Table II. Brain levels of choline, acetylcholine, acetylcholinesterase and nicotine following nicotine monomethiodide

	NaCl control	Nicotine monomethiodide	P
Choline (nmoles/g)	37.10 ± 5.37	42.71 ± 6.52	ns
Acetylcholine (nmoles/g)	12.81 ± 0.76	13.50 ± 0.77	ns
Acetylcholinesterase (μmoles/min/g)	8.66 ± 0.10	8.88 ± 0.24	ns
Nicotine (μg/g)	0	0	ns

Data are reported as mean values ± S.E.M. for 6 rats

Additional effects of acute nicotine administration on gastro-duodenal function have recently been reported. KONTUREK et al.[16] have shown that nicotine reduced pancreatic bicarbonate output, and ROBERT et al.[17] that nicotine increased ulcer formation in rats given synthetic gastrin and carbachol. It remains to be seen whether these effects are also produced by nicotine monomethiodide.

As far as peripheral activity goes, nicotine monomethiodide produces cardiovascular effects in spinal cats comparable with those of nicotine hydrogen tartrate[9]. For example, BARLOW and DOBSON[9] reported that nicotine monomethiodide was at least as active as, if not more active than nicotine hydrogen tartrate, and that the responses could be abolished by prior treatment with hexamethonium. However, the action of the two compounds may be somewhat different since the shape of the blood-pressure response to the two drugs was different, and it was impossible to produce complete blockade of sympathetic ganglia with nicotine monomethiodide.

Based upon intraventricular injections of nicotine and the choline ester carbachol in cats, ARMITAGE and HALL[18] found that carbachol had two actions, one of which resembled that of nicotine. The nicotine-like effect was potentiated by cholinesterase inhibitors and prevented by hemicholinium, in agreement with the hypothesis that nicotine acts centrally by releasing acetylcholine. Mean concentrations of choline and acetylcholine in the brain did not differ significantly from previously published normal values[19]. This is not surprising since nicotine monomethiodide does not cross the blood brain barrier. It is theoretically possible that some nicotine monomethiodide could be converted within the body to a non-quaternized form, which could then cross the blood brain barrier. However, no nicotine or nicotine methiodide was detected in brain tissue by a method with a sensitivity of 8.0 ng/g brain[20].

Résumé. L'action de la nicotine monométhyliodine (NMI) sur la sécrétion gastrique basique et sur les concentrations de choline de cervelles, d'acétylcholine et de nicotine et sur l'activité de la transacétylcholinestérase a été étudiée chez des rats. Le NMI, sel quaternaire de nicotine, qui ne traverse pas la barrière hématoencéphalique, a été administré dans de la gélatine à 6% en dosage sous-cutané de 1000 μg/ml/kg/jour pendant 14 jours. Le NMI n'a pas changé de paramètres et aucune trace de nicotine n'a été découverte dans les homogénates de cervelles complètes.

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Peritubular Capillary Permeability of Albumin in Saline and Water Diuresis

The significance of peritubular physical factors in the control of renal proximal tubular fluid reabsorption has received special attention in recent years. The evidence is in favor of a positive correlation between the oncotic pressure in peritubular capillaries and the rate of tubular reabsorption[1,2]. This positive correlation suggests that the oncotic pressure gradient across the peritubular capillary wall plays a significant role in the removal of tubular reabsorbate from the interstitium and in turn the tubular lumen. The extent of the gradient, however, must be dependent not only on intracapillary protein concentration but also on the concentration in the interstitium. An important factor in the regulation of interstitial protein concentration is the permeability of the peritubular capillaries. In order to provide information on this problem we have compared the mean transit time of labelled albumin from arterial blood to renal capsular and hilar lymph ($\bar{t}_{a1b}$), obtained under control conditions, with that obtained in the same kidney during saline or water diuresis. Moreover, with the aid of other tracers we have interpreted these results in terms of modulated permeability of the peritubular capillaries to albumin.

Material and methods. The experiments were carried out on chloralose anesthetized dogs. Capsular and hilar

