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Relationship between glomerular filtration rate and maximum tubular reabsorptive rate of glucose

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Relationship between glomerular filtration rate and maximum tubular reabsorptive rate of glucose. Evidence is conflicting concerning whether maximum tubular reabsorptive capacity for glucose changes in proportion to changes in glomerular filtration rate (GFR). In paired studies in female dogs, we studied the effects of raising GFR on the maximum tubular reabsorptive rate of glucose (Tm_G) without extracellular fluid (ECF) volume expansion. Glucose titrations were performed on fasted dogs in a control state. Creatinine clearance (C_{Cr}) averaged 3.6 ml/min/kg of body weight; Tm_G/C_{Cr} averaged 2.68. Each dog was restudied after four weeks, following three days of high protein diet and glucocorticoid administration. C_{Cr} averaged 6.2 ml/min/kg of body weight; Tm_G/C_{Cr} averaged 2.69, indicating a proportional increase in GFR and Tm_G. Two additional studies, utilizing bovine growth hormone to increase GFR, confirmed that Tm_G increases with GFR. Simultaneous ^{125}I-iothalamate clearances were significantly lower than the C_{Cr} in these glucose-loaded dogs; since the values were considerably lower than expected for the state of hydration, we conclude that iothalamate clearances were in error. Nevertheless, choosing either C_{Ioth} or C_{Cr} as the true marker of the GFR, Tm_G increased in proportion to increases in GFR.

Relation entre le débit de filtration glomérulaire et le débit maximal de réabsorption tubulaire du glucose. Il existe des arguments contradictoires quant à l'éventuelle variation de la capacité tubulaire maximale de réabsorption du glucose proportionnellement aux modifications de GFR. L'effet de l'augmentation de GFR sur Tm_G, en l'absence de toute expansion, a été étudié chez des chiennes dont chacune était son propre témoin. Les courbes de titration du glucose ont été réalisées sur les animaux à jeun en situation de témoin. C_{Cr} était en moyenne de 3,6 ml/min/kg de poids corporel et Tm_G/C_{Cr} de 2,68. Chaque chien a été étudié à nouveau aprés 4 semaines, au terme de trois jours d'administration d'un régime riche en protéines et de glucocorticoïdes. C_{Cr} était en moyenne de 6,2 ml/min/kg de poids corporel et Tm_G/C_{Cr} de 2,69 ce qui traduit des augmentations proportionnelles de GFR et Tm_G. Deux études supplémentaires où l'hormone de croissance bovine a été utilisée pour augmenter GFR ont confirmé que Tm_G augmente avec GFR. Les clearances du ^{125}I-iothalamate réalisées en même temps que C_{Cr} ont été significativement inférieures à ces dernières chez les animaux surchargés en glucose. Du fait que les valeurs obtenues avec ^{125}I-iothalamate sont trés inférieures à celles attendues en fonction de l'hydration nous concluons qu'elles sont erronées. Quoiqu'il en soit, que l'on considère C_{Ioth} ou C_{Cr} comme l'indicateur glomérulaire vrai, Tm_G augmente en proportion de l'augmentation de C_{Cr}.

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Shannon and co-workers first described the kinetics of glucose reabsorption in modern terms [1, 2]. They demonstrated that the renal tubules reabsorb all of the filtered glucose presented to them until the filtered load of glucose exceeds the reabsorptive capacity of the tubule. In any one species, the point above which glucose spills into the urine is fairly constant and reproducible, and it has been referred to as the tubular maximum (Tm_G). The observation that, in human subjects, there was a small but reproducible difference between the plasma glucose concentration at which glucose first appeared in the urine, and at which tubular reabsorption of glucose failed to increase further, led to a further refinement of the theory [3]. This finding was interpreted as indicating that some nephrons had a lower tubular maximum than others, leading to a "splay" in the glucose titration curves.

Although several studies have failed to show that Tm_G varies significantly with changes in glomerular filtration rate (GFR) [2, 4, 5], the available evidence on this question is conflicting [5]. Smith concluded, based on the available evidence in 1951, that the Tm_G did not vary with GFR [6]. Many of the studies that either showed or failed to show a relationship between GFR and Tm_G in any animal failed to take into account the profound influences of changes in extracellular fluid (ECF) volume on Tm_G. In 1968 Robson, Srivastava and Bricker [7] showed in rats that ECF volume expansion with saline could markedly decrease renal glucose reabsorption and Tm_G. This has been confirmed [5] and has led to the hypothesis that glucose and sodium reabsorption are closely related.

