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Volume of Blood Plasma and Intestinal Drug Absorption in the Fasted Rat

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The present work was designed to make clear the effect of plasma volume expanders on both the transmucosal fluid movement, that is, fluid absorption through the epithelial layer of the small intestine, and the intestinal sulfanilamide absorption in fasted rats, with particular attentions to homeostatic fluid transfer within body.

Arterial hematocrit value of the subjected animal was measured during the course of the intestinal perfusion experiments and employed to monitor intensively the homeostatic fluid transfer.

The circulation volume expansion induced by an infusion of a fresh plasma obtained from non-fasted healthy donnor rats produced a rise in both the fluid and sulfanilamide absorption from intestine, whereas infusions of commercial expanders showed an opposite result, that is, the transmucosal fluid absorption decreased with a reduction in the drug absorption from intestine.

Although a transfusion solution is said to serve for an improvement of the body fluid environment up to the normal in a dehydrated situation as a fasting, any plasma volume expander may not have always a definite effect on the intestinal absorption in fasted rats.

From these results, it was suggested that body fluid enviroment, or physiological conditions concerning extracellular body fluids should be taken into considerations in studying the gastrointestinal absorption in rats. And some discussions were made to evaluate the plasma volume expanders.

Keywords——rat; fasting; intestinal absorption; plasma volume expander; homeostatic fluid transfer; transmucosal fluid movement; sulfanilamide

Several reports in literatures had cited that fasting might produce numerous physiological and biochemical changes which would affect normal functions of animals.[2] Gastrointestinal absorption cannot be an exception. The previous report[3a] from our laboratory elucidated that over-24-hour fasting caused a reduction in intestinal drug absorption in rat, and demonstrated that the reduced absorption would be due to a decrease in effective surface area of the intestine which was brought about by the fasting. Based on an evidence that an extent of the reduction in drug absorption was more than that of the rat pretreated with antineoplastic agents which are known to produce a similar reduction in nature in the surface area of the intestine, another possible mechanism should be taken into considerations.

In the course of our studies, it was found out that the blood concentration of a drug was apparently high in the fasted rat although the intestinal absorption of the drug was apparently decreased.[3b] This evidence suggested that a volume of body fluid including blood in which the drug might diffuse would be decreased in the fasted animal. Many reports indicated that the deprivation of food accompanied deprivation of water.[4] These evidences suggested that the fluid in the body of fasted animal might be decreased and a dehydration might be

1) Location: *Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606, Japan.*

2) P. Felig, E.B. Marliss, and G.F. Cahill, *J. Clin. Invest.*, **50**, 411 (1971); C.O. Enwonwu, R. Stambaugh, and L. Sreebny, *J. Nutr.*, **101**, 337 (1971); M.M. Stanley, *Metabolism*, 19, 865 (1970); T.E. Gram, A.M. Guarino, D.H.Schroeder, P.C. Davis, R.L. Reagan, and J.R. Gillette, *J. Pharmacol. Exptl. Therap.*, **175**, 12 (1970).

3) *a*) T. Komuro, S. Kitazawa, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 400 (1975); *b*) *Idem*, *ibid.*, **23**, 909 (1975).

4) E.F. Adolph, *Am. J. Physiol.*, **151**, 110 (1947); L.J. Cizec and M.R. Nocenti, *ibid.*, **208**, 615 (1965); S. Lepkovsky, R. Lyman, D. Fleming, M. Nagumo, and M.M. Dimic, *ibid.*, **188**, 327 (1957).

brought about and, moreover, compensating fluid transfer, that is, homeostatic fluid transfer in the animal body might be reduced. Reflecting these evidences, hematocrit value was apparently increased in the fasted animal.

One of the authors demonstrated in the previous paper[5] that transmucosal bidirectional osmotic fluid movement influences the drug absorption from the rat small intestine. However, it should be taken notice of that the transmucosal fluid movement is not always induced by the difference in osmolarity between mucosal and serosal sides of the small intestine, but also there should be such a movement induced as a result of changes in pyhsiological functions or, conditions as mentioned before, and in such a case as fasting, a volume of fluid moved should be dependent on the amount of fluid contained in a whole body of the animal. A fluid volume decrease produced by fasting might confuse a water balance within body and might introduce a fall in a homeostatic activity or function which maintains a required constancy in the fluid movement of body. In a dehydrated animal, some retardation of fluid transfer was speculated. As was expected, in the fasted rat, the transmucosal fluid movement, that is, fluid absorption through the epithelial layer of the small intestine was apparently decreased and this reduction accompanied a fall in intestinal drug absorption.[6]

In clinical medicine, such a dehydrated situation is often encountered by a deprivation of food after a gastrointestinal surgery and a duration of high body temperature. However, evidences obtained in the previous studies from our laboratory suggested that an oral administration of water would not always effective in the therapy of such conditions. Any other therapeutic treatments should have to be kept in mind. In these patients, parenteral administrations of both drugs and water seem to be most valuable.

