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THE SIMULTANEOUS MEASUREMENT OF ABSORPTION AND TRANSIT IN THE GASTRO-INTESTINAL TRACT OF THE RAT

By P. C. REYNELL and G. H. SPRAY

From the Nuffield Department of Clinical Medicine, University of Oxford

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It has been our object to devise a method by which gastric emptying, intestinal transit and the absorption of test substances from the gastro-intestinal tract of the intact conscious animal can be measured simultaneously. To this end we have administered a test solution, together with a soluble marker which is almost completely unabsorbed. The distribution of the marker along the gastro-intestinal tract can be used to calculate gastric emptying and intestinal transit, and the ratio of test substance to marker in a sample from any part of the gastro-intestinal tract can be used to calculate the percentage absorption of test substance at that level. Phenol red has been used as marker and glucose and iodide as test substances. Glucose was selected as a substance which is preferentially absorbed by a vital mechanism (Cori, 1925), and iodide as a substance not known to be absorbed by any special mechanism.

The use of markers in the study of gastro-intestinal function is not new. Gastric absorption in man and dog has been studied in this way (Holtz & Schreiber, 1930; Freund & Steinhart, 1931). Inert substances such as chromic oxide have been given by mouth to animals, and the ratio of various substances to the inert marker have been compared in diet and faeces so as to measure the percentage net absorption without the necessity for full balance studies (Schürch, Lloyd & Crampton, 1950). Goodman, Lewis, Schuck & Greenfield (1952) have used Evans blue to measure intestinal transit in animals; but to the best of our knowledge no satisfactory technique has yet been evolved for the simultaneous measurement of intestinal absorption and transit.

METHODS

Experimental methods

Adult male rats of the Wistar strain (200–400 g wt.) were used in these experiments. They were deprived of food but allowed water for 24 hr before the experiment. Each rat was then given just sufficient ether to cause it to submit passively to intubation with a gum elastic catheter and 4 ml. of a solution containing approximately 3 mg of phenol red, 400 mg glucose and 2 μc of ^{131}I was

introduced into the stomach. One rat was immediately killed and used as a control, and others were killed by a blow on the head at intervals of 1, 2 and 3 hr after intubation. Duodenum, terminal ileum and oesophagus were rapidly ligated, and the stomach and small intestine were excised and divided into the following four segments: (*a*) stomach, (*b*) proximal half of small intestine, (*c*) third quarter of small intestine, (*d*) distal quarter of small intestine. If any phenol red had passed into the caecum, this was obvious on inspection as the contents of the terminal ileum are alkaline. Each segment was placed in a measuring cylinder, and the volume made up to 60 ml. with 1·95% (w/v) cadmium sulphate solution and homogenized for 5 min in a Waring blender. 2·5 ml. of 2N-NaOH was then added to 40 ml. of homogenate, the volume was made up to 80 ml. and the suspension well mixed and filtered (Fujita & Iwatake, 1931). Phenol red and glucose estimations were carried out on the filtrate and iodide estimations on the remaining 20 ml. of homogenate.

Analytical methods

Phenol red was determined colorimetrically using a Hilger Spekker photoelectric absorptiometer with green filters (absorption maximum 530 mμ). A standard curve was obtained relating the concentration of phenol red to the optical density of the solution in 0·01N-NaOH, and the concentration of phenol red in the alkaline filtrates was read off from this curve.

Glucose was determined as fermentable reducing substances by a modification of the method of Fisher & Parsons (1953). Total reducing substances in an aliquot of the cadmium hydroxide filtrates were determined by the method of Hulme & Narain (1931) before and after fermentation with yeast. The difference between the amounts of reducing substance before and after fermentation was taken as the amount of glucose in the sample.

Radio-iodine was given in the form of sodium iodide of high specific activity without carrier iodide, and the radioactivity of 5 ml. aliquots of homogenate was determined on a scintillation counter.

Calculations

The following values are all expressed as percentages. In each case 'control rat' means rat killed immediately after intubation.

