reaction of the STR was obtained at a dose of 40 μg/mouse. However, the STR induced by the higher dose of morphine 50 μg/mouse, was mitigated as compared to the 40 μg/mouse of morphine. Morphine 100 μg/mouse, proved to be lethal.

On the other hand, the STR was elicited in all mice tested when injected with morphine 10 mg/kg, *s.c.* Meprobamate, haloperidol, DFZ and baclofen, respectively, in the doses shown in Table I, showed a significant inhibition of the STR induced by morphine. Moreover, the STR was noticeably inhibited in mice injected *i.c.* with DFZ or baclofen. Especially, the dose of the latter required for this inhibition was as low as approximate one-thousandth of that by systemic administration.

The STR may be partly due to the central excitatory effects of morphine since this reaction was observed by *i.c.* administration of morphine. It has been stated that DFZ (*i.p.*) acts on the reticular formation in the brain stem[6] and has muscle relaxant activity in the rotarod, traction and inclined plane tests.[4] In the meantime, Fukuda, *et al.*[7] have shown that baclofen have an inhibitory action on the spinal reflex in rats. It is further noted that meprobamate acts on the polysynaptic pathways of the CNS and the muscle relaxant action of haloperidol results from the inhibitory action on a higher center of animals. In the present experiment, the STR induced by morphine 10 mg/kg, *s.c.* was markedly inhibited by DFZ and baclofen when injected *i.c.* or *i.p.* It was also shown, unlike the results reported by Srimal, *et al.*,[2] that the STR was suppressed by the relatively low dose of meprobamate and haloperidol which believed to have a central muscle relaxant action. From these findings, it would be reasonable to speculate that DFZ and baclofen inhibit the STR through the mediation of the CNS in mice.

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Transmucosal Fluid Movement and Its Effect on Rectal Sulfanilamide Absorption in Rat

Sulfanilamide absorption from the rectum in rats was studied using the recirculating perfusion method with perfusion solutions having different levels in tonicity by changing concentration of sodium chloride and revealed that the absorption was influenced by the apparent transmucosal bidirectional fluid movements.

Keywords——drug absorption; recirculating perfusion method; rectal absorption of drug; rectum; sulfanilamide; sulfanilamide absorption; transmucosal fluid movement

Studies concerning the effect of transmucosal fluid movement on drug absorption from rat gastrointestinal tract using the method of recirculating perfusion[1] with perfusion solutions

1) L.S. Schanker, D.J. Tocco, B.B. Brodie, and C.A.M. Hogben, *J. Pharmacol. Exptl. Therap.*, **123**, 81 (1958).

having different levels in tonicity by changing concentration of sodium chloride have been reported from our laboratories.[2] Findings were accumulated to support the conclusion that drug absorption was subtly affected by the apparent transmucosal bidirectional fluid movements, and fluid inflow into the animal increased the absorption of drug and, on the contrary, fluid outflow into the lumen diminished the drug absorption.[2,3]

After studying the absorptions of various drugs having various charges in the physiological pH of the rat small intestine[4] in five parts of the alimentary tract such as stomach, duodenum, jejunum, ileum, and colon, a report from our laboratories[5] has revealed that the largest amount of these drugs were absorbed in parts of the jejunum and ileum, and that the effect of the fluid movement on drug absorption was not observed in the stomach segment, and that the influence of the movement was fluctuated in the absorption of drugs from the colon segment, that is, the influence was apparently not observed in the case of sulfanilamide, while other drugs were affected to some extent. These findings suggested that the effect of the fluid movement was exaggerated in segment where drug absorption was mostly proceeded and hardly observed in such terminal parts of the gastrointestinal tract as stomach and colon, especially in the case of sulfanilamide.

