increase in weight on a diet of Rockland Rat pellets and drinking water for the next 1-2 years. This permits an adequate period for chronic or repeated experiments without need to consider the influence of changes in body weight which can alter gastric secretion(6).

As a rule, animals with such fistulae remain in excellent condition without stomach ulceration, erosions of the abdominal wall or leakage of gastric contents. No more than one experiment per week was done on any animal to permit adequate recovery after prolonged fasting. During the past 3 years we have produced chronic fistulas suitable for experimental purposes in 166 animals. Three or more experiments were performed in each of 84 rats, and in 16 animals, between 20 and 40 experiments. Valuable information concerning the mechanisms of the interdigestive phase of gastric secretion, influence of some anesthetics and effect of insulin hypoglycemia and of gastrin on this secretion have been obtained with this type of preparation (1,7-9). Long range investigations with almost weekly studies following total adrenalectomy(10), thyroparathyroidectomy and radioactive I^{131} have also been done.

Summary. A simple technic for preparation of a chronic rumenal fistula in the rat using a specially designed Pavlov's type of cannula is described.

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Does "Restricted Diffusion" Occur in Muscle Capillaries?* (28075)

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The concept "restricted diffusion" implies a deviation of the ratio between the permeability coefficients from the ratio between the free diffusion coefficients. The occurrence of "restricted diffusion" is usually taken as evidence of the existence of pores in a membrane. Pappenheimer(7) took the finding as evidence for existence of pores in the capillary membrane of the hind limb of the cat. His ingenious method of determining the permeability coefficients involved application of van't Hoff's law: $\Delta\pi = RT\Delta c$, where $\Delta\pi$ is the osmotic pressure difference across the membrane, Δc is the difference in concentration, R is the gas constant and T is the absolute temperature. As the capillary membrane is permeable to both solutes and solvent and thus does not behave ideally, the introduction of a correction factor, σ, the reflection coefficient of Staverman(9), becomes important. Lack of knowledge of the magnitude of the correction factor (which, of course, varies for molecules of different sizes) may disturb the calculation of a true permeability coefficient. This point of view was put forward by Ussing(10) and by Grim(4) and later by Kedem and Katchalsky(5).

The criticism advanced on theoretical grounds has not been tested experimentally. It is, however, possible to calculate the permeability coefficients from data obtained by use of another experimental principle, the

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"indicator diffusion" method (Crone 2,3). As the question of the existence or non-existence of a pronounced diffusion restriction has implications for the physical models of the capillary wall, an attempt was made to reinvestigate the problem.

Material and methods. A mixture of inulin and C-14 sucrose together with iodinated radio-albumin was injected within 1-2 seconds into the femoral artery of a dog. The injection solution contained 35 mg inulin, 10 μC C-14 sucrose and 10-15 μC iodinated radio-albumin. The total volume was 2 ml. Blood from the femoral vein was collected from about 5 seconds after the injection in 6-7 separate samples; collection of each sample lasted 2-3 seconds. Albumin does not leave the hind limb capillaries to a significant extent and is therefore an indicator of intravascular dilution. It is thus possible to calculate the fractional loss (= the extraction) of inulin and sucrose. It was found that the extraction remained constant for at least 30 seconds after the start of the arterial injection; samples collected within this time could therefore all be used in the calculations. The average ratio given below is the arithmetic mean of the results of the individual samples from all the experiments.

C-14 activity was determined on dried aliquots of the same supernatant as that on which the inulin concentrations were determined. It was, however, found that not all the I-131 activity was removed by the precipitation. The samples were therefore counted twice at 1-2 week intervals. Knowledge of the decay rate of I-131 permitted calculation of the activity due to C-14 only. I-131 activity was determined on dried blood samples with a scintillation counter. Inulin was estimated according to Bojesen(1). All determinations were made *in duplo* and the extraction values are given with an accuracy of about 4% (coefficient of variation).

