formed simultaneously and not sequentially, due to the fact that physiologic variations and circadian rhythms of the renal function substantially influence the results (*5,6*). Since clearances should be determined during steady-state or at least be calculated according to the same model, the regression coefficients indicated by Müller-Suur et al. (*1*) concerning the relation of the $^{99m}$Tc-$MAG_3$ clearance to the OIH clearance cannot be considered to be representative. Another requirement in this context should have been the precise determination of the radiochemical purity of the agent by HPLC.

Müller-Suur et al. presumed that the clearance of $^{99m}$Tc-$MAG_3$ was lower than that of OIH, due to a lower gomerularly filtered portion and a lower renal secretory transport capacity of $^{99m}$Tc-$MAG_3$. The filtration fraction of the human kidney, which amounts to 20%, only considers the "free" (i.e. the non-protein-bound) fraction in the plasma. Therefore, only 6% of OIH (protein binding ~ 70%) and 2% of $^{99m}$Tc-$MAG_3$ (protein binding 90%) are eliminated by glomerular filtration (*2,3,7*), which implies that the differences are insignificant. As opposed to the statement by Müller-Suur et al. (*1*) asserting that other authors have observed a lower secretory transport capacity of $^{99m}$Tc-$MAG_3$ as compared to OIH, these reports, and particularly the paper published by our group (*8*) and quoted by Müller-Suur, deal with studies regarding the affinity of the respective radiopharmaceuticals to the tubular transport system. The maximum transport capacity of the tubular cell (Tm) represents a totally different parameter which, until now, has not been determined for $^{99m}$Tc-$MAG_3$ due to the fact that no technetium isotope is available for in vivo application in amounts of several grams. We assume that the higher plasma protein binding of $^{99m}$Tc-$MAG_3$ is the main reason for the lower clearance of this agent, as compared with OIH, because the peritubular transit time is too short for complete dissociation of $^{99m}$Tc-$MAG_3$ from the plasma protein so as to be available for the active tubular transport (*2,3*).

Furthermore, Müller-Suur et al. state that it has been reported that the "whole-blood clearance for $MAG_3$ was found to be the same or even higher (*7,9*) than that for hippurate." This is incorrect: Coveney and Robbins (*9*) performed their studies in rats, which have a different binding to plasma proteins and to red blood cells (RBCs) than humans, and Taylor et al. (*7*) obtained results in their sequential study, which were based on an error, later discovered by the authors, concerning decay corrections (*10*). According to our results (*2,3*), the relation between the whole-blood clearances of $^{99m}$Tc-$MAG_3$ and OIH is higher than the relation between the respective plasma clearances by a factor which can be calculated precisely, taking into account the different fraction of these radiopharmaceuticals bound to RBCs (*3*). This can be explained by the fact that the RBC-bound fractions do not participate in the process of tubular secretion because the diffusion of these agents out of the RBCs into the plasma is very slow (*11*).

For comparative clearance determination of kit-prepared $^{99m}$Tc-$MAG_3$ and OIH, it is indispensable that preparations with an exact radiochemical definition be used, namely in simultaneous studies. Measurements carried out under steady-state conditions are preferable, however, the minimum requirement using a slope technique is that the clearance calculation be done according to the same model.

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**REPLY:** The subject of our article (*1*) deals with the evaluation of kit prepared $MAG_3$ used for dynamic renal scintigraphy in patients in comparison with our reference substance $^{123}$I-hippurate, and it was not a detailed study of the mechanism of the renal clearance of $MAG_3$. For that particular purpose, we have performed different studies published elsewhere (*2–4*), as pointed out in our discussion.

Our study was a combined study of renal scintigraphy and clearance measurements. A gamma camera cannot distinguish between $^{123}$I and $^{99m}$Tc. Therefore, we had to make the examinations on different days. From a clinical point of view, stable kidney function existed between the two studies. Simultaneous constant infusion, clearance studies using both $^{125}$I-hippurate, $^{51}$Cr-EDTA, and $^{99m}$Tc-$MAG_3$ have been used in our earlier experimental studies in rats with results similar to those obtained in our patients and also similar to those published by other authors (*5–8*).

Our comparative scintigraphic study (*1*) was based on 17 patients. In a separate paper published recently in the *European Journal of Nuclear Medicine* (*4*), we focused only on the clearance of $MAG_3$ and expanded the number of patients and got substantially the same results. These are also in accordance with results of other authors (*5–8*). Thus, our results seem to be representative. In this context, we want to point out that from an ethical point of view we think it is important to restrict the number of double radionuclide studies to the lowest acceptable level. Our ethical and regional isotope committee uses this restrictive policy.