The current study was designed to reevaluate the relationship between GFR and renal glucose reab-

sorption in the dog. Careful attention was directed toward monitoring sodium balance and excretion. A technique was utilized for increasing GFR markedly without ECF volume expansion. The results indicate that in any one animal there is a very close relationship between GFR and Tm_G.

Methods

Ten experiments were performed on four healthy, female, mongrel dogs weighing between 20 and 30 kg. One of the following three protocols was followed in preparation for each experiment: *a*) Low level GFR: Four dogs were fasted for 36 hours but were allowed water *ad libitum*. *b*) High level GFR: The same four dogs were fed 2 lb of horsemeat and received 40 mg of methylprednisolone acetate suspension, *National Formulary* (Depo-Medrol), intramuscularly daily for three days. On the day of the experiment they received $\frac{1}{3}$ lb of horsemeat. *c*) High level GFR study: Two of the dogs were treated the same as in *b*, but in addition received bovine growth hormone, 5 mg intramuscularly daily for two days, and 7.5 mg on the third day. Each dog was studied after protocol *a* and restudied two to four weeks later under protocol *b*; two of the four dogs were studied a third time two to four weeks later under protocol *c*. The order of the studies was not reversed because of the very long duration of action of such massive doses of methylprednisolone acetate. At the conclusion of each study the bladder was irrigated with a neomycin solution, and small doses of iron-dextran were given based on estimated blood loss.

The dogs were anesthetized with thiopental sodium (Pentothal Sodium) intravenously, an endotracheal tube was inserted and oxygen was administered at a rate sufficient to keep the arterial P_{O_2} in excess of 100 mmHg. After priming doses, creatinine (Matheson, Coleman and Bell, Norwood, Ohio) and ^{125}I-iothalamate sodium (Glofil-125, Abbott Laboratories, Chicago, Illinois) were infused in 5% dextrose in water at a rate of 0.5 ml/min such that the blood creatinine concentration was constant at approximately 0.25 mg/ml and ^{125}I-iothalamate concentration approximated 200 counts per minute (cpm)/ml. Urine collections via an indwelling bladder catheter were 10 to 15 min in duration unless urine flow was low, in which case urine collections were 20 to 30 min in duration. In every case the total volume collected exceeded 50 ml and the completeness of the collection was assured by manipulation of the catheter.

A solution of 20% dextrose in water and 20 mEq/liter of potassium chloride, was infused initially at 3.5 to 4.5 ml/min in order to raise the plasma glucose concentration and exceed the renal threshold. The first urine collection was begun when urine glucose was 3 to 4+ as estimated by Labstix (Ames Co., Elkhart, Indiana). After each urine collection was terminated, the rate of infusion of 20% dextrose and potassium chloride was increased by 1 to 1.5 ml/min and a 30-min equilibration period was allowed before the next urine collection was begun. Five collection periods were carried out for each experiment. Arterial blood samples were taken at the start and finish of each urine collection period for measurement of glucose, sodium, potassium, creatinine and ^{125}I-iothalamate concentrations.

The net sodium balance (total sodium in minus sodium out) was continuously monitored throughout each experiment. When urine volume exceeded the volume of dextrose and creatinine solutions infused, half normal Ringer's solution was infused at a rate sufficient to make up the difference.

Glucose was measured by the *o*-toluidine micro method, using a spectrophotometer (Gilford, Model 300-N, Gilford Instrument Co., Overland, Ohio). Creatinine was measured by the alkaline picrate method which was shown to be insensitive to glucose concentrations in excess of those found in the final urine if samples were read at exactly 15 min [1]. Creatinine recoveries from plasma and urine averaged 103%, and were constant over a range of glucose concentrations of 5 to 80 mg/ml. Sodium and potassium concentrations were measured on a flame photometer (Instrumentation Laboratories, Inc., Lexington, Massachusetts). The concentration of ^{125}I-iothalamate was measured in an automatic gamma counter (Nuclear-Chicago, Model 1185, Des Plaines, Illinois). Arterial blood P_{CO_2} and P_{O_2} were monitored throughout each experiment, using a blood gas analyzer (Corning, Model 16, Corning Glass Works, Corning, New York). Blood P_{CO_2} was found to remain constant without the use of a respirator.