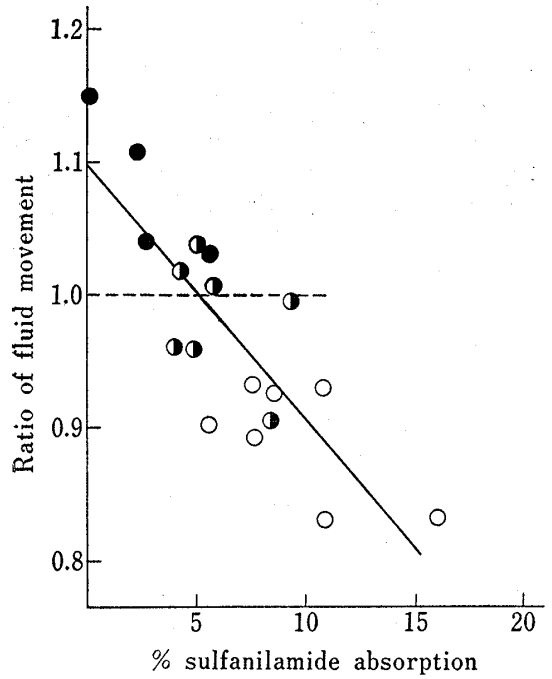

Fig. 1. Relation between Ratio of Fluid Movement and Sulfanilamide Absorption in the Rat Rectum

The perfusion solution was adjusted with sodium chloride to hypertonic, isotonic, and hypotonic, respectively. The perfusion rate was 5 ml/min. The regression line was calculated by the least squares method.

Key: ●, hypertonic; ◐, isotonic; ○, hypotonic.

Recently our attentions were extended to more terminal segment which has been recognized as an important site of drug administration, rectum, and perfusion experiment using rat rectum was undertaken following the method developed by Kakemi and his coworkers with slight modifications.[6] The results obtained were treated and illustrated in the graph as the same manner as described in the previous reports.[2,3,5]

Figure 1 shows the relation between the transmucosal fluid movement and rectal sulfanilamide absorption. As is evident from Fig. 1, scattered plots have a regression line which is not perpendicular to the horizontal axis but has a certain inclination. The regression equation appears as $y=-0.0192\cdot x+1.0963$ ($n=18$, $r=-0.822$, $P<0.001$). This evidence does suggest that sulfanilamide absorption from the rectum is affected by the transmucosal bidirectional fluid movements as have been observed in the jejunal and ileal segments.

It is of interest that, although the fluid movement did not affect on sulfanilamide absorption in the segment of colon, the fluid movement did apparently influence on the absorption in the rectum, the successive and the most terminal segment of the alimentary tract.

For application of drug for rectal absorption, suppository is often selected as an appropriate dosage form. Suppository contains large amounts of base of high molecular weight

2) S. Kitazawa, H. Ito, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 1856 (1975).
3) S. Kitazawa, M. Ishizu, and E. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 3169 (1976).
4) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.* (Tokyo), **12**, 421 (1964).
5) S. Kitazawa, H. Ito, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 19 (1977).
6) K. Kakemi, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.* (Tokyo), **13**, 861 (1965).

substances such as cacao butter, witepsols, macrogols, and surfactants.[7] Although the mechanisms are not elucidated clearly yet, many lines of evidences concerning influences of these bases on rectal absorption have been accumulated.[6]

In elucidating mechanism of decreasing effect of surfactants in drug absorption in rat small intestine where the transmucosal fluid movement was observed in considerable extent, "water-molecule-holding" effect of surfactants was proposed in the previous report.[8]

Evidence found in the present study may open one of the ways of elucidating the mechanism of influences on rectal drug absorption of these bases. Many evidences are now under accumulation and will be published in near future.

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7) "Remington's Practice of Pharmacy" ed. by E.W. Martin and E.F. Cook, 12th ed., Mack Pub. Co., Easton, Pennsylvania, 1961, p. 430.
8) S. Kitazawa, M. Ishizu, and K. Kimura, *Chem. Pharm. Bull.* (Tokyo), **25**, 590 (1977).