetal oil, 6%; minerals and vitamins, 4%). The food was either solid (compressed cylinders) and given ad libitum or semi-liquid (powder mixed with 60% w/w water) and 10–15 g was given twice a day (9 a.m. and 5 p.m.).

2.2. Gastrointestinal pellet distribution kinetics measurement

Three kinds of pellets were chosen: two with the same diameter but different densities and two with the same density but different diameters. Table 1 lists their name, size and apparent density, which was calculated from the volume measured in a 100 ml graduated test-tube and the weight of preparation.

Glass pellets were given in semi-liquid food. Avicel®PH101 pellets obtained by extrusion/spheronisation were placed behind the teeth of slightly diethyl ether-anaesthetized rats, in order to avoid the pellets being crunched. Deglutition was artificially induced with a saccharose solution.

At predetermined time intervals (3, 6, 9 and 24 h) and for each kind of pellet, three (or in a few cases, two) rats were sacrificed and the gastrointestinal tract was removed. The content of the different gastrointestinal parts (stomach, small gut, caecum, colon) was filtered in order to recover the pellets which were dried and weighed. The distribution of the pellets was expressed by the mean percentage of pellet weight found in each gastrointestinal part ($\pm$ S.E.M.), in relation to the pellet weight ingested.

2.3. Determination of the mean transit time of pellets

In order to assess the influence of size and density, the transit of pellets in the gastrointestinal tract was expressed in terms of the time required for 50% to leave the stomach (G50) and to leave the small gut (SG50), which is the same as the time required for 50% cumulated pellets to

Table 1
Characteristics of particles used in the study

	High density pellets	Low density pellets
Density (g cm^{-3})	D2, 1.5	D1, 0.9
Particles	Glass Poly Labo	Microcrystalline cellulose (Avicel®PH101) Seppic
Size (diameter, mm)	S1, 1.00	S1 or S2, 0.71–1.00 or 1.25–1.60
Amount administered (g)	1	0.5

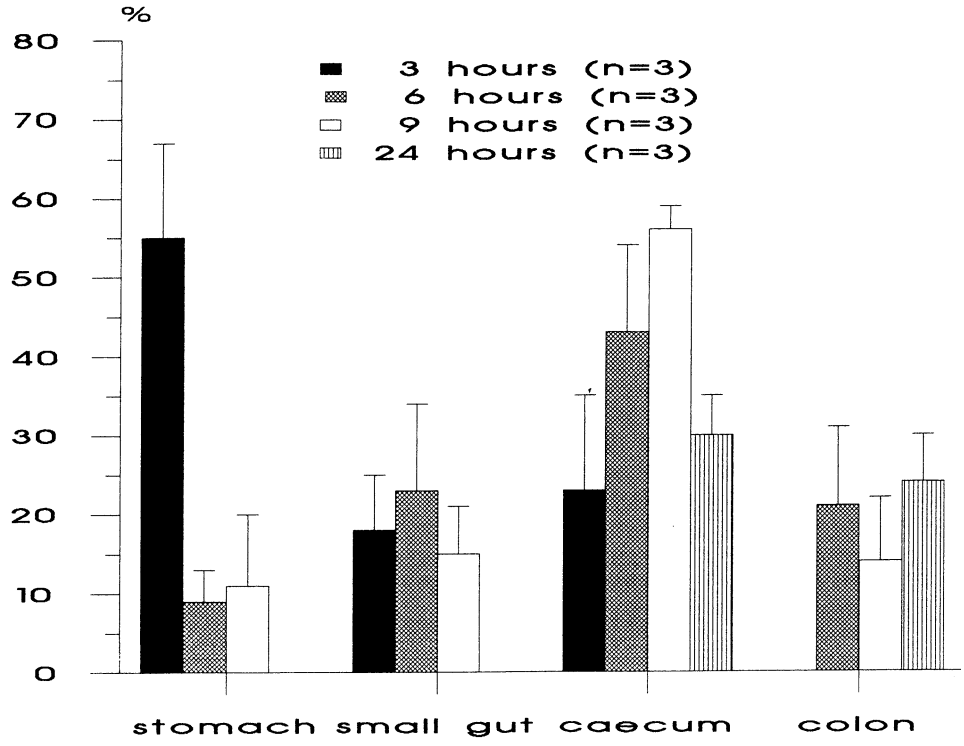

Fig. 1. The gastrointestinal pellet distribution of D2–S1 in terms of percentage of pellets found in various parts of the gastrointestinal tract at each sacrifice time (± S.E.M.).

reach the caecum (CAE50), and the time for 50% to arrive at the colon (C50).