Results

In three dogs, not reported here, it was found that simultaneous ^{125}I-iothalamate clearance and inulin clearance were very nearly identical ($C_{Ioth}/C_{Inulin} = 0.96$). However, when the dogs were infused with large amounts of hypertonic glucose, iothalamate as a marker for GFR proved to be highly variable and probably inaccurate, inasmuch as there were instances of apparent glucose secretion, and the average GFR was 2.6 ml/min/kg, far below the normal value of 4 ml/min/kg. Therefore, in the current studies GFR was measured using two methods simultaneously, exogenous creatinine clearance and ^{125}I-iothalamate clearance.

The average creatinine clearance of 3.6 ml/min/kg of body weight (protocol *a*) is very near the normal value expected for hydropenic dogs; the average C_{Ioth} of 3.0 is less than one would expect for hydropenic dogs.

Table 1 shows a representative study in a dog which yielded low values for GFR; Table 2 shows a representative study (protocol *b*) in the same dog which yielded high GFR's. Table 3 shows the changes that occurred in creatinine clearance and maximum tubular reabsorption of glucose in each dog, protocol *a* compared to protocol *b*. Note that in three of four dogs the change in maximum reabsorption nearly equalled or exceeded the change in creatinine clearance, whether the latter increased 38% or increased up to 108%. Fig. 1 shows all the data from the ten experiments. Note that the range of plasma glucose concentration was roughly the same during the low and high GFR studies. It appeared that, under the conditions of the present experiments, Tm_G was achieved at plasma glucose concentrations in excess of 3.5 mg/ml. Above

Table 1. Low level glomerular filtration rate study

Time	Blood glucose	Urine glucose	Flow rate	Glucose, *mg/min*			C_{Cr}	T_G/C_{Cr}	$U_{Na}V$
BW[a] 24 *kg*	*mg/ml*	*mg/ml*	*ml/min*	Filtered	Excreted	Reabsorbed	*ml/min*		*mEq/min*
8:55	Anesthesia		Creatinine and iothalamate started						
9:50	20% dextrose, 3.5 ml/min								
10:15	20% dextrose, 4.5 ml/min								
10:45 to 11:15, U1	2.82	32.3	1.17	256	37.8	218	90.7	2.4	0.023
11:15	20% dextrose, 5.5 ml/min								
11:45 to 11:55, U2	3.72	27.7	5.85	343	162	181	92.3	2.0	0.123
11:55	20% dextrose, 6.5 ml/min								
12:25 to 12:35, U3	5.20	31.1	8.80	458	274	184	88.0	2.1	0.128
12:35	20% dextrose, 7.5 ml/min								
1:05 to 1:15, U4	6.40	31.8	10.60	538	337	201	84.0	2.4	0.196
1:15 to 1:25, U5	6.76	34.0	11.00	606	374	232	89.6	2.6	0.242
							average,	2.3	

[a] BW = body weight.

Table 2. High level glomerular filtration rate study

Time	Blood glucose	Urine glucose	Flow rate	Glucose, *mg/min*			C_{Cr}	T_G/C_{Cr}	$U_{Na}V$
BW,[a] 24 *kg*	*mg/ml*	*mg/ml*	*ml/min*	Filtered	Excreted	Reabsorbed	*ml/min*		*mg/min*
9:45	Anesthesia		Creatinine and iothalamate started						
10:35	20% dextrose, 3.5 ml/min								
11:05 to 11:15, U1	3.2	17.2	6.25	503	107	395	157.2	2.51	0.140
11:15	20% dextrose, 4.5 ml/min; 1/2 normal Ringer's, 2 ml/min								
11:45 to 11:55, U2	2.8	8.0	6.85	447	55	392	159.6	2.45	0.236
11:55	20 dextrose, 5.5 ml/min; 1/2 normal Ringer's, 1.5 ml/min								
12:25 to 12:35, U3	3.1	8.2	10	508	82	425	163.8	2.6	0.030
12:35	20% dextrose, 6.5 ml/min; 1/2 normal Ringer's, 3.5 ml/min								
1:05 to 1:15, U4	4.54	20.2	11.3	717	228	489	158	3.1	0.118
1:15 to 1:25, U5	4.56	24.6	9.9	721	244	477	158.2	3.0	0.232
							average,	2.73	

[a] BW = body weight.