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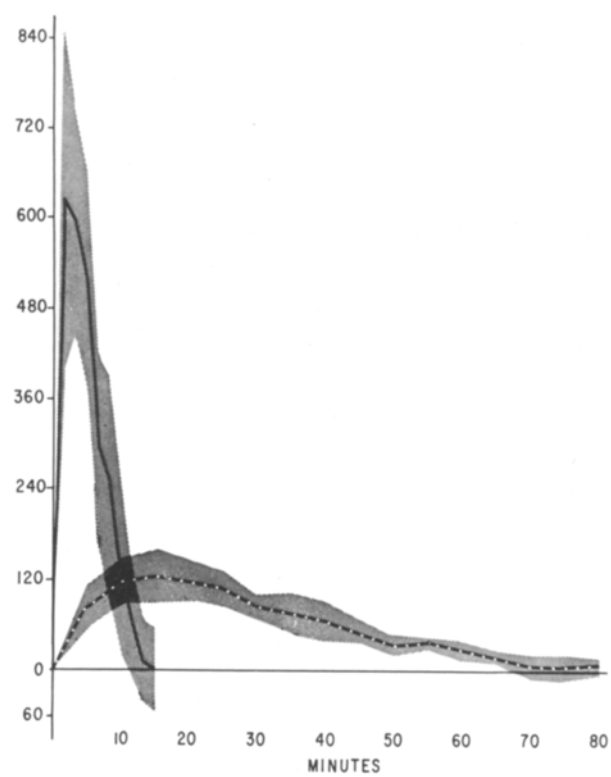
lymphatics were cannulated and sampled during consecutive 3 to 10 min periods[3]. In all studies ^{131}I-albumin and in most experiments ^{3}H-inulin and in some ^{35}S-thiosulfate were injected i.v. Albumin specific activity and concentrations of the other tracers were measured in arterial plasma and renal lymph, by means of gamma and liquid scintillation spectrometry.

Transit times of tracers from arterial blood to renal lymph were calculated by deconvolution[4] using an IBM 360 computer. In each experiment 2 determinations were carried out, the first serving as a control. In the majority of experiments the first determination was made on the concentrating kidney and the second after the infusion of 0.9% saline solution or a hypotonic solution containing 0.23% NaCl and 2.5% glucose. Each infusion amounted to 4% of the body weight of the dog, and was followed by a sustaining infusion of the same solution. In 2 experiments the physiological conditions were not altered between determinations so that the linearity of the system could be confirmed.

Results. The average mean transit times of albumin, inulin and thiosulfate obtained under control conditions are shown in the Table. The Figure shows the average of the normalized distribution of albumin and inulin transit times under control conditions.

In earlier studies[3] we used a different technique to estimate the turnover time of interstitial albumin, and under similar experimental conditions derived a value of 37 min which is to be compared to our present result of 24.5 min. In using the earlier method the assumption has to be made that a single well mixed compartment exists between the sampling sites of input and output. Such an assumption is not invoked when deconvolution is employed; it is implied, however, that the system is linear.



Density functions of transit times of ^{3}H-inulin (solid line) and ^{131}I-albumin (interrupted line) between arterial blood and renal lymph. Shaded areas show the 95% confidence intervals.

Our control studies support the validity of these assumptions.

In most experiments albumin and inulin transit measurements were repeated in saline or water diuresis. The results were statistically evaluated by paired comparisons, and are shown in the Table. The mean transit time of albumin was shortened by nearly 50% in water diuresis ($p < 0.001$) and only by about 10% ($p < 0.05$) in saline diuresis when compared to control values. Under both diuretic conditions the mean transit times of inulin and thiosulfate decreased to the same degree i.e. by approximately 15%.

Discussion. It seems unlikely that a significant quantity of albumin reaches the interstitium by tubular reabsorption because of the low concentration of albumin in the glomerular filtrate[5], and also, because at least part of the reabsorbed albumin may be metabolized during its passage through the tubular cells[6]. Therefore, the $\bar{t}_{alb}$ measured in our experiments is the sum of 3 component mean transit times: 1. passage through the capillary wall, 2. transit through the interstitium proper and 3. entry into and flow through the intrarenal lymphatic vessels. By measuring $\bar{t}_{alb}$ alone it was not possible to differentiate between these components. We attempted to analyse the delay component in the interstitium with the aid of 2 other tracers injected simultaneously with albumin: ^{3}H-inulin and ^{35}S-thiosulfate. Both of these smaller molecules should cross the peritubular capillary membrane freely. If passage through the interstitium occurs solely by diffusion, then because of their respective molecular weights and charges, inulin and thiosulfate would have different transit times between capillary blood and lymph. We interpret the lack of such a difference as an indication that either the path of diffusion is very short or passage across the interstitium occurs by convection. The relatively large volume of tubular reabsorbate moving through the interstitium could be the factor responsible for convective transport. For this reason, we tend to rule out the interstitium as the main component in the delay of albumin relative to other tracers of smaller molecular weight. It also seems improbable that the major delay

Control mean transit times for albumin, inulin and thiosulfate; and average shortening of these times (paired comparisons) during saline and water diuresis

	Mean transit times (min) of		
	Albumin	Inulin	Thiosulfate
Control ± S.E.M.	24.5 ± 1.6	4.46 ± 0.40	4.00 ± 0.42
(*n*)	(23)	(15)	(12)
Saline[c] ± S.E.M.	2.6 ± 0.9[a]	0.96 ± 0.63	0.64 ± 0.37
(*n*)	(7)	(5)	(5)
Water[c] ± S.E.M.	10.0 ± 1.4[b]	0.55 ± 0.51	0.63 ± 0.73
(*n*)	(4)	(4)	(3)

[a] Significant at the 5% level
[b] Significant at the 0.1% level
} two sided t-test
[c] Change in mean transit time from control.

