Generality in Effects of Transmucosal Fluid Movement and Glucose on Drug Absorption from the Rat Small Intestine

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The generality in effects of transmucosal fluid movement and glucose on drug absorption from the rat small intestine was investigated using twenty three drugs having different charges in the physiological pH of the intestine of the animal with the in situ recirculating perfusion method. All of the regression lines representing the relation between ratio of the transmucosal fluid movement on the vertical axis and intestinal absorption of respective drugs on the horizontal axis were not perpendicular to the horizontal axis but have some inclinations without exception. These evidences did support the concept that intestinal drug absorption was subtly affected by the transmucosal fluid movement and thus the generality in effect of the movement was apparently demonstrated.

Concerning the glucose effect, two regression lines, one was of sodium chloride and another was of glucose in the perfusate, were obtained in all of the drugs. However, these two regression lines were overlapped in the cases of unionized drugs. On the other hand, in the cases of cationic drugs the regression lines of glucose were always shifted significantly to the right hand side of those of sodium chloride and in the cases of anionic drugs the regression lines of glucose were shifted to the left hand side without any exception. These evidences demonstrated that glucose increased the absorption of cationic drugs and decreased that of anionic drugs and, moreover, these findings were supported by investigating blood level of respective drugs in the subjected animal. Thus the generality in the glucose effect was apparently demonstrated.

Moreover, the glucose effect was also recognized when two drugs were coexisted simultaneously in the perfusate. The glucose effect in drug absorption might be one of mechanisms of drug interactions which have been observed in clinical medicine.

Keywords—glucose; glucose effect; intestinal drug absorption; partition coefficient; ratio of fluid movement; recirculating perfusion method; transmucosal fluid movement

In the course of studies investigating effects of the transmucosal fluid movement on drug absorption from the rat small intestine using an in situ recirculating perfusion technique,² peculiar fluctuations in absorption of ionized drugs were observed when sodium chloride in the perfusate was replaced to D-glucose (glucose). Glucose apparently increased absorption of metoclopramide, a cation in the experimental condition, and decreased absorption of sulfisoxazole, an anion, and did not influence absorption of sulfanilamide, an unionized compound.³ These peculiar effects caused by the presence of glucose in the perfusate on the drug absorption were difficult to be understood even if the concept of the transmucosal fluid movement was taken into considerations in analyzing the absorption results, and these findings could not be explained not only by the transmucosal fluid movement but also by any findings and hypotheses⁴ which have been established in the studies of drug absorption. These peculiar effects of glucose was termed arbitrarily the glucose effect for the sake of convenience in the previous study.³

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Along with development in the study concerning the effect of the transmucosal fluid movement on drug absorption, some evidences relating to the glucose effect were also accumulated gradually in our laboratories.\(^5\) Based on the findings, it was elucidated that the glucose effect was also observed in in vivo experiment,\(^5\) and that the segment of the alimentary tract of the animal in which the glucose effect was dominantly observed was the upper part of the small intestine.\(^6\) These lines of evidences might be clues in elucidating mechanism of the glucose effect and encouraged authors to accumulate more efforts in the elucidation of mechanism. However, before driving our studies further in advance, it should be necessary to confirm that the glucose effect might also be observed in other drugs than those which have been used in the previous studies.\(^5,6\)

In the present study, many drugs including anions, cations, and unionized compounds in the experimental conditions were selected and generality in the effects of transmucosal fluid movement and glucose was investigated.

After certifying that the generality was observed in all cases of drugs employed in the present study. Further attempts were undertaken to demonstrate whether the glucose effect was observed when two drugs were coexisted in the perfusate. As the results of these trials, the glucose effect was observed consistently even in such complicated systems in the perfusate.