Table 3. Average clearance values in *a* and *b* studies[a]

Dog No.	C_{Cr}, *ml/min*			Tm_G, *mg/min*		
	Low (*a*)	High (*b*)	Change	Low C_{Cr} (*a*)	High C_{Cr} (*b*)	Change
52	70.7±2.15	94.4±4.18	+38%	189.8±20.5	268.1±15.1	+33.8%
53	89.1±2.77	138.2±2.06	+55%	253.8±25.0	334±66.7	+31%
305	88.5±2.80	158	+79%	199.5±20.2	483	+114%
740	93.7±4.04	195.4±4.62	+108%	270±10.3	574.2±62.7	+112%
average			+70%			+72.8%

[a] Only collections in which plasma glucose concentration exceeded 3.5 mg/ml are included.

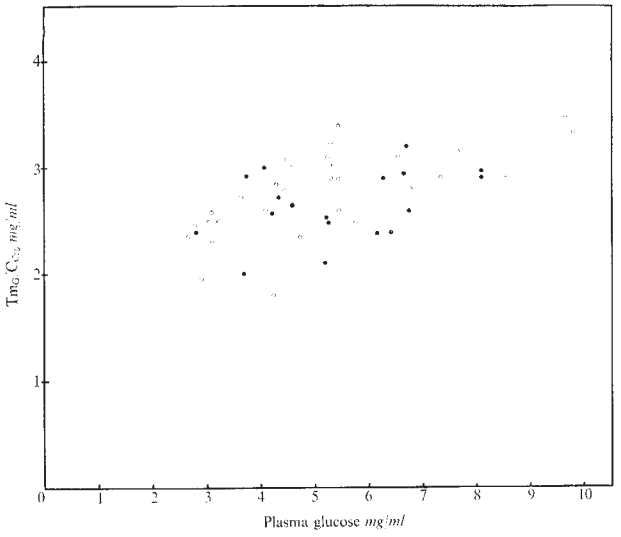

Fig. 1. *Relationship between plasma glucose concentration and glucose reabsorption (T_G) in ten experiments in four dogs.* Glucose reabsorption is factored by the simultaneous creatinine clearance. *Closed circles* represent findings of low GFR (four studies); *open circles* represent findings of high GFR (six studies).

this concentration of plasma glucose, the regression line for the lower GFR studies, calculated by the method of least squares, is $y=2.2+0.084\times(\pm 0.29)$, a slope not significantly different from 0 ($P>0.1$). The regression line for the high GFR data is $y=2.2+0.113\times(\pm 0.32)$, a slope which is not significantly different from the low GFR slope [9]. Creatinine clearance was constant in each of the studies and did not tend to fall as plasma glucose concentration rose.

Comparing the *a* studies to *b* studies: creatinine clearance in the *a* studies averaged 3.6 ml/min/kg and Tm_G divided by C_{Cr} averaged 2.68 mg/ml. In the *b* studies creatinine clearance averaged 6.2 ml/min/kg and mean $Tm_G/C_{Cr}=2.69$ mg/ml, indicating a proportional change in Tm_G and GFR. During the *c* studies the increases in creatinine clearance were less impressive; creatinine clearance averaged 5.1 ml/min/kg of body weight, whereas $Tm_G/C_{Cr}=2.96$ mg/ml. Thus, the addition of bovine growth hormone in these experiments did nothing to augment the increase in GFR already achieved by glucocorticoids and high protein feeding; indeed, it appeared that bovine growth hormone may have had a negative effect in this regard.

Sodium and water balance was always slightly negative at the end of each experiment and was similar in high and low GFR studies. Sodium balance approximated −20 to −40 mEq, in spite of infusion with half-normal Ringer's solution. Water balance ranged between +15 and −230 ml. In *a* studies, $U_{Na}V$ averaged 211 mEq/min (range, 112 to 311), representing 2% of the filtered load. In *b* studies, $U_{Na}V$ averaged 163 mEq/min (range, 129 to 202), which was 1% of the filtered load. In two *c* studies, $U_{Na}V$ was 157 and 141 mEq/min, which represented 1% of the filtered load in each.

Clearances of ^{125}I-iothalamate were always less than simultaneous creatinine clearances; the fractional increases in GFR during the *b* studies when estimated in this manner were similar in two dogs, and less in two dogs. During *a* studies, C_{Ioth} averaged 3.05 ml/min/kg, and during *b* studies it averaged 4.39 ml/min/kg. Average Tm_G/C_{Ioth} in *a* and *b* studies remained constant at 2.12. It can be seen, therefore, that whether the filtered load and the GFR were estimated using exogenous creatinine clearance or iothalamate clearance the average increase in GFR and Tm_G was proportional.