Recently, transfusion therapy is frequently employed to improve the hypovolemic plasma volume in patients. Such a therapy may be of value to increase the circulation volume and, moreover, to bring fluid conditions of body up to the normal. Accordingly, when such a subject receives a suitable volume of a transfusion, it was suggested that a fluid expansion occurred in body might be favorable for the transmucosal fluid movement, and consequently drug transfer in the lumen-to-blood direction. In the present work, this problem was undertaken to be made clear with fasted rats and some discussions about plasma volume expanders are made.

Experimental

Drug and Chemicals——Sulfanilamide and other chemicals used in the present work were of analytical grade and were obtained from a commercial source (Nakarai Chemical Co., Ltd., Kyoto, Japan) and used without further purifications.

Animal——Male albino rats of Wistar strain were used in all the experiments. The rats purchased were housed in a stainless steel cages in an animal room[7] maintained at $23° \pm 2°$ and free access to tap water and a commercial solid food for laboratory rats (Oriental Yeast Industry Co., Ltd., Tokyo, Japan) for periods of at least three days before the experiments in order to acclimatize to laboratory conditions. All cages had wide mesh floors to prevent coprophagy.

Rats of about 170 g in body weight were randomly separated into two groups, one group was deprived of food for a given period but allowed free access to tap water and housed in an individual cage to prevent devouring one another during the fasting period, and the other group of animals, also housed in an individual cage, provided both food and water freely. The former group was nominated the fasted group and the latter was called the control group.

Unless otherwise stated, 60-hour-fasted rats were used as the "fasted rats" in the present work, since daily water intake and urinary sodium output appeared to become in a steady state after 60-hour fasting.[6]

Hematocrit Measurement——A polyethylene catheter of 0.5 mm outside diameter (ATOM Polyethylene Tube for Infusion, Atom Co., Ltd., Tokyo, Japan) was placed in a femoral artery and about 50 μl of blood was obtained in a glass capillary tube through the catheter. Blood samplings were made every five minutes during the experiments. To prevent blood coagulation during periods of the sampling procedures, a small

5) S. Kitazawa, H. Ito, and H. Sezaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 1856 (1975).
6) S. Kitazawa and T. Komuro, *Chem. Pharm. Bull.* (Tokyo), "in press."
7) S. Kitazawa and T. Komuro, *Igaku no Ayumi*, "in press."

amount of sodium heparin solution (40 units/0.04 ml/100 g body weight) was injected intravenously to all the animals before the experiments. One end of the capillary was sealed with clay and the other end was closed by fusion and then the capillary was centrifuged for five minutes at 12000 r.p.m. precisely with a centrifuge for hematocrit measurement (Hemato KH 120, Kubota Manufacturing Industry Co., Ltd., Osaka, Japan). Plasma and erythrocytes were separated each other and hematocrit, or percentage of volume of the packed erythrocytes to that of whole blood was measured with a hematocrit reader (Kubota Seisakusho Co., Ltd., Tokyo, Japan).

Water Content——Water content of blood plasma was determined by desiccation. Arterial blood samples were drawn into glass capillary tubes, which were closed at both ends and spun for five minutes at 12000 r.p.m. and then separated plasma was removed to be weighed exactly in a chemical balance (wet weight). Thereafter the specimens were dried in a silica-gel containing desiccator to reach a constant weight (dry weight) and thus water content was calculated as a percentage of a difference between wet and dry weight to the wet one.