Gastric emptying is defined as that percentage of the administered phenol red which has left the stomach during any given period of time and is calculated from the formula

$$\frac{Px-Pa}{Px}\times 100,$$

where Pa = phenol red recovered from the stomach, Px = phenol red recovered from the whole gastro-intestinal tract. If any phenol red is found to have entered the caecum, this amount is calculated by difference from the control animal assuming 90% recovery in the test animal, this being approximately the average fraction of the administered phenol red recovered from different animals in preliminary experiments (Table 1).

Intestinal transit can be determined for each segment of small intestine separately, for any adjacent pair of segments or for the small intestine as a whole. The transit through any segment is that percentage of the amount of phenol red entering the segment during the time since intubation which has moved on to the next segment during the same period of time. For example, the transit through the first half of the small intestine is given by the ratio

$$\frac{Pd}{Pb+Pd}\times 100,$$

where Pb = phenol red recovered from the first half of the small intestine, Pd = phenol red recovered from all parts distal to the mid-point of the small intestine, including any which has entered the caecum.

Intestinal absorption index for a test substance at any level of the small intestine is the proportion of the administered substance which has been absorbed by the time the intestinal contents have reached that level. The figure is obtained by comparing the ratio of test substance to phenol red recovered from a segment of the small intestine of the test rat to the ratio of test substance to

phenol red recovered from the control rat, and is calculated from the formula

$$\left(1-\frac{Py\,Ti}{Pi\,Ty}\right)\times 100,$$

where Py = total phenol red recovered from the control rat, Pi = phenol red recovered from relevant segment of test rat, Ty = total amount of test substance recovered from control rat, Ti = amount of test substance recovered from relevant segment of test rat. If this ratio is calculated for each segment of the small intestine, the series of values obtained represents an 'absorption gradient' which gives an indication of the site of maximum absorption. The value obtained for the distal segment of the small intestine is a measure of the *completeness* of absorption of the test substance by the small bowel.

Rate of absorption of a test substance is the percentage of the administered dose which is absorbed during any given period of time since intubation, and is calculated from the formula

$$\frac{Ty-Tx}{Ty}\times 100,$$

where Ty = amount of test substance recovered from control rat, Tx = amount of test substance recovered from test rat.

Gastric absorption of a test substance cannot be directly measured, but if the ratio of test substance to phenol red recovered from the stomach of the control animal is greater than the same ratio in an animal killed some time after intubation, it may be assumed that some test substance has been absorbed from the stomach. The following index, obtained from these ratios, gives a value for 'maximal' percentage gastric absorption since it involves the assumption that the ratio of test substance to phenol red leaving the stomach during the time since intubation is the same as that found in the stomach when the animal is killed. It therefore overestimates 'true' gastric absorption

$$\left(1-\frac{Pc\,Ta}{Pa\,Tc}\right)\times 100,$$

where Pc = phenol red recovered from stomach of control rat, Pa = phenol red recovered from stomach of test rat, Tc = amount of test substance recovered from stomach of control rat, Ta = amount of test substance recovered from stomach of test rat.

RESULTS

Selection of phenol red as marker. A number of substances were tested as possible markers. Animals were killed at hourly intervals after intubation, and the amount of marker recovered from the gastro-intestinal tract was compared with the amount recovered from an animal killed immediately after intubation. Evans blue (T 1824) and carmine were found to be unsatisfactory because the amount recovered decreased progressively with time, suggesting a significant absorption. Eventually phenol red was tried as Fisher (personal communication) found that this indicator did not appear in significant amount in the outer circuit of the isolated rat intestine after it had been introduced into the inner circuit. The amount of phenol red recovered from the stomach and small intestine of rats at intervals of time varying from 1 to 3 hr after intubation was usually more than 90% of the amount recovered from the control rat killed immediately after intubation (Table 1).