Bubeck and Brandau's argument that "the clearance values

were performed during slope with the aid of totally different methods" is an exaggeration. For both $^{123}$I-hippurate and for $MAG_3$ the single-injection plasma clearance method was used. For $^{123}$I-hippurate, the one-sample method according to Tauxe (*9*) was used. For $MAG_3$, the conventional multi-sample method was used. Tauxe's method has been documented extensively, correlates well to the multi-sample technique, and is our routine method for $^{123}$I-hippurate.

The radiochemical purity of our $MAG_3$ kit is specified by the manufacturer to be better than 95% (*10*), and our own measurements using HPLC in 10 preparations showed 97.9% ± 0.9%. These measurements were published in our paper on clearance investigations (*4*). Our papers (*1,4*) deal with the evaluation of a commercial $MAG_3$ kit. It is clear that for clinical routine use it is not practical to use HPLC-purified $MAG_3$ as Bubeck et al. (*6*) did in their study.

In our discussion of the renal handling of $MAG_3$, we refer to our earlier studies using the same kit (*2,3*). In these studies, we used both constant infusion and micropuncture technique on glomerular and different nephron levels. We could show, that both the tubular secretion and the glomerular filtration of $MAG_3$ were significantly lower than that of $^{125}$I-hippurate. This is in contradiction to Bubeck and Brandau's assumption that due to high protein binding the filtration of both $MAG_3$ and hippurate is "low" which implies the differences to be *insignificant* without any experimental and statistical support. Tubular secretion rate of $MAG_3$ also has been measured in our micropuncture study (*3*). In our discussion (*1*), we refer to these results. We refer also to other results (*6*), e.g., the lower affinity to the tubular transport system as one possible cause for the decrease in tubular secretion.

Concerning our discussion about whole blood-clearance values in the literature, we wanted to point out in our paper that such measurements do not give sufficient information about the renal handling. The reason is that both blood cell content and the penetration process are included in blood clearances. Since these two parameters are significantly different for $MAG_3$ and hippurate, as shown in our earlier study (*2*), it is improper to use those values to characterize the renal handling of $MAG_3$. Bubeck and Brandau claim that the "relation between whole blood clearance of $MAG_3$ and OIH is higher than the relation between the respective plasma clearance by a factor which can be calculated precisely." This statement is correct, but we do not understand why one should measure this factor precisely (i.e., blood cell activity and plasma activity) in order to determine renal clearance. Blood clearances alone are not, as we and others outline, sufficient for that purpose.

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## Prevention of Metoclopramide-Induced Akathisia During Gastric Emptying Imaging.

**TO THE EDITOR:** During radionuclide gastric emptying (RGE) studies, we sometimes administer the drug metoclopramide (MCP) to hasten gastric emptying in those patients having prolongation of gastric emptying half-time to reveal function or presence of gastric outlet obstruction (*1*). We also have found intervention with MCP to be of considerable value in prediction of its therapeutic efficacy in patients with diabetic gastroparesis (*1*), anorexia nervosa (*2*), or bulimia (*3*). One of us (RWB) has noted akathisia, or motor restlessness, in certain patients receiving the drug at his institution. The response is characterized by an inability of the patient to lie still and the inner need to arise and depart from the imaging bed after injection of MCP. In our experience, older male patients (over age 34 yr) are resistant to akathisia; while females of all ages and younger males are more susceptible. The response occurs after intravenous injection of 10 mg MCP as a bolus over 2–3 min. The onset of restlessness is fairly rapid and usually occurs within 10 min after administration. It has caused premature termination of the imaging study on several occasions. A prospective study at one or our institutions (RMH) over a 7-mo period revealed four akathisic episodes in 20 female patients (20%) and one episode in six male patients (17%).

Akathisia is an important adverse effect of drugs like MCP or antipsychotic medications having dopamine receptor-antagonist activity (*4*). In volunteers, akathisia is described as very common after intravenous MCP but not after oral dosing (*5*).

Management of akathisia is possible. Ratey and Salzman (*6*) report that reduction of dose or elimination of the neuroleptic (antipsychotic) drug is the only truly effective method. However, they found that the beta blockers propranolol and nadolol are somewhat effective. However, the effect of such drugs on RGE is unknown.

Over a decade ago, Bateman et al. (*5*) reported that in normal males receiving oral MCP, akathisia occurred only in subjects who had peak plasma concentrations of drug above 100 ng/ml. That suggested that we should slow the rate of MCP injection. Accordingly, 10 mg of MCP are now added to 50 ml physiologic saline in a flexible bag; the resulting dilution is then infused into the patient intravenously at a rate of 60 drops per min through a heparin lock. To evaluate efficacy of that new dosing technique,