Plasma Volume Expanders——The following two dextran preparations were used and obtained from a commercial source (Midori Juji Co., Ltd., Osaka, Japan). One is a Macrodex®, 500 ml of which contains a 30 g of dextran composed of about 70000 of a mean molecular weight and a 25 g of glucose. This dextran solution is abbreviated as a "6% dextran-70" in the present work. The other is a Rheo-macrodex®, whose 500 ml contains a 50 g of dextran composed of about 40000 of a mean molecular weight and a 25 g of glucose. Rheo-macrodex® is abbreviated as a "10% dextran-40" in this report. A physiologically isotonic saline solution as a plasma volume expander was prepared freshly on occasion and its osmolality was checked with an osmometer (Freezing Point Osmometer Model 3D, Advanced Instrument INC, U.S.A.). Plasma infused for a plasma volume expansion was obtained each time from non-fasted healthy control rats and the plasma was employed after making sure of that the infusing plasma does not coagulate a blood of a subjected animal.

Infusion of Plasma Volume Expanders——Plasma volume expansion was made by an infusion of fresh plasma, 6% dextran-70, 10% dextran-40 or physiologically isotonic saline solution of 0.9%. Each solution was infused into a right femoral vein of a fasted rat in a volume of 2.2 ml per 100 g of body weight at a rate of 1.1 ml/min, where the infusion volume was determined to be 1.5 times as large as the volume of plasma lost during the 60-hour-fasting, because under our experimental conditions, about 1.5 ml of plasma per 100 g of body weight was found to be lost during the fasting.

Depletion of Blood——A polyethylene catheter of 0.5 mm outside diameter was inserted into a femoral artery as mentioned in the paragraph of 'Hematocrit Measurement' and about 1.6 ml of blood per 100 g of body weight was drawn out at a rate of about 2 ml/min.

Intestinal Absorption——According to the recirculating perfusion method which was devised by Schanker, *et al.*,[8] an amount of the drug disappeared from the perfusate was regarded as the amount absorbed from the site of the intestine which was exposed to the perfusate. The method was employed with entire small intestine from the proximal end of the duodenum to the distal end of the ileum in all of the present experiments. The animals were anaesthetized with an intraperitoneal administration of sodium pentobarbital and the doses were 35 mg/kg for the fasted and 50 mg/kg for the non-fasted rats.

Perfusion was proceeded re-circulatingly in order of duodenal to ileal at a rate of 5 ml/min with 40 ml of the perfusion solution reservoired in a graduated cylinder of 50 ml volume which had been kept in a water bath at 37°. The perfusion solutions employed in the experiments contained one millimole of sulfanilamide and a sodium chloride in the concentration of 0.45%.

In order to investigate an effect of plasma volume expanders on the intestinal absorption in the fasted rats, each expander was intravenously injected in the volume of 2.2 ml per 100 g of body weight, 30 minutes before starting the absorption experiments.

Absorption of sulfanilamide from intestine was determined by subtracting the amount remaining in the perfusate after the one hour recirculation from the initial amount of that in the perfusion solution. Analytical method of sulfanilamide in the perfusate was followed by the method described previously by the authors.[3] Transmucosal fluid movement was estimated by measuring the volume change of the perfusate during the perfusion study and a ratio of the transmucosal fluid movement was obtained following the method of Kitazawa[5] by using the initial volume of the perfusate and that of the final, which were measured by the graduated cylinder. Details are mentioned in the other paper.[6]

Results

Infusion of Plasma and Fluid Transfer in Body

A fresh plasma obtained from non-fasted healthy donnor rats is generally recognized to be an ideal plasma expander in therapeutics and an effect of infusion of the fresh plasma was examined.

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

Changes in the fluid transfer into or out of the circulation were pursued by the time course observations of both hematocrit value and water content of blood plasma and the results obtained are depicted in Fig. 1. In order to catch a subtle change in the fluid behavior between fluid compartments including the intestinal lumen, in this experiment, perfusion solutions were adjusted to be isotonic by changes in a concentration of saline. First, intestinal perfusion was undertaken with a 40 ml of isotonic saline solution like the previously reported method[3] and after a given period of time which is indicated as an arrow in Fig. 1, 2.2 ml of plasma per 100 g of body weight, gained from non-fasted healthy donor rats, was intravenously injected. As was expected, there observed both a moderate increase in a water content of blood plasma and slightly decreasing slope in hematocrit value with increasing time, which are apparent in the course of an experiment from the beginning till the time of plasma infusion.