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component occurs at the lymph capillary wall, since these capillaries lack a continuous basement membrane, and according to COURTICE[7] do not present an effective barrier to entering albumin. Thus it would appear that the major factor which slows the equilibration of albumin between plasma and lymph is the limited permeability of the peritubular capillary membrane.

Since $\bar{t}_{alb}$ is equivalent to a ratio of the albumin pool (A) divided by the rate of passage of albumin through this pool (F) (i.e. $\bar{t}_{alb} = A/F$), a change of $\bar{t}_{alb}$ may be the result of an altered pool size, an altered rate of passage or both. Direct evidence on the size of the interstitial albumin pool in saline and water diuresis is not at present available. It is possible that the increased flow of fluid through the interstitium after fluid loading may have depleted the interstitial albumin pool. However, because of the similar changes in $\bar{t}_{in}$ and $\bar{t}_{thio}$, any depletion should have been the same after both types of fluid loading. The significantly greater reduction in $\bar{t}_{alb}$ in water diuresis than in saline diuresis, therefore, indicates an increased rate of passage after hypoosmotic fluid load. Thus, if the main component of albumin delay occurs at the blood capillary membrane, our results provide evidence for a significant increase in albumin permeability of the peritubular capillaries in water diuresis. The mechanism for this altered capillary permeability is unknown. It is possible that a different pattern of peritubular capillary pressure changes after the infusion of saline and hypoosmotic fluid may play a role in evoking the responses we observed, but at the present time no experimental evidence is available to support such a mechanism[8].

Résumé. Ce travail compare le passage de l'albumine marquée, de l'inuline, et du thiosulfate à partir du lit capillaire dans la lymphe rénale capsulaire et hilaire, chez le chien soumis à des diurèses salines et aqueuses. Les résultats suggèrent que la perméabilité capillaire péritubulaire est influencée de manière différente par la variation des conditions de diurèse.

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Running Activity and Gastric Ulcers in the Rat

It has been reported that rats offered laboratory chow diet for 1 h/day only and allowed to run in activity wheels ate less food than correspondingly food-restricted animals in standard laboratory cages. In spite of the reduced food intake, animals in activity wheels continued to run and most of them died within 2 weeks[1]. This 'self-starvation' effect of the combined temporary food deprivation and running activity was confirmed in additional experiments[2-7]. The present study was designed to investigate whether the 'self-starvation' conditions lead to any organ changes, which could explain the early deaths of these animals.

Male Sprague-Dawley rats, weighing about 155 g each, were assigned at random either to cages with activity wheels (10 animals) or to standard laboratory cages (5 animals). A semi-synthetic high carbohydrate diet containing 20% casein and 65.6% dextrin[8] was offered for 1 h/day, between 09.00 and 10.00 h. Animals in the activity wheels consumed an average of 6.8 g food per day, while the animals in the standard cages averaged 7.8 g/day. Three rats in the activity group died during the 2-week study. These animals, and all the survivors sacrificed at the end of the experiment, were autopsied and their organs examined for gross pathologic changes. The tissues were then preserved in 10% buffered formaldehyde for subsequent histological study.

Eight of the 10 rats kept in activity wheels showed stomach lesions, ranging from superficial mucosal erosions (2 animals) to point-like ulcerations (3 animals) and large confluent areas (3 animals) of hemorrhage (Figure, B). The intestinal tract of the animals with ulceration and hemorrhage contained both fresh and digested blood. All the lesions were confined to the body and antral area of the stomach (Figure, B). The fundic area seemed to be intact. Histological examination of the gastric tissue revealed mucosal hemorrhage, superficial erosion of the mucosa, and multiple ulcers, frequently reaching the submucosa. No damage was evident either on gross or histological evaluation of the stomachs of the animals kept in standard laboratory cages (Figure, A). The remaining organs examined, adrenals, liver and kidneys were without any remarkable or consistent pathologic changes.

The reduced food intake in 'self-starved' animals has been explained either by faulty physiological signals to the hypothalamus, which simulated the feeling of satiety[1], or by a 'starvation anorexia'[7]. Our data indicate that development of bleeding gastric ulcers might have been another factor responsible for the diminished food consumption. Since all animals which died during the present experiment showed extensive gastric ulceration and presence of fresh blood in the intestinal tract, it can be assumed that the extensive loss of blood contributed to their early death.

The gastric damage observed in the present study seemed to be more extensive than the 'exertion ulcers' produced in fasting rats forced to run for several hours[9].

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