It was necessary to use a control rat since the phenol red recovered from such an animal always gave a lower colorimeter reading than that obtained by simple dilution of the injected fluid. We have been unable to find the reason for

this discrepancy. Phenol red can be recovered quantitatively if added to a tissue homogenate or to the filtrate obtained after adding NaOH to a homogenate, but not if injected into the stomach of the living animal, even if the rat is killed within seconds of intubation. Phenol red is also lost if the stomach is washed out and the contents analysed, instead of homogenizing the contents and stomach wall together. There may be some binding of phenol red by the stomach tissue, because a little phenol red was lost when it was added to a stomach immediately after removal from the animal, although this loss was not as great as that found when the phenol red is injected into the living animal. If this binding does occur, our recoveries show that there can be little further loss of phenol red by this means during the ensuing 3 hr. There is undoubtedly a little absorption of phenol red, since traces of it can be detected in the urine, but the recoveries indicate that the amount absorbed must be very small. We have felt it necessary to administer phenol red in strong solution (75 mg/100 ml.), as recovery seemed to be less good if weaker solutions were used.

TABLE 1. Phenol red recovered from test animals expressed as percentage of control values

Time after intubation (hr)	No. of animals	Mean recovery (%)	S.E. or range
1	15	93	±2·0
2	3	91	88–93
3	1	94	—

Phenolphthalein is a substance chemically similar to phenol red, though of smaller molecular weight, and there is evidence that an appreciable quantity of phenolphthalein is absorbed and re-excreted into the intestine with the bile (Abel & Rowntree, 1909). A significant enterohepatic circulation of this kind might invalidate our results. In order to exclude this source of error, the bile ducts of two rats were divided between ligatures, and 5 days later the animals were killed 1 and 2 hr after administration of the test solution. The amount of phenol red recovered was 102% of control value at 1 hr and 92% at 2 hr, and it was concluded that there was no significant enterohepatic circulation of phenol red. Phenolphthalein is a purgative, although it is believed to act mainly on the large intestine (Goodman & Gilman, 1941). We found no evidence that phenol red, in the doses used by us, had any purgative effect. The animals did not develop diarrhoea, the caecal contents were of normal consistency, and the contents of the terminal ileum were jelly-like and not fluid.

Gastric emptying. Percentage gastric emptying was determined in thirty-three normal rats at intervals of time varying from 1 to 3 hr after intubation (Table 2). The variation between animals was very great, but if the mean of the logarithms of gastric residues is plotted against time, emptying is linear

over the first 2 hr at least (Fig. 1), suggesting that when a fluid meal is taken into the stomach, gastric emptying is an exponential function of time. This is consistent with experimental findings in man (Hunt & Spurrell, 1951).

TABLE 2. Percentage gastric emptying after varying intervals of time

Time after intubation (hr)	No. of animals	Mean gastric emptying (%)	S.E.
1	15	52	±4·1
2	11	75	±5·2
3	7	86	±3·4

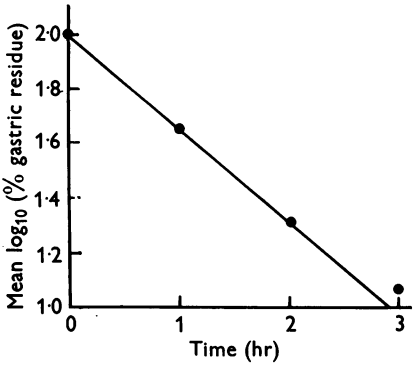

Fig. 1.

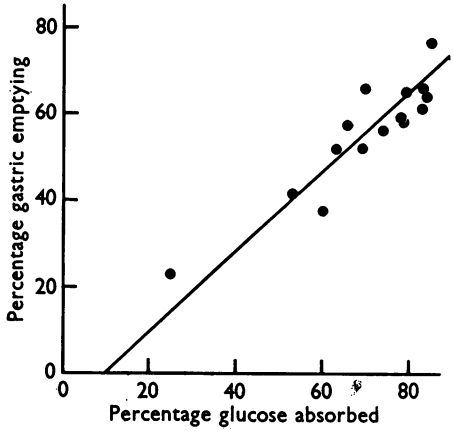

Fig 2.

Fig. 1. Gastric emptying. Mean logarithms of percentage of initial dose of phenol red remaining in the stomach plotted against time after intubation.