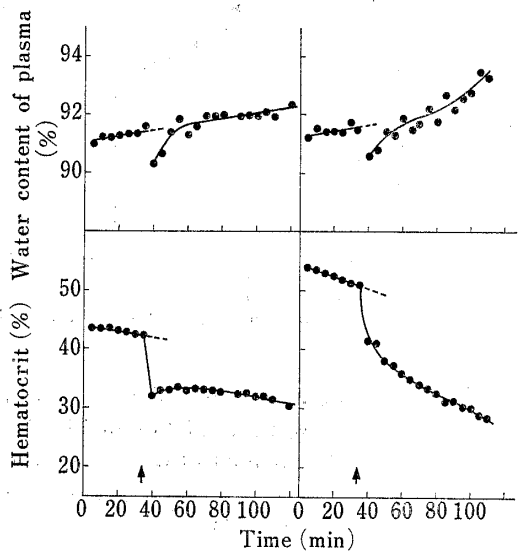

Fig. 1. Time Course Observation of Arterial Hematocrit Value and Water Content of Blood Plasma before and after an Intravenous Infusion of Plasma in the Fasted Rat and the Control

Arrows indicate the infusion time of plasma.
left hand graphs: control, right hand graphs: fasted

Immediately after the infusion of plasma, there brought about a rapid fall in hematocrit in both the fasted and the non-fasted rats, but for a short time later different behaviors were elucidated between the fasted rat and the control. In the former case, hematocrit decreased consistently during periods of the experiment and moreover became far away from the predicted level with increasing in time, where the predicted level was denoted as a dotted line in Fig. 1. In the latter case, however, the hematocrit increased immediately for a short time and then decreased gently with restoration toward the predicted level which was also displayed as a dotted line in Fig. 1 and finally declining curve became to parallel that obtained in the course of experiments before the infusion of plasma.

These results reflect in changes of the water content of blood plasma. In the non-fasted control, no change was observed before and after the infusion of plasma, whereas in the fasted animal the water content of the circulation plasma increased gradually after the infusion, that is, the slope of the regression curve became more steep, which indicates that a water inflow into the circulation from extravascular spaces surpassed the outflow out of the circulation toward extravascular spaces.

In such a hypovolemic situation as fasting, plasma expansion caused by the fresh plasma infusion seems to be favorable for fluid transfer into the circulation from any other fluid compartments including intestinal lumen.

Plasma Volume Expander and Fluid Transfer in Fasted Rat

In the fasted rat, an infusion of fresh plasma produced a rise in the inflow of extravascular body fluid into the circulation, as mentioned above. One of the reasons may be probably due to an improvement of blood flow in the peripheral capillary. This permits us to confine our attentions to the efficacy of a plasma volume expander which is clinically of most value in an improvement of the capillary circulation as well as a restoration of the circulation volume.

With commercially available preparations of transfusion solution, plasma expansion was studied in fasted rat, and the results obtained are depicted in Fig. 2. As it was elucidated in the above paragraph that time course observations of water content of blood plasma are

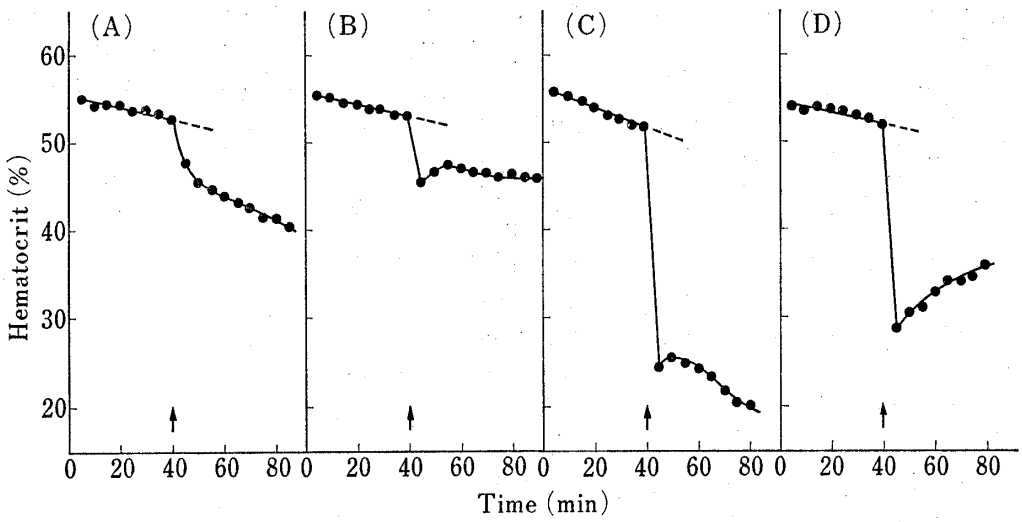

Fig. 2. Time Course Observation of Arterial Hematocrit Value before and after a Depletion of Blood and/or an Intravenous Infusion of Plasma Volume Expander in the Fasted Rat

Arrows indicate the depletion time of blood (A) or the iufusion time of plasma volume expander (B,C,D).

closely related to behaviors of hematocrit values, in this experiment, time course observations of arterial hematocrit were kinetically employed as an index of plasma volume change.

