

## Estimating Glomerular Filtration Rate in Children

**TO THE EDITOR:** We read with interest the letter to the editor by Fleming and Waller (1). We regret that we were not presented the opportunity to reply earlier. We believe that the publication of a letter and a reply in two different issues does not best serve the interest of the readers.

We take note of Fleming and Waller's "paternity claim" of the concept of a universal method for both adults and children. After carefully reviewing their original article (2), we still believe that this concept was first described by Bubeck et al. (3) and Bubeck (4). Moreover, we maintain that the concept of a "single-sample adult method using prescaled plasma sample" has not been validated for glomerular agents. Because the article by Waller et al. (2) was published in the widely available *The Journal of Nuclear Medicine*, the nuclear medicine community can make its own judgment concerning this claim.

Our study (5) was undertaken to verify the concept that any validated single-sample adult method can be used in children provided the plasma sample was prescaled. We selected three well-known adult methods (6-8), including the one recommended by the Consensus Committee of Radionuclides in Nephrourology (9). The results indicated that the single-sample adult method using prescaled plasma concentration had a lower accuracy than the specific pediatric single-sample method.

In our article, we did not say that there was no method that can be used in both adults and children. Such a method does exist, but its performance is usually slightly inferior to specifically designed adult or pediatric methods. The data in the literature (6-8), including those of Waller et al. (2), show that for a glomerular agent, the optimal time for a single-sample technique in adults is approximately 240 min. A slight decrease in accuracy occurs when a 180-min sample is used. In children, the optimal time is between 90 and 120 min (10). The 180-min sample can also be used if a slightly lower accuracy is accepted (1). Fleming and Waller wrote that their 180-min single-sample method worked well in both adults and children. However, they have not demonstrated that the accuracy of their method was superior or equal to a specifically designed adult or pediatric method.

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Hamprey R. Ham  
Amnon Piepsz  
Saint-Pierre Hospital  
Brussels, Belgium

## Physical and Chemical Nature of Technegas

**TO THE EDITOR:** The article by Senden et al. (1) concerning the physical and chemical nature of technegas implies that the carbon coating of technetium metal particles is chiefly responsible for the extended retention time of this agent in the lungs. This conclusion was reached using the results from microscopic and thermogravimetric analysis.

We would like to draw readers' attention to two articles that preceded the article by Senden et al. in which microscopic techniques were also used in the analysis of technegas particles (2,3). Although the high-resolution transmission electron microscope (HRTEM) study of technegas and pertechnegas particles by Isawa et al. (2) has drawn some criticism (4), it still represents the first study of high-resolution imaging of carbon particulates collected by impaction/deposition in which the most notable result was the identification of two distinct types of metal-containing carbon particles differentiated by the size of the associated metal phase. The carbon particles containing smaller metal phases bear a striking resemblance to those detected by Jackson et al. (3) using scanning TEM (STEM). On the basis of the HRTEM images alone, Isawa et al. (2) proposed that the metal was encapsulated by the associated graphite.

X-ray photoelectron spectroscopic (XPS) results for the analysis of technegas particulates and the crucible residue containing technetium are presented by Jackson et al. (3), along with results from a STEM investigation. Radiographic fluorescence indicated that oxygen was associated with the metal in the particles analyzed. This result agreed with the XPS measurements, for which the chemical shift of <sup>99m</sup>Tc could only be rationalized by an oxygen association. The XPS result for the crucible residue confirmed that the high temperature of the graphite during the crucible burn is sufficient to reduce some of the technetium to either the pure metal or the metal carbide. In view of this result, Senden et al. (1) confirm previously published spectroscopic results.

Isawa et al. (2) and Jackson et al. (3) cast doubt on the assertions that one particular type of technegas particle, that is, pure metal wrapped in graphite, is solely responsible for the properties of this agent. A review of the literature concerning the mechanisms and types of metal crystallites encapsulated by carbon revealed an article by Seraphin et al. (5) in which metal oxide particles were encapsulated by graphite at much higher temperatures (3500°K) than those used to generate technegas. More recent articles by Dai et al. (6) and Guo et al. (7) suggest that midtransition-row metals, particularly those adjacent to technetium in the periodic table, may act as templates for the growth of both amorphous and ordered carbon phases. These studies establish a link between the size of the metal particle and the nature of the associated carbon particle in which smaller metal crystallites, approximately 5 nm, act as templates for the growth of carbon phases from one face of the particle, whereas metal crystallites 50 nm or larger were found to be exclusively encapsulated. The very presence of metal crystallites, on the order of a few nanometers, associated with carbon in all three electron microscope investigations (1-3) infers that conclusions based on analysis of the results for larger metal crystallites alone are invalid.

Senden et al. (1) assert that carbon encapsulation of the radionuclide is critical for passivation of the metal, yet direct evidence that refutes such a claim is found in the article by Pillai et al. (8), who used a <sup>99m</sup>Tc-labeled iron oxide colloid and achieved a lung clearance rate in canines similar to that of technegas. Hydrated TcO<sub>2</sub>, that is TcO<sub>2</sub>.nH<sub>2</sub>O, is also colloidal and would be expected to behave in a fashion similar to the <sup>99m</sup>Tc-labeled iron oxide colloid. The chemical shift observed in the XPS analysis of technegas supports this hypothesis (3).

We are also concerned about the possibilities for particle modification by the electrostatic precipitation method used to collect the samples for atomic force microscopy (AFM) study (1). We believe it is possible that

entrainment of the aerosol onto a static surface may result in the deposition of a carbon film over any precipitated metal particles already on the collection surface. When the holey carbon grids used in the STEM study (3) were positioned just above and facing the crucible, vaporized graphite was observed to completely cover any "holes" in carbon film. This phenomenon may give the false impression that the metal phase was indeed encapsulated and was not adequately addressed in the discussion of the AFM and TEM results (1).