Fig. 2. Correlation of percentage gastric emptying after 1 hr and percentage of initial dose of glucose absorbed after 1 hr. ($r = 0{\cdot}915$; $x = 9{\cdot}83 + 1{\cdot}066y$.)

Intestinal transit. Transit through each of the three segments of the small intestine was determined at intervals of time varying from 1 to 3 hr after intubation (Table 3). Once more there was considerable variation between different rats, but it was clear that the intestinal contents moved more slowly as they approached the caecum. Transit was more rapid through the first half of the small intestine than through the third quarter, and through the distal quarter it was exceedingly slow. There was never any phenol red in the caecum after 1 hr, but a little was sometimes present after 2 hr, and at 3 hr it was present in the majority of animals.

Absorption of glucose

Intestinal absorption index for glucose. The percentage absorption of glucose was calculated for each segment of the small intestine. Only insignificant amounts of fermentable reducing substances were recovered from the distal

half of the small intestine, indicating that a dose of 400 mg glucose is completely absorbed in the upper half of the small intestine (Table 4).

Rate of glucose absorption. When 400 mg glucose is given, some 70% is absorbed after 1 hr and some 85% after 2 hr (Table 5). The amount of glucose recovered after 3 hr was usually insignificant. The percentage absorption varies greatly from one animal to another, but if absorption is plotted against gastric emptying there is a close linear correlation (Fig. 2). This illustrates the

TABLE 3. Intestinal transit calculated for each segment of small intestine after varying intervals of time

Time after intubation (hr)	No. of animals	1st half of small intestine: Mean transit (%)	1st half of small intestine: S.E.	3rd quarter of small intestine: Mean transit (%)	3rd quarter of small intestine: S.E.	4th quarter of small intestine: Mean transit (%)	4th quarter of small intestine: S.E.
1	12	78	±3·1	51	6·1	0·0	—
2	9	89	±3·4	71	7·5	11	±4·9
3	6	95	±1·6	86	3·9	28	±14

TABLE 4. Percentage of glucose absorbed at different levels in the small intestine 1 hr after giving 400 mg glucose by stomach tube

Intestinal segment	No. of animals	Mean % glucose absorbed	S.E.
1st half	11	64	±7·1
3rd quarter	11	98	±0·63
4th quarter	11	98	±0·51

TABLE 5. Rate of glucose absorption expressed as a percentage of the administered dose absorbed after 1 and 2 hr

Time after intubation (hr)	No. of animals	Mean (%)	S.E.
1	15	70	±4·1
2	6	84	±5·8

importance of making allowance for variations in gastric emptying when absorption rates are being studied. In our experiments, intestinal absorption of glucose was so rapid that differences between normal animals were attributable mainly to variations in gastric emptying time, to a lesser extent to variable gastric absorption of glucose and hardly at all to differences in intestinal absorption. The regression line of glucose absorption on gastric emptying crosses the X-axis at +9·83% (Fig. 2). This suggests that some 10% of the administered glucose may be absorbed from the stomach in one hour.

Gastric absorption of glucose. When 4 ml. of a 10% solution of glucose is introduced into the stomach, there is apparently progressive gastric absorption of glucose, although the actual mass absorbed by this route cannot be

computed (Table 6). Among animals killed at the same time after intubation, the gastric absorption of glucose was usually found to be greater when gastric emptying was more complete, suggesting that there may be a maximum rate at which the stomach can absorb glucose.

It is apparent that both the relation of absorption rate to gastric emptying and the gastric absorption index indicate absorption of glucose from the stomach under the conditions of these experiments. Other workers using marker techniques have found evidence of gastric absorption of glucose (Holtz & Schreiber, 1930; Freund & Steinhardt, 1931), but this has been

TABLE 6. Gastric absorption index for glucose, calculated from the change in the ratio of glucose to phenol red

Time after intubation (hr)	No. of animals	Mean index	S.E.
1	12	41	±4·3
2	8	73	±7·2
3	4	86	±3·1

TABLE 7. Gastric absorption of glucose in animals with the pylorus ligated

Time after intubation (hr)	Glucose recovered from stomach (mg)	Glucose/phenol red ratio
0 (control rat)	342	23·5
1	372	26·4
2	378	24·7
3	385	25·5

denied by workers using animals in which the pylorus has been obstructed and glucose disappearance measured directly (Macleod, Magee & Purves, 1930, Maddock, Trimble & Carey, 1933). After ligation of the pylorus we too found that glucose was not absorbed from the stomach (Table 7), but we regard this as a highly unphysiological preparation since the stomach becomes greatly distended with fluid under these conditions, and the animals are in a state resembling the syndrome of acute dilatation of the stomach which is sometimes seen in man.