To make sure of a homeostatic volume change of the circulation in fasted rat, a case of fasted animal depleted a certain amount of whole blood was illustrated in Fig. 2-A. A declining curve before the depletion of blood was observed and this is probably due to both fluid inflow from intestinal lumen which is perfused with isotonic saline solution and samplings of blood for hematocrit measurement. After the depletion of blood, hematocrit value was decreasing with a steeper slope than the predicted level which was denoted as a dotted line in Fig. 2, and this means that there should occur a larger inflow of fluid into the circulation from the extravascular spaces including intestinal lumen owing to regulate the circulation volume back toward pre-depleted level. In other words, in fasted rat as well as a non-fasted one, the fluid transfer in body is thought to bring about for the purpose of regulating the circulation volume. Under these conditions, the following experiments were undertaken.

In Fig. 2-B, an effect of physiologically isotonic saline solution is illustrated. An extent of decreasing in hematocrit after the infusion was smaller than that obtained by the plasma infusion depicted in Fig. 1. This indicates that saline solution was much rapidly disappeared from the circulation even in the course of the infusion, in other words, there occurred a rapid repletion of interstitial spaces.

In Fig. 2-C and -D, results for 10% dextran-40 and 6% dextran-70 are shown, respectively. Infusion of both preparations resulted in a marked fall in hematocrit, which indicates a rapid rise in the circulation volume and this is in agreement with an efficacy that an initial effect of these preparations is in the restoration of the circulation volume of patients whose extracellular fluid volume is deficient because of a hemorrhage, a dehydration and surgical operations. Concerning the effect of circulation volume expansion, 10% dextran-40 was apparently more effective than 6% dextran-70. A 27% decreasing in hematocrit value was observed by the infusion of the former, whereas the latter caused a 23% decreasing in hematocrit. In the course of experiments after the infusion, there observed an obvious difference between the two. In a case of 10% dextran-40, hematocrit decreased consistently even after the cessation of the infusion, however, progressive increase in hematocrit was observed in a case of 6% dextran-70. These evidences demonstrate that the former took extravascular water into the circulation, on the other hand, the latter pushed out a plasma water to the

extravascular spaces. This difference may be probably dependent on properties of each dextran preparation.

Infusion of Plasma Expander and Intestinal Absorption

Although plasma expanders were surely observed to bring about a rise in the circulation volume, it is uncertain whether such a circulation volume expansion should become to be of advantage to the drug therapy which is dependent on drug absorption from gastrointestinal tract and this was examined.

A given amount of each plasma expander was intravenously infused at a constant rate into 60-hour-fasted rat and after a certain period of time, absorption experiments with hypotonic saline solution with sulfanilamide were undertaken for one hour. The results obtained are summarized in Table I.

Table I. Effect of Circulation Volume Expansion on Intestinal Absorption in 60-hour-fasted Rats

	Absorption of sulfanilamide (%/hr)	Ratio of fluid movement
Non-treated Rats	57.3±4.2	0.672±0.026
Plasma-infused Rats	64.4±4.7	0.614±0.037
Isotonic-saline-infused Rats	52.9±6.0	0.725±0.044
10% dextran-40-infused Rats	50.4±5.1	0.690±0.044
6% dextran-70-infused Rats	48.3±6.2	0.734±0.057
Non-fasted Control Rats	80.1±5.8	0.547±0.047

Figures are means and standard deviations of values in five rats.

It is apparent from Table I that sulfanilamide absorption was increased after the infusion of fresh plasma obtained from non-fasted healthy donor rats, and at the same time, there observed an increase in net fluid absorption from intestine which is represented in Table I as a fall in a ratio of fluid movement. This result indicates that the infusion of fresh plasma may be favorable for the drug absorption from intestine in fasted rats but that the effect is not so strong as the absorption increases to reach up to the level observed in the non-fasted control rats.