Knowledge of the average extraction of the test substances in the early samples permits calculation of the permeability coefficient in accordance with the equation (Crone, 2, 3):

$$(1) \qquad P = \frac{\dot{Q}}{A} \log_e \frac{1}{1-E}, \text{ where}$$

P = the permeability coefficient,
$\dot{Q}$ = blood flow per g of tissue per sec,
A = capillary surface in cm^2 per g of tissue,
E = the average extraction $(1>E>0)$.

If one is interested only in the ratio between two permeability coefficients, the ratio is related to the extractions by the equation:

$$(2) \qquad \frac{P_1}{P_2} = \frac{\log(1-E_1)}{\log(1-E_2)}.$$

The advantage of this equation is that it contains only values determined in the experiments, whereas a calculation of the permeability coefficients involves assumptions about capillary surface area and rate of perfusion.

The advantage of this experimental approach to that of Renkin and Pappenheimer (7,8) is that the 2 test substances were investigated at the same time, so that differences in perfusion rates and capillary surface in different experimental animals were eliminated.

Results. In 8 experiments 45 samples were collected. The average ratio calculated from these experiments was 2.53 $\pm$ 1.65 (S.D., n = 45). In none of the experiments was the ratio as high as that found by Pappenheimer: 9.8.

Discussion. This implies that the question of the best physical model of the capillary wall must be reconsidered. It appears that the figure for the average pore radius which Renkin and Pappenheimer(8) deduced from their experiments, 35 Ångström units, is not in accordance with a ratio between the permeability coefficients of sucrose and inulin, which is almost equal to the ratio between the free diffusion coefficients.

The problem is, then, whether the pore model is still adequate or if a model in which a continuous non-porous layer is interposed somewhere between the blood and the interstitial fluid can explain the findings more adequately. Kruhøffer(6), in his experiments on distribution velocities of sucrose and inulin in the extracellular space of the rabbit, found a ratio between rates of distribution which corresponded very closely to the ratio between the free diffusion coefficients which he

TABLE I. Permability Coefficients for Sucrose and Inulin in Capillaries of the Hind Limb of the Dog.

Author	Test substances: Sucrose ($cm \cdot sec^{-1}$)	Test substances: Inulin ($cm \cdot sec^{-1}$)	Technic
Renkin and Pappenheimer (1957)	4.9×10^{-5}	$.5 \times 10^{-5}$	Transient osmotic
Crone	$.74 \times 10^{-5}$	$.26 \times 10^{-5}$	Indicator diffusion

determined as being 2.98. This probably means that the major obstacle during dilution in the extracellular space is the passage through the capillary walls.

The permeability coefficients of the hind limb capillaries for inulin and sucrose were calculated from the initial extraction values, the perfusion rate and the value for the capillary surface area per gram of tissue found by Renkin and Pappenheimer. Insertion of these figures in equation (1) gives the permeability coefficients, the values of which are shown in Table I.

Though there is a significant difference between the figures of the permeability coefficients for sucrose, they do agree quite well considering that they have been obtained by completely different experimental technics.

Kedem and Katchalsky(5) found values for σ which were to be used in Pappenheimer's calculations: 0.058 and 0.375 for sucrose and inulin. If the permeability coefficients calculated by Renkin and Pappenheimer are corrected accordingly, their figures are 0.29×10^{-5} and 0.15×10^{-5}, and there is now a close correspondence between the figures obtained with the two different methods. This may lend support to the suggestions of Ussing and Grim.

Summary. The ratio between the sucrose and inulin permeability coefficients of the hind limb capillaries in dogs was 2.53 ± 1.65 (S.D., $n = 45$). This value is not significantly different from the ratio between the free diffusion coefficients and is considerably lower than the figure given by Pappenheimer and coworkers. The implication of our results is that the pore model of the hind limb capillaries must be reformulated to explain the fact that "diffusion restriction" seems not to occur.

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