**Experimental**

**Drugs and Their Analytical Procedures**—Drugs that the intestinal absorption was demonstrated to obey the first-order kinetics in the preliminary experiment were selected. They were aminopyrine,\(^5\) barbita,\(^5\) caffeine,\(^5\) chloramphenicol,\(^5\) isoniazid,\(^5\) paramidine,\(^5\) phenylbutazone,\(^5\) pyrazinamide,\(^5\) sulfanilamide,\(^5\) theophylline,\(^5\) thiopental,\(^5\) triamterene,\(^5\) chlorpheniramine maleate,\(^5\) diphenhydramine,\(^5\) ephedrine·HCl,\(^5\) metoclopramide,\(^5\) quinidine·HCl,\(^5\) salicylic acid,\(^5\) p-aminobenzoic acid,\(^5\) p-aminosalicylic acid,\(^5\) sulfamethizole,\(^5\) sulfamethoxazole,\(^5\) and sulfisoxazole.\(^5\) They were purchased from commercial sources in reagent grade and were used in the experiment without further purifications. Analytical procedures for these drugs were followed to the method presented in each reference as shown above. These analytical procedures were found to be utilized even though glucose presents in the perfusate.

**Perfusion Procedures**—Male albino rats of Wistar strain weighing about 150 g were purchased. The in situ recirculating perfusion experiment was conducted in the same manner as described in full in the previous report.\(^6\) All the recirculating perfusions conducted in the present study used the entire small intestine of the animal from a proximal end of the duodenum to a distal end of the ileum. Thirty milliliters of perfusion solution were recirculated in order of the proximal end to the distal end of the small intestine at a rate of 5 ml per minute. Ten minutes after the beginning of the perfusion, an initial sample of the perfusate was pipetted out from the reservoir which was located in the closed circuit of the recirculating system. Almost of the recirculating perfusions were for one hour, however, in cases of drugs which have been found well absorbed in the preliminary experiments, the periods of the perfusion

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were shortened to 15 or 30 minutes depending on the extent of absorption of the subjected drug. After
ceasing the perfusion, a final sample was pipetted.

Blood samples were collected during and after the perfusion experiment, if necessary, into a small
heparinized beaker by cutting off the end of the tail of the animal\(^{23}\) at a given interval. These samples
were stored in a refrigerator until analysis. Analytical procedures were followed as the same manner reported
previously.\(^{5}\)

**Perfusion Solution**—Perfusion solution used in the recirculating perfusion experiment consisted of
either sodium chloride or glucose in concentration to make at least three levels in tonicity of hypertonic,
isotonic, and hypotonic. Physiological isotonic concentration of sodium chloride and glucose are 0.9% and
5.0%, respectively. Perfusion solutions having concentrations more than these isotonic concentrations of
the solute were regarded as hypertonic perfusion solution, and solutions having less than the isotonic
concentration were nominated as hypotonic solution in the present report. All the perfusion solutions contained
phenol red in an appropriate concentration as a nonabsorbable indicator.

Perfusion solutions contained 1 mg of the drug as a rule, however, the concentration of the drug having
high sensitivity in the determination was decreased to an appropriate concentration so that both of the
initial and the final concentrations of the drug in the perfusate were able to determine without any dilution.

**Determination of the Drug Absorption and Evaluation of the Glucose Effect**—According to the recirculating
perfusion method which was devised by Schanker and his co-workers,\(^{9}\) amount of the drug disappeared
in the perfusate was regarded as the amount absorbed. Taking into considerations the transmucosal fluid
movement which was determined by measuring the concentration change of the nonabsorbable indicator
during the perfusion, drug absorption from the small intestine of the animal was determined following an
equation:

\[
\text{drug absorption (\%)} = 100 - 100 \left( \frac{C_{\text{drug final}}}{C_{\text{drug initial}}} \times \frac{C_{\text{indicator initial}}}{C_{\text{indicator final}}} \right)
\]

where \(C\) is the concentration of the drug or phenol red in the perfusate and \(C_{\text{indicator initial}}/C_{\text{indicator final}}\) is
estimated as the transmucosal fluid movement or ratio of fluid movement in the present study.

Individual results of absorption were obtained following the method mentioned above, however, the
results were fluctuated depending on the ratio of the transmucosal fluid movement. To obtain the most
proper result in absorption which might be indifferent to the fluid movement, the protocol in determining the
drug absorption which was presented in the previous report was applied.\(^{23}\)

The absorption of the drug from the perfusates having various tonicities with sodium chloride or glucose
were obtained and all the results were plotted in an illustration which had the ratio of fluid movement on the
vertical axis and the absorption in percent on the horizontal axis. After confirming that a straight regression
line of the scattered plots might be obtained, an extent of the absorption at an intercept of the regression
line and a horizontal line at 1.0 in the ratio of the fluid movement was regarded as the drug absorption which
was indifferent to the fluid movement.