A good linear relationship (Philippe, 1967; Fleury, 1987) between various percentage of pellets and ln(time) was found (r from 0.73 to 0.94). This was confirmed by the test of fit to a linear model. Thus, SG50 (= CAE50) and C50 were calculated with the regression equation. The differences between CAE50 and G50, and between C50 and SG50, were taken as representing, respectively, transit time in the small gut and caecal residence time (Mori et al., 1989). The sum of those two values represents the gastro-colonic mean transit time.

2.4. Bacterial degradation of pellets

In order to avoid losses in the recovery of pellets, the bacterial fermentation of Avicel®PH101 pellets was tested to determine whether degradation of the pellets could occur during their long residence in the caecum. Avicel®PH101 pellets (1 g) were incubated in half-diluted caecal content for 60 h at 37°C under anaerobic conditions. Ninety-six percent (mean value, $n = 4$) of the pellets were recovered, indicating that no degradation occured in the caecum.

3. Results

3.1. Gastrointestinal pellet distribution kinetics

3.1.1. High density pellets, small size pellets (D2–S1)

Fig. 1 represents the gastrointestinal pellet distribution of D2–S1 in terms of the percentage of pellets found in various parts of the gastrointestinal tract at each sacrifice time (± S.E.M.). After 3 h, 55% of the pellets were still in the stomach and 18% in the small gut; some pellets (23%) had started to reach the caecum. The distribution of

the pellets appeared similar at 6 and 9 h: approximately 10% in the stomach, 18% in the ileum, 50% in the caecum and 17% in the colon. Almost no pellets were found in the duodenum and jejunum: all the pellets found were at the end of small gut (ileum). No real excretion seemed to occur before 9 h. After 24 h, 30% of pellets remained in the caecum and 24% in the colon; the rest had been excreted.

3.1.2. Low density pellets, small size pellets (D1–S1)

Fig. 2 represents the gastrointestinal pellet distribution of D1–S1. For the same size (S1), stomach emptying appeared faster with low density pellets than with high density pellets as, after 3 h, 45% of the pellets were in the stomach and 33%, quite totally, in the ileum. After 6 h, almost no pellets remained in the stomach: gastric emptying seemed to be over. Almost all the pellets had reached the large intestine (32% in the caecum and 9% in the colon) and some could be found in the faeces. After 9 h, no more pellets remained in the upper part of the gastrointestinal tract but the caecum and the colon still contained, respectively, 20 and 17% of the pellets. After 24 h, all the pellets had been excreted.

3.1.3. Low density pellets, large size pellets (D1–S2)

Fig. 3 represents the gastrointestinal pellet distribution of D1–S2. 35% of the pellets were still in the stomach at 3 h and the same percentage had reached the ileum. After 6 h, 14% remained in the stomach and 19% in the small intestine. After 9 h, gastric emptying appeared almost over. When arrived in the caecum, pellets stayed longer than D1–S1 as, after 9 h, 34% were still there. Pellets also stayed longer in the colon as, after 9 h, almost 33% were still there. After 24 h, about 10% were still in the caecum and in the colon.