Discussion

This study demonstrates that in dogs without ECF volume expansion, if GFR is increased to supernormal values, there is an increase in the maximum capacity of the tubules to reabsorb glucose. Inasmuch as Tm_G/C_{Cr} remained relatively constant over a wide range of changes in GFR (+38 to +108%), it is appropriate to call this phenomenon some form of glomerulotubular balance. There are a number of different possible explanations for the observed increase in Tm_G.

The first possibility, that during the studies at low GFR a tubular maximum was not reached, is effectively ruled out. Fig. 1 (*closed circles*), shows that over the range of plasma glucose concentrations 3.5 to 8.0 mg/ml, glucose reabsorption did not increase (i.e., the slope of the regression line is not significantly different from 0). These data are consistent with the previous observations that in normally hydrated dogs, glucose reabsorption is essentially constant over a range of plasma glucose concentrations 3.0 to 20.0 mg/ml [6]. Moreover, during the normal (low) GFR studies, at a fractional sodium excretion of 1 to 2%, the average Tm_G of 2.7 mg/ml GFR is comparable to that observed in another recent study [8]. As further evidence that the increase in Tm_G was real, note that in the *b* studies, Tm_G reached values of 500 to 600 mg/min, values which are far greater than those previously reported for dogs of this size [1, 2, 4, 8].

A second possibility is that during the period of time between the *a* and *b* studies, renal hypertrophy or hyperplasia could have occurred. Since during the *a* studies GFR was essentially normal, the increase in GFR and Tm_G during the *b* studies could not represent an increase in the number of functioning nephrons. There is no reason to suppose that either renal hypertrophy or hyperplasia occurred in these animals. Negative nitrogen balance and growth inhibition are the usual consequences of pharmacological doses of glucocorticoids. High protein feeding decreases renal vascular resistance and increases renal blood flow and GFR [10]. This effect is short-lived and it is thought to be a functional change [11].

Based on the original work of Shannon and Fisher [1] widely quoted in physiology textbooks [6, 12, 13], the tubular reabsorption of glucose is likened to an enzymatic reaction. In this analogy, glucose reabsorption is the reaction rate and filtered glucose is the substrate concentration. It has been hypothesized that as the number of molecules of glucose reaching the reabsorptive sites increases, either by increasing plasma glucose concentration or by increasing GFR, the reabsorptive rate of glucose increases until it reaches a maximum. This maximum is presumed to be determined by the number or activity of some energy-requiring carriers present in fixed but limited amounts in or on the tubule cells. The results of the present experiments do not support this hypothesis. However, it is possible that the increased GFR and glucose load might have induced an increase in the activity or in the number of these hypothetical carrier proteins, thus accounting for the increase in Tm_G. Our data neither support nor reject this hypothesis.

Alternatively, the increased glucose reabsorption might be related to the increased reabsorption of sodium and water [14] and secretion of hydrogen ion [15] and *para*-aminohippuric acid (PAH) [16] seen after increases in GFR, if ECF volume is not expanded. This latter form of glomerulotubular balance is probably related to acute and readily reversible changes in the physical forces which regulate transfer of tubule fluid into peritubular capillaries [14]. However, to account for the more rapid expenditure of energy as sodium reabsorption increases, it has been shown that Na-K-ATPase is increased in association with increases in GFR [17].

The apparent relationship between glucose and sodium reabsorption seen in this study is consistent with previous studies that have shown changes in sodium reabsorption induced by ECF volume expansion or contraction are accompanied by changes in glucose reabsorption [5, 7, 8]. The Starling forces which are thought to regulate the reabsorption of sodium in the proximal tubule presumably operate by controlling the movement of water (secondarily of sodium) from the tubule cell into the peritubular capillaries. There is every reason to believe that the reabsorptive rate of other substances dissolved in this water (such as glucose, phosphate and bicarbonate) also would be influenced, thus explaining why the reabsorption of these substances apparently is so closely tied to the reabsorption of sodium [5, 7, 8, 15, 18, 19].

Previously, a close relationship between the Tm_G and GFR has not been demonstrated conclusively. Glomerulotubular balance for glucose reabsorption, as shown by Kurtzman et al in a group of animals of different sizes [8], is to a large extent based upon a structural correlation between the filtering and reabsorbing portions of the nephron. It is not so easy to obtain convincing evidence that in any one animal a marked change in GFR is accompanied by a corresponding and proportional change in Tm_G. In a recent review of this problem, Baines [5] has concluded that such a functional glomerulotubular balance remains unproved.