These procedures were conducted both of the perfusates having sodium chloride and glucose and the
two regression lines were compared statistically in all cases. When the significant difference was observed,
it was concluded that the effect of glucose on the absorption of the subjected drug was found.

**Determination of Partition Coefficient**—Drugs were dissolved in an isotonic buffer solution of pH 6.5
containing a half volume of an isotonic phosphate buffer of which the components were \(\text{KH}_{2}\text{PO}_{4}\) and \(\text{Na}_{2}\text{HPO}_{4} \cdot 12\text{H}_{2}\text{O}\) and a half volume of an isotonic solution of sodium chloride or glucose. After adding
the equivalent of chloroform or isomyl acetate, partition ratio was determined following regular manner\(^{23}\)
at 37°. Three levels in concentration (0.1, 1.0, 10.0 mg) of respective drugs were conducted in determining
partition ratio and after ensuring that the ratios were found to be approximate same values, the partition
coefficient was calculated as an average of these ratios.

**Results**

**Generality in Effects of Transmucosal Fluid Movement and Glucose**

Twenty three drugs were classified into unionized drugs, cationic drugs, and anionic drugs
with considerations of their \(pK_a\) values and the physiological pH\(^{24}\) of the small intestine of the animal. All the data obtained, when the respective drugs were subjected in the perfusate,
were listed in Table I and in three of these having different charges in the pH the relation

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<table>
<thead>
<tr>
<th>Drugs</th>
<th>M.W.</th>
<th>pKa</th>
<th>Value(s) of</th>
<th>Glucose Effect on Intestinal Absorption of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>213.3</td>
<td>5.96</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Bicaline</td>
<td>184.2</td>
<td>7.60</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>323.2</td>
<td>0.96</td>
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<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
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<tr>
<td>Isosafroline</td>
<td>316.3</td>
<td>1.59</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>308.3</td>
<td>1.49</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
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<tr>
<td>Phenylbutazone</td>
<td>312.3</td>
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<td>Thiorphan</td>
<td>316.3</td>
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<tr>
<td>Triamterene</td>
<td>332.3</td>
<td>0.96</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Cholinergic drugs</td>
<td>390.9</td>
<td>6.39</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Diphenylamine</td>
<td>265.4</td>
<td>8.46</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>241.7</td>
<td>8.46</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
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<tr>
<td>Glutaric acid</td>
<td>156.8</td>
<td>8.46</td>
<td>10 - 9.87</td>
<td>Molar weight, pKa, Values, and Glucose Effect on Intestinal Absorption of Drugs</td>
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<td>Anticoagulants</td>
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- **a.** Number of experiments
- **b.** Coefficient of correlation
- **c.** The expression equation between intestinal absorption of drug and the intestinal absorption of drugs with the expression equation of drug and the intestinal absorption of drugs

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*Note: The table continues with similar entries.*
between ratio of fluid movement and intestinal absorption of drugs was depicted in Fig. 1—3. As presented in Table I and Fig. 1—3, all the regression lines representing the rela-

![Fig. 1. Relationship between Percent Absorbed of Chloramphenicol and Fluid Movement](image)

![Fig. 2. Relationship between Percent Absorbed of Ephedrine and Fluid Movement](image)

![Fig. 3. Relationship between Percent Absorbed of p-Aminobenzoic Acid and Fluid Movement](image)

...tionship between ratio of fluid movement on the vertical axis and intestinal absorption of each drug on the horizontal axis obtained with the perfusion solution containing sodium chloride or glucose demonstrated fairly straight and $p$ values of the $t$ test for their correlation coefficients were found to be $p<0.01$. Moreover, evidences that all the regression lines including of sodium chloride and of glucose had certain inclination did indicate that the absorptions of these drugs were influenced by the transmucosal fluid movement.