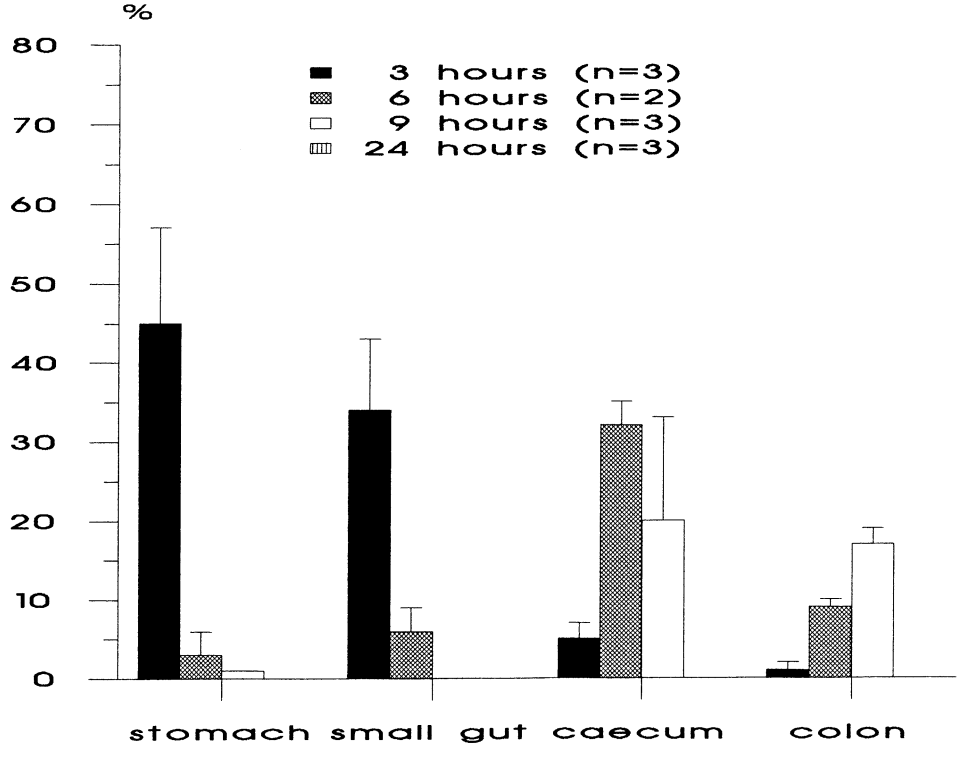

Fig. 2. The gastrointestinal pellet distribution of D1–S1.

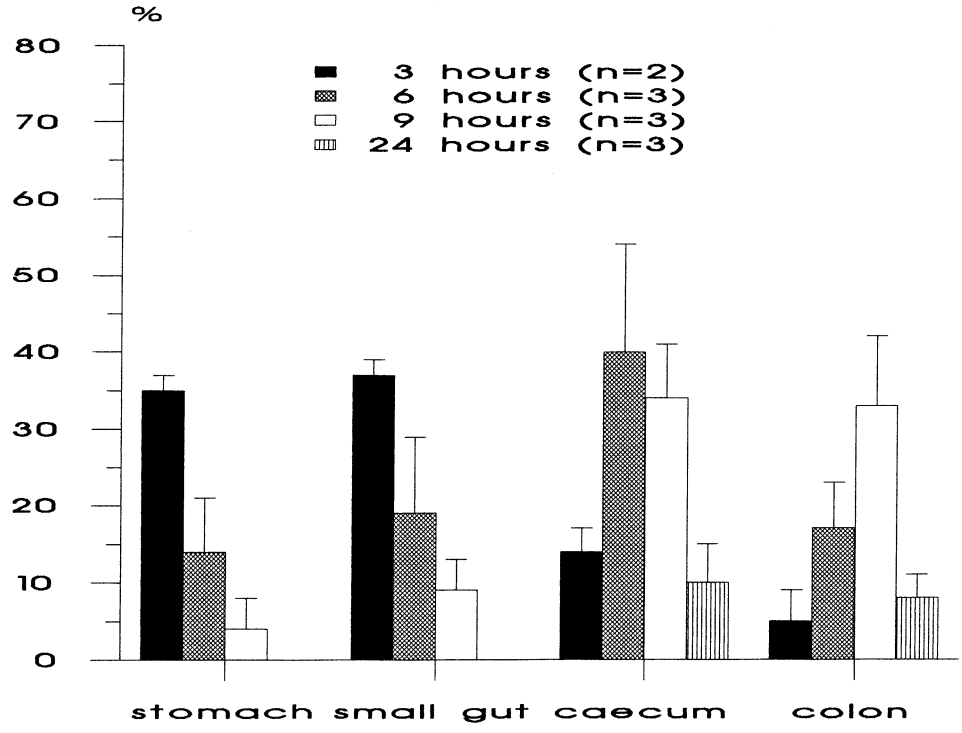

Fig. 3. The gastrointestinal pellet distribution of D1–S2.

3.2. Mean transit time of pellets

The time for 50% of each kind of pellet to live the stomach or to arrive in the caecum and colon are reported in Table 2. Figures in parentheses indicate 95% confidence intervals calculated by Fleury (1987).

The mean gastric emptying times were from 0.7 h for D1–S2, to 1.3 h for D1–S1 and 2.1 h for D2–S1. The magnitude of the confidence intervals reflected the importance of inter-individual variabilities through the three (or two) rats sacrificed in order to perform calculations. Nevertheless, the comparison with data which had been processed by the same mathematical treatment was justified.

The mean caecal arrival times were almost the same (about 4 h) whatever the size or the density of the pellets. In opposition, the mean colon arrival time was very different for each kind of pellet: faster for D1–S1 (5.8 h), 8.8 h for D1–S2, and slower for D2–S1 (15.6 h); and, for each group, the confidence intervals were distinct.