On the other hand, after the infusion of the other plasma expanders, opposite results were obtained. Absorption of the drug was in any cases decreased with an increase in the ratio of fluid movement. Infusion of both 6% dextran-70 and 10% dextran-40 caused a larger decrease in the sulfanilamide absorption than that of the isotonic saline solution and between both dextran preparations, 6% dextran-70 showed a more severe effect on the drug absorption than 10% dextran-40. As for an effect on fluid absorption, 6% dextran-70 caused a marked decrease, whereas 10% dextran-40 did not decrease the net fluid absorption so largely as that of the isotonic saline solution.

Judging from the above results, it was suggested that any plasma expander may not have always a definite effect on the intestinal absorption in fasted rats.

Discussion

When the experimental animal is deprived of food, total water intake decreases and volume of body fluid, particularly the circulation volume decreases progressively with increasing in time of fasting, and a dehydrated situation occurs.[9] Accordingly, a confusion of

9) J.A. Archambeau, P. Stryckmanns, and H. Brenneis, *Radiat. Res.*, **36**, 396 (1968); L. Wade and L.B. Sasser, *J. Appl. Physiol.*, **29**, 64 (1970).

water balance in fluid compartments of body, that is, a depression of homeostatic activity on which a maintenance of constant conditions of body fluids is dependent, is speculated in the state of fasting. In the present work, a study was made to elucidate a drug absorption from small intestine in fasted rats.

As was often mentioned, fluid absorption from gastrointestinal tract is restricted in such a dehydrated situation as fasting, and accordingly oral administration of water is not always preferable for body. In such clinical therepeutics, fluid infusion *via* parenteral routes is usually employed for an improvement of body fluid conditions and the improvement is achieved with plasma expanders.

Plasma expanders are classified roughly into three groups as follows: 1) plasma solution, 2) crystalloid solution and 3) colloid solution. Each expander is useful in its own way. Fresh plasma is ideal because of the actually identical components with the bleeding plasma, except for a difficulty of the preservation and a danger of the infection of serum hepatitis.[10] Crystalloid solutions such as a saline solution and Ringer's solution can temporarily bring about an expansion of the circulation volume as well as the other plasma expanders, but the maintenance of the circulation volume is not necessarily long because of the chemical components such as sodium, chloride and so on which can pass away freely out of the circulation across the capillary wall. On the other hand, colloid solution such as dextran preparations remains for a long time in the circulation because of a macromolecular component and this seems to be preferable for the capillary circulation flow. As for the preparation products, dextran solutions are of great advantage for therapeutics because of a manufacturing easiness, a low price, a long preservation, no-dangers of any infections and so on.[11] But a difference in the molecular weight of dextran seems to affect subtly a balance of water between intra- and extra-vascular spaces, which will be discussed below. It is interesting from pharmaceutical as well as clinical fields how the difference in characteristics of plasma expanders improving the body fluid conditions affect the fluid and drug absorption from gastrointestinal tract.

Table I indicates that plasma infusion alone was responsible for an increase in absorption of both fluid and drug in fasted rats.

When non-fasted healthy rats receive the infusion of plasma obtained from another animals, the circulation volume expansion may occur rapidly, and thus may be followed by a rapid rise in the hydrostatic pressure and this may not be favorable for fluid transfer into blood stream from extracellular spaces. This will be reasonably explained on the basis of Starling's hypothesis[12] that transcapillary changes of body water are mainly due to the unbalance between hydrostatic pressure and protein oncotic pressures on the two sides of the capillary wall.

In the fasted rats, however, this may not be so. Even if the fasted rats should receive the infusion of plasma, the circulation volume expansion should not be brought about more than the value predicted in the non-fasted control. In such a case as fasting, it is rather expected that the infusion of an adequate amount of plasma might serve to restore the circulation of blood toward the normal level, thus resulting in a smooth exchange of water in any parts of body.

Moreover, since albumin concentration of infused plasma obtained from non-fasted healthy rats is somewhat higher than that of the fasted ones, there should be brought about a rise in the plasma colloidal osmotic pressure in the fasted animals received the infusion. This may be also one of the important factors determining the volume of fluid-inflow into blood. The present observation is in agreement with the view that an infusion of concentrated albumin increased passive absorption of Na^+ from intestine.[13]

10) U.F. Gruber, "Blutersatz," Igaku-Shoin, Tokyo, Japan, translated by R. Naito, 1971, p. 51.
11) U.F. Gruber, "Blutersatz," Igaku-Shoin, Tokyo, Japan, translated by R. Naito, 1971, p. 65.
12) E.E. Starling *J. Physiol.*, **19**, 312 (1896).
13) M.H. Humphreys and L.E. Earley, *J. Clin. Invest.*, **50**, 2355 (1971).