In 1967 van Liew, Deetjen and Boylan [20] purported to show a relationship between GFR and Tm_G in rats. Their conclusions were based on the observation that in rats given hypertonic glucose but no sodium-containing fluids, Tm_G fell as GFR spontaneously fell to very low levels. Most of the data are clustered at either the range of normal GFR (0.8 to 1.0 ml/min/g of kidney weight), or at approximately 30% of normal, raising the possibility that the proportional fall in Tm_G in these studies was due in large part to the cessation of flow in and collapse of certain nephrons (i.e., glomerular intermittancy). A similar objection can be raised toward some of the other

clearance studies which apparently demonstrated that a fall in Tm_G accompanied a fall in GFR [8, 21].

The several studies [2, 4, 21, 22] that have failed to show a fall in Tm_G with moderate decreases in GFR are likewise difficult to interpret, since in many of the subjects hydropenia, dehydration and hemorrhage or congestive heart failure accompanied or were responsible for the fall in GFR. Since the recent demonstration that ECF volume and sodium excretion are important determinants of Tm_G [5, 7, 8], it should be apparent that in the older studies, whereas glucose reabsorption may have been diminished by decreases in GFR, it may have been simultaneously stimulated by the decreases in ECF volume and sodium retention [2, 4, 21, 22]. In such experiments it might have been very difficult to detect significant changes in Tm_G.

We chose to study the phenomenon of glomerulotubular balance for glucose by raising GFR to supernormal levels. Clearance studies by others which have shown small or negligible increases in Tm_G with GFR have accomplished the increase in GFR by saline loading [4, 5]. Again the possibility exists that changes in ECF volume may have masked the change in Tm_G with GFR. Recently, Schultze and Berger have shown less than proportional increases in Tm_G relative to increases in GFR after saline loading [23].

In a recent study, Deetjen and Boylan [24] showed that in microperfused proximal tubules, glucose reabsorption varied with perfusion rate. However, these data are probably not pertinent to the phenomenon of individual nephron Tm_G, since glucose reabsorptive capacity of the individual nephrons apparently was undersaturated. The methodologic and technical difficulties with this study [24] cast some doubt on the validity of their data and conclusions [5, 25]. A very recent *in vitro* study by Tune and Burg [25] in isolated rabbit tubules showed that there was a transport maximum for glucose in the proximal tubule that was independent of perfusion rate. These results, however, do not rule out the possibility that in the *in situ* proximal tubule with intact peritubular capillary circulation there is glomerulotubular balance for glucose reabsorption similar to that seen for sodium and water reabsorption.

It is not certain what effect, if any, bovine growth hormone had in these experiments. This agent was originally used in an attempt to further increase GFR above levels achieved by glucocorticoids and high protein diet. Used alone it has been shown to modestly increase GFR over an eight-day period, with less or little change in Tm_G [26]. However, it is possible that the species difference prevented or attenuated the action by growth hormone more acutely in the dog. The lesser increase in GFR could be attributed to a negative influence of the growth hormone; alternatively, since these experiments were the third clearance experiments for these two dogs, it is possible that factors related to repeated anesthesia and venipuncture were more important.

It is difficult to decide which of the methods in the present study used for estimating GFR was most correct. It should be noted that the values for C_{Cr} (ml/min/kg of body weight), at least in the control state (*a* studies), seem closest to those expected for fasted dogs. We clearly showed that glucose in high concentrations did not interfere with the analysis of creatinine, and that plasma concentrations and C_{Cr} were stable in each experiment. Although the increases in C_{Cr} in the *b* and *c* studies were large, they are comparable to those shown by us and others previously [11, 15].

It is not clear why iothalamate was apparently an inaccurate marker of GFR in glucose-loaded dogs. In dogs which were not glucose-loaded, it has been shown by others [27] and by us that iothalamate and inulin clearances are nearly identical. However, in glucose-loaded dogs iothalamate consistently gave estimates of GFR that were appreciably lower than one would anticipate for the state of hydration. Nevertheless, even if one assumes that the true GFR was somewhere between iothalamate and the creatinine clearances, it is clear that using either method for the estimation of GFR, Tm_G increased proportionally with GFR.

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