The calculated mean small gut transit time is reported in Table 3 with caecal residence time and gastro-colonic transit time.

The mean small gut transit time of small pellets with low (D1) and high (D2) density were the same: 2.6 h. But for the low density pellets (D1), the mean transit time is longer (3.3 h) for larger pellets (S2) than for smaller (S1). The range of caecal residence time was very large: for high density pellets (D2–S1), it was more than 10 h and it took twice the time for large pellets (D1–S2). The low density and small size pellets (D1–S1) stayed almost 2 h in the caecum. The gastro-colonic transit time was proportional to the caecal residence time: 13.5 h for D2–S1, 8.2 h for D1–S2 and 4.5 h for D1–S1.

Table 2
50% Transit time of pellets[a]

Transit time (h)	Abbreviation	D2–S1	D1–S1	D1–S2
Gastric emptying time	G50	2.1 (0.8; 5.8)	1.3 (0.3; 5.2)	0.7 (0.1; 3.0)
Caecal arrival time = small gut emptying time	CAE50, SG50	4.73 (3.1; 7.2)	3.87 (2.2; 6.9)	4.03 (2.3; 7.0)
Colon arrival time	C50	15.6 (9.5; 25.6)	5.8 (4.6; 7.3)	8.8 (6.9; 11.3)

[a] Figures in parentheses indicate 95% confidence intervals.

4. Discussion

4.1. Gastric emptying

The study protocol was designed to reduce factors known to affect gastrointestinal transit such as stress, which is known to delay gastric emptying (Enck et al., 1989). However, since rats receiving low density pellets were stressed by anaesthesia, we supposed that the differences (Table 2) between G50 of each type of pellet should have been more important than the data indicated. For the low density pellets (D1), the smaller the size, the longer the gastric emptying (1.3 h for S1 and 0.7 h for S2). Ch'ng et al. (1985) found a stomach half transit time (2.25 h) almost equivalent to the longest gastric emptying measured in our study (D2–S1). The pellets they tested were 30–40 mesh Amberlite resin beads (0.4–0.5 mm). The amount administered was 0.15 g in a number 3 capsule surgically inserted into the stomach of rats. The comparison on the size point of view was difficult as the density of those pellets was not specified, the amount administered was small and the level of stress in their experiment was high. Anyway, our results and those of Ch'ng seemed to agree: the smaller the size, the longer the gastric emptying.

Also, whatever the size of pellets, the heavier the density, the longer the gastric emptying. We could argue this finding by the fact that low density pellets were homogeneously mixed in the stomach content compared with high density pellets, which could also be the explanation of the longer stomach transit time observed for small size pellets (D1–S1) compared with large size pellets (D1–S2). But, even if claims about the effect of density had been conflicting (Davis et al., 1986b), gastric emptying was influenced in rats by density as it was in dogs (Meyer et al., 1989; Gupta and Robinson, 1995) and in humans (Devereux et al., 1990). A proposed explanation (Clarke et al., 1993) for the difference in rate of gastric emptying could be that the heavy pellets may be able to settle deeper into the folds of the stomach, thus offering even more protection against normal emptying. In dogs, Gupta and Robinson (1995) also postulated that the fed state motility was not so strong as to empty high density pellets (such as glass particles) as fast as low density pellets (such as Avicel® particles). Specific physical characteristics other than size and density can also affect gastric emptying such as hardness and softness. Meyer et al. (1989) showed that those characteristics may be of importance in the gastric residence time and that hard particles emptied slower than softer ones. Thus, the glass pellets used in the study emptied slower than the Avicel® particles. This parameter could also be considered for an explanation of the delay.

In humans, food is known to be another factor influencing gastric emptying (Coupe et al., 1991). In our study, whatever the consistency of food, the amount ingested was the same: the quantity of semi-liquid food (10–15 g) has been calculated to mimic the usual ingested solid food and all rats have been adapted for 2 weeks before experi-

Table 3
Calculated mean transit time of each kind of pellets

Time (h)	D2–S1	D1–S1	D1–S2
Small gut transit	2.6	2.6	3.3
Caecal residence	10.9	1.9	4.8
Gastro-colonic transit	13.5	4.5	8.2

ments. Thus, rats were in the same fed state and food influence could be not considered.