Figure 1 indicates concretely the effect of plasma infusion in the progressive expansion of the circulation. Considering that albumin is able to hold water of about 18-fold albumin's weight,[14] in fasted rats, infused plasma seems to have displayed an effect as a plasma volume expander.

A value of plasma protein in the circulation volume expansion can be more emphasized by comparison with that of a substance which is free from water-holding capacity, for instance, isotonic saline solution. An effect of isotonic saline infusion instead of plasma on the intestinal absorption in the fasted rats was investigated as shown in Table I. An opposite result was obtained. This reason may be as follows. Although the infusion may produce an adequate volume expansion of the circulation with a smooth blood flow, blood plasma may be immediately diluted, in other words, there may occur a fall in the plasma colloidal osmotic pressure, and this may be followed by a removal of water out of blood in order to decrease the volume of blood toward the pre-infused level. In addition, concerning a sodium in blood plasma, sodium retention was usually observed in the fasted rats, and therefore decreasing in body fluid which was presented in the previous report[3b] might produce a comparatively high concentration of sodium in blood. However, this high concentration might not be favorable to accelerate the transmucosal fluid inflow when the perfusion solution was the isotonic sodium chloride, since the isotonicity of the perfusate was kept during the course of the intestinal perfusion experiment.

As mentioned above, if drug absorption can be dependent on only the degree of blood volume expansion or that of the osmotic change of blood plasma, attentions should be given to plasma volume expanders such as dextran preparations whose colloidal osmotic pressures are higher than that of blood plasma. Contrary to our expectations, a similar effect like plasma was not obtained. Both absorptions of fluid and drug from intestine were extremely decreased in fasted rats. These unexpected results may be interpreted in Fig. 2 as follows.

Dextran is well known to be a macromolecular polysaccharide and to have a large water-holding capacity, for example, 10% dextran-40 or 6% dextran-70 can hold water of about 40 or 27 ml per g dextran, respectively.[15] Solution of 2.5% dextran-40 or 3% dextran-70 are equivalent to blood plasma in a colloidal osmotic pressure.[15] Therefore, 10% dextran-40 or 6% dextran-70, which are frequently used clinically, have a higher colloidal osmotic pressure than blood plasma.

When such a hyper-colliodal osmotic solution is infused to fasted rats, it is properly expected that an increase in plasma volume should occur immediately. In fact, as is evident from Fig. 2, there observed a extremely large expansion with a markedly rapid rate by those infusion, however, falls in hematocrit value by both dextrans were by far larger than that of plasma. The extents of falls in hematocrit by 10% dextran-40 or 6% dextran-70 were 2.7 or 2.3 times as large as that of plasma, respectively. This suggests that considerable hypervolemia should occur in fasted rats after the infusions. Accordingly, further inflow into the circulation blood may be prevented completely. Fluid movement in the intestinal lumen-to-blood direction may be also prevented thoroughly.

The main purpose of the fluid therapy is said to be as follows[16]: 1) supplement of water and normalization of water partition of body, 2) supplement of electrolyte and arrangement of electrolyte unbalance in body and 3) supplement of calory and a substance necessary for a protein constitution. Accordingly, plasma volume expander may be probably essential for an improvement of body fluid conditions, that is, a maintenance of life. However, in the points of absorption of fluid and drug from gastrointestinal tract, unfavorable results were obtained in the present work. It was also suggested in the present study that the intestinal absorption

14) U.F. Gruber, "Blutersatz," Igaku-Shoin, Tokyo Japan, translated by R. Naito, 1971, p. 60.
15) U.F. Gruber, "Blutersatz," Igaku-Shoin, Tokyo, Japan, translated by R. Naito, 1971, p. 70.
16) "Mizu Denkaishitsu no Kiso to Rinsho," ed. by E. Kato and A. Koshikawa, Shinko Koeki Co., Ltd., Tokyo, Japan, 1974, p. 266.

is subtly dependent on changes in the amount and composition of extracellular fluid including plasma in blood stream of the subjected animal, in other words, such physiological conditions concerning extracellular fluid should attract attentions and/or should be taken into considerations in promoting the studies on the absorption of substances from the gastrointestinal tract.