Absorption of iodide

In calculating the absorption of iodide there were two sources of error which were not applicable in the case of glucose:

(1) No allowance was made for absorbed iodide re-secreted into the stomach and small intestine. Fifteen to twenty per cent of a single tracer dose of ^{131}I given intraperitoneally or intramuscularly to three normal rats was recovered from stomach and small intestine (most of it from stomach) after 1 hr. This fraction and its distribution along the gastrointestinal tract appear to be fairly constant, so that a correction factor could be introduced if so desired.

(2) Separate analyses of intestinal washings and intestinal wall showed that small amounts of radioactivity could be recovered from the latter even after all the phenol red had been washed out.

These two sources of error become formidable when absorption is calculated for segments of intestine containing little phenol red; consequently, no reading has been included in Table 8, unless the amount of phenol red recovered from the segment concerned was at least 5% of the total amount given to the animal.

TABLE 8. Percentage of iodide absorbed at different levels in the small intestine 1 hr after intubation

Intestinal segment	No. of animals	Mean % iodide absorbed	S.E.
1st half	11	47	±3·5
3rd quarter	11	86	±4·0
4th quarter	11	93	±0·63

TABLE 9. Rate of iodide absorption expressed as a percentage of the administered dose absorbed after varying intervals of time

Time after intubation (hr)	No. of animals	Mean (%)	S.E.
1	13	53	±3·2
2	5	73	±5·7
3	5	80	±3·1

Intestinal absorption index for iodide. The percentage absorption of iodide was calculated for each segment of the small intestine as in the case of glucose. Intestinal absorption of iodide is shown to be slower than that of glucose under the conditions of these experiments, and it continues throughout the whole length of the small intestine. Since the percentage absorption of iodide is 90% or more in the distal quarter of the small intestine, it may be assumed that the amount of iodide passing into the caecum is negligible and that iodide is completely absorbed in the small intestine when given in small doses (Table 8).

Rate of iodide absorption. As in the case of glucose there were considerable differences between animals (Table 9), but there was good correlation between absorption rate and gastric emptying (Fig. 3). In the twelve animals in which rates of glucose and iodide absorption were measured simultaneously, the absorption of glucose was more rapid in every case. The regression line of iodide absorption on gastric emptying crosses the X-axis at 5%, suggesting that a little iodide may be absorbed from the stomach.

Gastric absorption of iodide. There was usually evidence that some iodide was absorbed from the stomach (Table 10), but in every animal it was less than the gastric absorption of glucose. In animals killed 3 hr after intubation, especially

if the gastric residue was small, the ratio of iodide to phenol red in the stomach was often abnormally high, suggesting that iodide secreted by the stomach produces a significant error under these conditions.

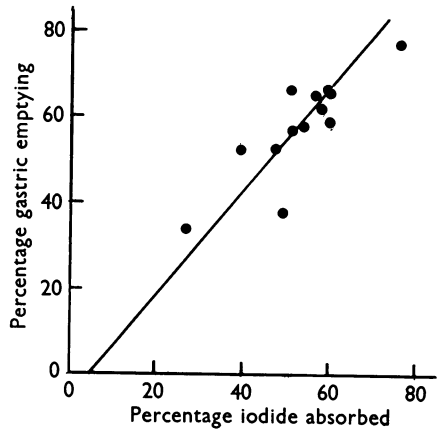

Fig. 3. Correlation of percentage gastric emptying after 1 hr and percentage of initial dose of iodide absorbed after 1 hr. ($r = 0{\cdot}845$; $x = 5{\cdot}03 + 0{\cdot}828y$.)