The amount of pellets administered can also be discussed. In practice, rats had free access to heavy pellets (glass) in semi-liquid food. They only ingested 750 ± 250 mg of heavy pellets. Therefore, we administered 500 mg to the light pellets' group, for which we could not give more by mouth fill-up. We had to give the pellets this way in order to avoid the pellets being crunched. But, the difference between the pellet loadings cannot be considered, as the amount administered was large for both groups. No publication took care on the influence of the amount of pellets given to the subject. Mori et al. (1989) also gave pellets to fed rats, allowing us a comparison. They gave 20 pellets. We gave about 530 pellets for D2–S1, 734 for D1–S1 and 127 D1–S2. Their gastric emptying was 1.7 h while ours was between 0.7 and 2.1 h, which was in the same range. As the size and the density of their pellets was almost the same as our pellets, the amount administered did not seem to be influential. Moreover, in contrast with humans, the stomach of rodents is divided into a small glandular and a large non-glandular portion. This part has a specific motor activity, which creates the intragastric tone or pressure gradient between the stomach and the duodenum (Moes, 1993). Thus, even if the rat stomach is very small, it can empty a large amount of heavy pellets. But, gastric emptying seems difficult to compare between human and rodents as their stomach anatomy and physiology are very different. Nevertheless, even if oral administration is not easy and several factors influence gastric emptying and interspecies comparisons, rats could also be a model to test pellets containing an active ingredient, from a gastric emptying point of view.

4.2. Small gut transit time

The calculated mean small gut transit time (Table 3) indicated that the small gut transit time was not influenced by specific gravity but that it was slightly dependent on size. In rats, Mori et al. (1989) found also a mean small intestinal time of 3.1 h with soft food and hard food. The amount administered did not seem to influence the small gut transit time as they gave 1/35 pellets' loading compared with what we gave. Ch'ng et al. (1985) had also described the movement of pellets in the small gut. The calculated half transit time was 4 h, which was in the same range as our findings. Even if the pellets' density was not known, the small gut transit time seemed very slightly dependent on size and on loading as they gave one-fifth of the amount we administered.

In the case of humans, it has been reported that the mean transit time of various preparations through the small gut was 3–4 h, irrespective of the fed or fasted state of the subjects (Davis et al., 1984b) and of the type of dosage form ingested (Davis et al., 1984a.). Davis et al. (1986a) confirmed this: measured intestinal transit times were independent of the dosage form and fed state, and the average small intestinal transit duration was about 3 h (mean $\pm$ 1 h S.E.M.). Whatever the pellets, the mean transit time in rats seemed comparable with humans even if the lengths of their small gut are different. In rats, the transit in the small intestine seemed to be considerably more regular than in the stomach.

4.3. Caecal residence time and colon arrival

The differences between caecal residence time and colon arrival of pellets of various size and density (Tables 2 and 3) were highly significant. Those differences were major compared with the differences observed in gastric emptying and small gut transit time between each type of pellet. Thus, the passage through the caecum seemed to be restrictive for the global gastro-colonic transit. It is well known that the rat caecum is large and can be fully and independently considered as a compartment of the digestive tract (Kararli, 1995). The caecum is sacculated; it is capacious and never empty. We can imagine that the more the pellets are heavy or their size is important, the longer they stay in this kind of trap. In opposition, humans have a poorly defined caecal region which is continuous with the colon. In order to target an active drug in a solid oral dosage form to the colon, arrival is direct for humans but not for rats, for whom a mechanical retention of pellets occured during our experiments.

Mori et al. (1989) found a longer caecal arrival time: 6 h for their pellets, equivalent to our D1–S1 which we found to be 3.9 h. As they gave only 20 pellets, the amount administered seem to modify the caecal transit: the smaller the amount, the longer the caecal residence time. This can be explained by the fact that the pellets are more diluted in the caecal content.

Dietary fibre plays a key role in digestive physiology and particularly in the regulation of gastrointestinal transit time (Cummings, 1982). But, for both types of food, the diet was fibre-free. The fibre exerts its action in the hindgut. It has little effect on gastric emptying and small intestine (Focant et al., 1995). Thus, choosing a fibre-free diet permitted us to avoid any 'fibre effect', excepting a food ballast which is the same whatever the pellets.

5. Conclusion

The fact that density as a means of delaying the gastric residence time of pellets had little value compared with the influence of density (and slightly size) on caecal residence time meant that the gastro-colonic transit in the rat was mainly controlled by caecal emptying. The density and the size of the pellets influenced this: the higher the density and the larger the size, the slower the transit. In order to use the rat as experimental model for testing pellets containing active ingredients, even if oral administration is not easy, those experiments and their results could have implications for the design of pharmaceutical dosage forms, particularly those for controlled or timed release. Additionally, they also should have relevance to the design of dosage forms to release drugs at specific positions in the gastrointestinal tract.

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