The similarity in the initial pulmonary distributions of both pertechnegas and technegas is perhaps one of the keys to understanding the behavior of these agents. For such similar initial pulmonary distributions, it is likely that either a particle common to both aerosols is in the transport medium or that the technetium-containing phases generated under argon and argon plus 3% oxygen are equivalent, at least in size, because it is this property that determines the fraction of the agent deposited in the alveoli (9).

The introduction of 3% oxygen into the argon stream results in the oxidation/elimination of potential carbon-based carrier particles in pertechnegas (10). Similarities with pertechnegas were noted in ventilation studies using vaporized pertechnetate, in which carbon was excluded from the aerosol-generation procedure (11). The technetium-containing components of pertechnegas have also been analyzed using electron ionization Fourier transform mass spectrometry and XPS (10). The findings agreed with the proposal that this agent is merely vaporized pertechnetate with some carbon particles, carbon oxide gases, argon, oxygen, water and salt.

Lloyd et al. (12) have previously implicated salt particles, present in both agents, in the transport of the radionuclide-containing phases of both agents. Lung retention is then determined by the relative solubilities of the respective technetium phases in the lung surfactant layer. Technetium (VII) oxides, such as those found in pertechnegas, are hygroscopic, whereas  $^{99m}\text{TcO}_2 \cdot n\text{H}_2\text{O}$  [a Tc(IV)-oxide that could have been responsible for the XPS spectrum in (3)],  $^{99m}\text{Tc}$  and  $^{99m}\text{TcC}$ , the potential radionuclide phases of technegas, are all insoluble. A carbon coating would also render a metal phase insoluble.

If salt particles are indeed the transport medium of both agents, it appears that the discovery of technegas was serendipitous, and an agent may not have been developed in the absence of physiological saline from the  $\text{Na}^{99m}\text{TcO}_4$  generator eluant. In summary, technegas is successful as a result of the generation of insoluble (colloidal) technetium-containing phases, which then label the microcrystalline salt particles that are vaporized at lower crucible temperatures (10).

The plethora of molecular and colloidal carbon species present in the technegas aerosol (13) suggest other possibilities such as exohedrally labeled carbon clusters, or a metalcarbahedrene, such as  $^{99m}\text{Tc}_x\text{C}_y$ , might also label microcrystalline salt, giving rise to technegaslike behavior, although exohedrally labeled carbon clusters are considerably more labile than their endohedral counterparts and may not survive in the presence of moisture and oxygen. In our judgment, there is insufficient evidence to preclude these possibilities.

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**Phillip Jackson**

University of New South Wales  
Sydney, Australia

**Douglas Mackey**

**Hans Van der Wall**

Concord Repatriation Hospital  
Concord, Australia

**REPLY:** The comments by Jackson et al. cloud the issue of encapsulation by carbon considerably, particularly with respect to the technegas application. Our proposition (1) is that the major radiotracer species in technegas is a nanometric-sized crystal of technetium metal encapsulated by layers of graphitic carbon. This model is based on the determination of reaction products between the crucible and pertechnetate and structural information determined from electron microscopy.

In their letter, Jackson et al. state two main objections: the chemical state and the overall physical structure of the technegas particle. Their objections to the chemical state are concerned with the oxidation state of the technetium, and their objections relating to the physical structure pertain to the degree of encapsulation of the host technetium. Because the degree of encapsulation has relevance to the chemical stability of the technetium, we will address that issue first.

Jackson et al. first make the comparison with other carbon-encapsulated systems (2-4) in an attempt to illustrate that technetium is unlikely to be completely covered by carbon. None of the works cited bear any similarity in method to that of the technegas procedure. Intense electric fields used by Seraphin et al. (2) preclude comparison from the start. Moreover, they worked exclusively with two metals that form stable carbides, unlike technetium, in which the carbide decomposes in the vapor phase. The work of Seraphin et al. explicitly deals with encapsulated carbides and not oxides as incorrectly stated by Jackson et al. Similarly, Dai et al. (3) and Guo et al. (4) investigated only stable carbide-forming metals. The three cited methods, arc discharge (2), metal-catalyzed disproportionation of carbon monoxide (3) and laser ablation (4), could not be further from the standard method used in technegas production. In two of these studies (2,4), temperatures exceeded 4000°C and ionization became an important mechanism in particle growth and morphology, particularly for the method in which intense electric fields dominated plasma interactions (2). At the temperature of the technegas crucible, 2550°C, only neutral species exist in the gas phase, and resistive heating produces no electric field effects in the plume region. Metal-catalyzed disproportionation of carbon monoxide (3) is chemically so specific that comparison between this process and the technegas method is completely inappropriate. However, the central argument of Jackson et al., that encapsulation depends on particle size, is extended from observation in references (3,4). Unfortunately, these articles deal with the highly specific process of single-walled nanotube formation and not with encapsulates in general. Our proposal that encapsulation proceeds independently of particle size is based on simple surface thermodynamics. That is, the high-energy surface of a freshly formed metal condensate will be lowered by the adsorption of carbon. Where the metal cannot react with the carbon the two phases will stay separate and the carbon will form a "skin" around the metal crystallite. Conversely, the stable carbide-forming metals associate with carbon according to the phase diagram for carbon and the metal in study. The general encapsulation effect for the noncarbide-forming metals also was demonstrated in our article (1)