Differences in the regression lines obtained with both the sodium chloride perfusate and the glucose perfusate in each drug were established statistically\(^{25}\) and $p$ values less than 0.05 were considered to be significant in this paper. In the cases of unionized drugs, although there were observed some fluctuations and exact coincidences were hardly obtained, based on the results obtained from both of the perfusates, it could not be found significant differences between the regression line obtained with the sodium chloride perfusate and that obtained with the glucose perfusate ($p>0.05$). The evidence led to the conclusion that the effect of glucose was not observed in the absorption of these unionized drugs employed in the present study. In the cases of cationic drugs, the absorptions brought about in the presence of

glucose were exceeded than those of sodium chloride without exceptions, and the difference in these absorptions were more evident than those observed in the cases of unionized drugs. The significant differences between the regression line obtained with the sodium chloride perfusate and that obtained with the glucose perfusate were observed ($\beta<0.005$) in all cases. Based on these results, it might be possible to conclude that the effect of glucose was observed in all of the cationic drugs employed in the present study. Contrary to the cases of cationic drugs, the absorptions of anionic drugs in the presence of glucose were always inferior to those obtained in the presence of sodium chloride. The two regression lines obtained from the sodium chloride and glucose perfusates did not also coincide statistically ($\beta<0.02$). These evidences supported the conclusion that the effect of glucose was apparently demonstrated in these cases of anionic drugs used in the present study.

**Time Course Study of the Glucose Effect**

Phenomenal evidences of the glucose effect have been pursued. However, to promote better understanding of the glucose effect, it might be necessary to investigate the mode of absorption under these phenomena. Along with these purposes, time course observations of the drug in both the perfusate and blood of the animal during the perfusion experiment were examined. All the drugs showed essentially the same pattern in absorption, so the results obtained by metoclopramide, as one of the example of cationic drugs, and by sulfisoxazole, as one of the cases of anionic drugs, were illustrated in Fig. 4 and Fig. 5.

![Fig. 4. Time Course Study of Blood Level and Percent Remained of Sulfisoxazole](image)

**Fig. 4.** Time Course Study of Blood Level and Percent Remained of Sulfisoxazole

*Key: ▲: glucose in perfusate, ○: sodium chloride in perfusate.*

![Fig. 5. Time Course Study of Blood Level and Percent Remained of Metoclopramide](image)

**Fig. 5.** Time Course Study of Blood Level and Percent Remained of Metoclopramide

*Key: ▲: glucose in perfusate, ○: sodium chloride in perfusate.*

As depicted in Fig. 4, both of the modes of absorption of metoclopramide from the isotonic perfusates of sodium chloride and glucose apparently obeyed the first-order kinetics, however, the rate of absorption from isotonic glucose solution was demonstrated faster than that from sodium chloride. Reflecting these results in the perfusate, the drug levels in blood of the animal obtained during and after application of glucose perfusate were apparently higher than those of sodium chloride perfusate. These results did indicate that the glucose effect was observed not only in the drug disappearance in the perfusate but also in the blood levels of the drug which might be important in determining bioavailability and, moreover, development pharmacological effect of respective drugs.
Quite reverse results were obtained in the case of sulfisoxazole. Although the modes of absorption of the drug in both the isotonic sodium chloride and the isotonic glucose perfusates indicated the first-order kinetics, which were similar to those of metoclopramide, the rate of absorption from sodium chloride perfusate was observed to be always exceeded to that of glucose. These results were reflected directly to the drug levels in blood of the animal.

**Consistency in Appearance of the Glucose Effect in the Presence of Two Drugs in the Perfusate**

Investigations so far proceeded were concerned to the glucose effect observed in single drug system, in other words, the perfusate contained only one drug. Possibilities were still remained that the glucose effect might be modified when two drugs or more than two drugs were in the perfusate. Attempts were undertaken to elucidate the consistency or the modification of the glucose effect in such a double drug system with drugs of cationic–anionic, anionic–anionic, and cationic–cationic in combination. After confirming that the analytical procedures of one drug were not interfered by the presence of another drug, combinations of following drugs were decided, ephedrine–p-aminosalicylic acid, sulfisoxazole–salicylic acid, and metoclopramide–chlorpheniramine maleate.