TABLE 10. Gastric absorption index for iodide, calculated from the change in the ratio of iodide to phenol red

Time after intubation (hr)	No. of animals	Mean index	S.E.
1	10	14	±2·4
2	7	23	±4·7

DISCUSSION

There are already a number of methods available for studying absorption from the gastro-intestinal tract, but they all have certain limitations. Much information has been derived from the study of exteriorized loops and pouches, but these do not necessarily reflect the behaviour of the gastro-intestinal tract in normal continuity. Likewise, studies on isolated segments of intestine (Fisher & Parsons, 1949), while permitting more direct quantitative studies, cannot measure variations in the behaviour of the intestine as they occur in the intact, conscious animal. The serial measurement of blood concentrations of a substance administered by mouth is an indirect method influenced by many factors besides intestinal absorption. Balance studies can measure only the total net disappearance of a test substance between mouth and anus, which may be influenced by such factors as bacterial decomposition in the large intestine. Cori (1925) introduced a technique for measuring the rate of absorption of sugars in the intact animal by giving a sugar by stomach tube and then killing the animal and measuring the amount of sugar recovered from

the gastro-intestinal tract. This method is open to the objections that variations in gastric emptying and intestinal transit cannot be taken into account and the site of absorption cannot be determined. These difficulties can be overcome by our method.

None of the methods hitherto available for the study of intestinal transit are entirely satisfactory. Inferences have been drawn from pressure changes in balloons and other recording devices introduced into the small intestine (Meschan & Quigley, 1938; Posey, Dearing, Saver, Bargen & Code, 1948), but pressure changes in the lumen of the bowel do not necessarily imply movement of contents, and the behaviour of the intestine may be disturbed by the presence of a distended balloon. Macht (1930) first studied propulsive motility in the small bowel by measuring the distance travelled by the head of a column of charcoal introduced into the stomach. This presumably bears some relation to the intestinal transit in the sense that the circulation time bears some relation to the cardiac output, but it is not a true measurement of mass movement and is probably also affected by variations in gastric emptying. Goodman *et al.* (1952) have made some studies of intestinal transit using the dye T1824, but we have found a significant disappearance of this substance from the lumen of the bowel. Information has been obtained from barium meals, but the method is qualitative only, and inert substances may line the walls of stomach and intestine and behave differently from fluid chyme.

The accuracy of our method is at present limited mainly by our inability to get quantitative recoveries of phenol red, which renders it unsuitable for the study of poorly absorbed substances. However, errors due to technical factors of this kind are small when compared to the great biological variations of the functions studied that were found among normal animals. The usefulness of the method is also limited by the need to kill the animal. The advantages of the method lie in the fact that the intact, conscious animal is studied, in the simplicity of the technique, and in the wide range of functions which can be measured simultaneously in the same animal.

The absolute values obtained for the variables measured in this investigation are perhaps of no great value in themselves. They are valid only for rats studied under the particular conditions of these experiments. The main use of the method will lie in the comparison of groups of animals studied under varying conditions.

SUMMARY

1. If a test solution of glucose and iodide is given to a rat, together with phenol red, which serves as a marker, it is possible to measure gastric emptying, intestinal transit and gastric and intestinal absorption of glucose and iodide simultaneously.

2. The rate of gastric emptying varies greatly among normal animals, but is an exponential function of time.

3. Propulsive movement of small intestinal contents becomes progressively slower as the caecum is approached.

4. Glucose is absorbed from the stomach of the normal rat, but gastric absorption of iodide is relatively slight.

5. A dose of 400 mg of glucose is completely absorbed by the first half of the small intestine.

6. A tracer dose of iodide is absorbed from the small intestine more slowly than glucose. Absorption continues throughout the length of the small intestine, but is apparently completed before the caecum is reached.

7. Variations in the rate at which glucose and iodide are absorbed by normal animals are due mainly to different rates of gastric emptying.

8. The advantages, limitations and possible applications of the technique are discussed.

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