Before starting the experiment of recirculating perfusion, partition coefficients of these drugs were determined individually and in combinations between organic solvents of chloroform or isooamyl acetate and aqueous solutions containing either sodium chloride or glucose. The results were listed in Table II. As were apparent from Table II, partition coefficients

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Chloroform</th>
<th>Isoamyl acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sodium chloride</td>
<td>Glucose</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ephedrine + p-Aminosalicylic acid</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Sulfoxazole</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Sulfoxazole + Salicylic acid</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Chlorpheniramine maleate</td>
<td>49.7</td>
<td>41.7</td>
</tr>
<tr>
<td>Metoclopramide + Chlorpheniramine maleate</td>
<td>2.6</td>
<td>2.2</td>
</tr>
</tbody>
</table>

All values were raised at two places of decimals.

- Sodium chloride or glucose was added to a half isotonic phosphate buffer solution of pH 6.5 of which the components were KH₂PO₄ and Na₂HPO₄·12H₂O and an isotonic buffer solution was prepared.
- It suggests the respective partition coefficients when two drugs were coexisted in the aqueous phase.

of these drugs were not affected by the replacement of sodium chloride to glucose. These lines of results indicated decisively that glucose did not affect lipid solubilities of these drugs not only in the single drug system but also in the double drug system.

Moreover, partition coefficients of respective drugs in the double system consistently demonstrated the same values as those obtained in the single system, in other words, the partition coefficient of one drug did not change even when the other drug was introduced in the system. This evidence supported speculation that these drugs might not interact each other to form such as hydrophobic binding or ion pair complex which might influence considerably the drug absorption.
Fig. 6. Effect of Glucose on Absorption of Drugs Coexisted (p-Aminosalicylic Acid and Ephedrine)

Numbers in parentheses indicate number of experiments.


a: regression line of ephedrine obtained by the perfusate containing sodium chloride calculated with the least squares method.

a': regression line of ephedrine obtained by the perfusate containing glucose calculated with the least squares method.

b: regression line of p-aminosalicylic acid obtained by the perfusate containing sodium chloride calculated with the least squares method.

b': regression line of p-aminosalicylic acid obtained by the perfusate containing glucose calculated with the least squares method.

I: mean ± S.D.

After the results of preliminary experiment such as partition coefficient were presented, authors' attentions were turned to the recirculating perfusion experiment employing perfusion solutions of the double drug system.

Figure 6 shows the results obtained using the isotonic perfusate containing equimillimoles of p-aminosalicylic acid and ephedrine simultaneously. A straight line which is indicated as (a) represents the regression line of ephedrine in the sodium chloride perfusate which has been obtained from the experiment using the perfusate of the single drug system as depicted in Fig. 2, and broken regression line (a') was obtained when sodium chloride in the perfusate was replaced to glucose. The same relationship in the regression lines of (b) and (b') was obtained when p-aminosalicylic acid was subjected in the experiment. The results representing the relation between the absorptions of respective drugs and the transmucosal fluid movement obtained from the double drug system containing isotonic sodium chloride were plotted just on the respective regression lines of sodium chloride and when sodium chloride in the perfusate was replaced to glucose, the plots shifted to respective directions and appeared just on the respective regression lines of glucose. These results demonstrated that the glucose effect was consistently observed not only in the single drug system but also in the double drug system.

The modifications in absorption of drugs in the case of a combination of anionic–anionic drug were illustrated in Fig. 7. The absorptions of respective drugs of sulfisoxazole and salicylic acid from the isotonic perfusate containing sodium chloride were appeared approximately on the respective regression lines obtained when respective drugs were subjected for the absorption study in the single drug system containing sodium chloride. However, the absorptions of the respective drugs in the double drug system were shifted to the same direction of decreasing when sodium chloride was replaced to glucose, and appeared just on the respective regression lines of glucose obtained when these drugs were studied in the single drug system containing glucose.

These lines of results obtained so far apparently demonstrated that the glucose effect did take place even in such conditions of the double drug system in completely similar manner as was observed in the single drug system. Thus the consistency of the glucose effect was clearly demonstrated.
**Discussion**

Up to twenty three drugs were investigated in detail to demonstrate the glucose effect which was originally disclosed in our laboratories. The absorption of these drugs were affected subtly in the presence of glucose in the perfusate. The absorption of cationic drugs was enhanced and that of anionic drugs was decreased and, on the other hand, that of unionized drugs was not affected when sodium chloride in the perfusate was replaced to glucose. The generality of the glucose effect was clearly demonstrated in all of the drugs employed in the present study without any exception (Table I and Fig. 1—3).

However, detailed surveys of these results brought another finding of importance. Metoclopramide and sulfisoxazole have been selected as only the example of cationic and anionic drugs in the previous report. Although increasing and decreasing in the absorption of these drugs were observed when sodium chloride was replaced to glucose, the difference of these increasing and decreasing was always seemed to be constant and the extent was approximately 20%. This evidence suggests that the effect of glucose on drug absorption might be characterized not only by qualitative property but also by quantitative property, that is, direction of the variations in drug absorption brought about by the replacement of sodium chloride to glucose was determined by positive or negative charge of drug molecule in the perfusate and the differences were always fixed in approximate 20%.

However, the results obtained in the present study suggested that the difference of variations was not fixed, since the differences at 1.0 in the ratio of fluid movement were varied from 6.5% in the case of salicylic acid to 32.4% in the case of ephedrine hydrochloride (Table I). This finding did strongly support the quantitatively variable characteristic of the glucose
effect and might be one of clues and might open the way of investigating mechanism of the glucose effect.

Similar finding in analysis of the difference in drug absorption was turned to the results obtained by these unionized drugs employed in the present study. The respective regression lines obtained by the perfusates of sodium chloride and glucose were observed to be completely overlapped when sulfanilamide, an example of unionized drugs, was subjected in the perfusion experiment as reported in the previous publication.\textsuperscript{3)} Essentially the same results were obtained in the case of sulfanilamide and the extent in difference in the absorption was 0.2%, that was able to be regarded as the same absorption (Table I). However, these results were not always observed in all of unionized drugs employed in the present study. In the cases of phenylbutazone and caffeine, the differences in absorption were revealed to be 8.1% and 8.0%, respectively (Table I). These differences were apparently greater than the case of salicylic acid (6.5%) of which the absorption was regarded to be decreased when sodium chloride was replaced to glucose in the perfusate.

The comparison of respective regression lines obtained with the sodium chloride perfusate or the glucose perfusate in each drug was carried out statistically. Although the significant difference between the respective regression lines could not be found in the cases of unionized drugs, the significant differences were observed in the cases of ionized drugs. It seems reasonable to conclude that the glucose effect is not simply defined by the extent of difference in the drug absorption at 1.0 in the ratio of fluid movement, but is defined by the difference between the respective regression lines.

To examine further in detail the glucose effect, the time course studies of drug levels in both the perfusates and the blood of the animal during the course of the perfusion experiment were undertaken and the glucose effect observed in the perfusate reflected directly to the drug levels in blood of the animal (Fig. 4 and 5). Moreover, the consistency of the glucose effect in the double drug system was also demonstrated in the present study (Fig. 6–8). Evidences relating modification in intestinal absorption of one drug in the presence of another drug were presented in fields of clinical medicine and pharmaceutical sciences.\textsuperscript{26)} These evidences have been explained in terms of interaction between drugs in the gastrointestinal tract, and mechanisms of such interaction were not revealed completely yet. Any interactions between drugs were not observed in the combination of two drugs used in the present study.

Dietary carbohydrate is 50–60% of the American mixed diet and in many countries is a larger percentage. Carbohydrate intake ranges from 250 to 800 g per day and the major dietary form of carbohydrate is plant starch composed of straight and branched chains of glucose.\textsuperscript{27)} Hence there are enough evidences that glucose exists in the intestinal tract of both of animal and man as the results of digestive enzyme and digestive fluids. As one of clinical drug interactions in the gastrointestinal tract, nutrients may enhance or impair the intestinal absorption of drugs.\textsuperscript{28)} The glucose effect in drug absorption might be one of the mechanisms which might explain such interactions in the drug absorption which were observed in clinical medicine.

