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 $^{99m}TcO_2.nH_2O$ [a Tc(IV)-oxide that could have been responsible for the XPS spectrum in (*3*)], ^{99m}Tc and ^{99m}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 $Na^{99m}TcO_4$ 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 metallocarbahedrene, such as $^{99m}Tc_xC_y$, 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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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*)

for rhenium, and we will soon submit a study including gold, mercury, zinc, magnesium and thallium, all noncarbide-forming metals and all demonstrating this effect. If particle size did dictate the degree of encapsulation, then we can reasonably expect these chemically very different metals could show different results also. We assert that the degree of encapsulation for the noncarbide-forming metals is dependent only on the amount of available carbon in the vapor phase. We also have demonstrated that epitaxy is not critical, as liquid mercury can be encapsulated.

Jackson et al. propose that the method of collection via electrostatic precipitation might lead to excessively carbon-covered samples. Several observations contradict this (*1*). First, carbon does not go through a liquid phase at atmospheric pressure. Thus, the condensation of the gas-phase species, mostly C_3 species, onto a cool substrate does not permit rearrangement. Thus, amorphous and very porous carbon results. The sublimation of the crucible's graphite is a continuous process, so as a substrate approaches the temperature of the crucible the condensed material can revaporize or the deposited graphitic carbon can sinter and anneal out its defects in solid-state processes (Ostwald ripening). We did consider the practicalities of placing a substrate inside the chamber and rejected it for two main reasons: (1) we wished to sample the same material as inhaled by patients, and (2) we wanted to ensure that all oligomeric species of carbon produced had had a chance to collide in the gas phase to the extent that only chemically stable aggregates remained. This strategy avoids the complications of nonspecific coating of carbon on substrates to a larger degree than the method reported by Jackson et al. (*5*). For these reasons, we chose to trap the cold and chemically equilibrated output, not the hot, reactive plume directly from the crucible. The decision to collect the reactive plume directly may account for the apparent observation of a TcC-rich phase in the work of Jackson et al. (*5*). Our aim was to identify what the patients were inhaling, not to look at the kinetic deposition of reactive species. Any method for trapping dispersed particles must tend to orient them onto a surface, covering particles with successive layers of particles. However, ballistic aggregation by its very nature does not yield a dense, impermeable film. This film would easily allow oxygen to permeate. Thus, if the technetium metal particles had not been coated by the time they left the argon atmosphere then they would have surely reacted with the air. To this date, some 2 yr after production and after storage under ambient conditions, our samples are unchanged from their initial metallic state.

The proposition that hydrated TcO_2 is colloidal and therefore similar to iron oxide colloids is completely misleading. It is true that if the two materials can be dispersed as submicron-size particles in water they will form a "colloidal solution." However, colloidal stability in these systems depends largely on the dissociated surface charge and therefore the chemical identity of the surface groups. No data to our knowledge exists on the electrophoretic mobility of TcO_2 colloids. Iron oxides are peculiar colloidal systems (*6*). Unlike the greater number of metal oxide colloids, they typically bear a positive charge. This would explain why the ^{99m}Tc-labeled iron oxide "colloids" of Pillai et al. (*7*) adsorb the TcO_4^- anion. A point to note is the colloids of Pillai et al. (5–10 μm) are 100 to 1000 times larger than the average technegas particle and on the very limit of being colloidal. Furthermore, on pure clinical grounds the labeled iron oxide "colloid" and technegas systems do not bear comparison. Pillai et al. reported that the retention of the iron oxide colloids was 75% and 72% after 24 hr in beagles, very different from the 97%+ retention measured for technegas over the same period in humans.

Jackson et al. have relied on the misleading analogy between the "colloids" of Pillai et al. and hydrated TcO_2 in asserting that technegas is comprised of oxide species (*5*). Trace quantities of oxygen in their system might equally explain their initial observation. The fact that we do not see any evidence of oxides in our system when all other operating parameters are the same would suggest that we have excluded all traces of oxygen.

The chemical scenario advanced by Jackson et al. is bizarre. Pillai et al. bind the anion, technetium in its most *oxidized* form, to a cationic "colloid." There is no chemical potential for the Tc(VII) to oxidize further, and thus it is "passive." Technetium metal, however, is in its most *oxidizable* form, and in the form of small particles makes it an extremely reactive phase. Indeed, like most finely divided metals, technetium is pyrophoric. This is why technetium metal must be protected from oxygen and yet the pertechnetate anion can exist stably in sterile saline in contact with air. They make this even more confusing when they state that technetium metal is "insoluble." If finely divided technetium were not as reactive, then it may well be dispersible in water. Indeed, some more inert metals form very stable colloids in this size range, namely gold colloid. Similarly, nanometric colloidal carbon forms the basis of most black inks and is a chemically inert dispersion. We conclude that a carbon-encapsulated metallic colloid is not only stable chemically, but also dispersible.

Jackson et al. state that as the pulmonary distributions of technegas and pertechnegas are similar then it follows that the two tracers have similar particle size, or at least are carried by a common particle (i.e., NaCl, see below). The fractal structure of the lung, in combination with the low spatial resolution of gamma imaging, completely renders their statement ineffectual. By the 12th division of the bronchial tree, the outer limits of the lung's volume is delineated. The successively smaller divisions, from the 13th to the 23rd, simply fill this volume. With an intrinsic resolution no better than 5 mm, a gamma camera would not be sensitive to differences in particle size.

The suggestion of NaCl particles being implicated in the evolution of the active component of technegas can be easily discounted. For the past 2 yr we have used interchangeably two methods to produce carrier-free technetium-loaded crucibles. The simplest method is to simply heat the crucible to a temperature just above 1413°C, the boiling point of NaCl, and purge the chamber with argon, thus flushing out any particulate NaCl. At this temperature the pertechnetate is also reduced to the free metal and is immobile within the crucible awaiting vaporization (*1*). The other method, to be reported, uses a dry crucible preloaded with a technetium compound at room temperature. Both methods produce an output identical in clinical behavior to the standard technegas output.

The final paragraph of the letter by Jackson et al. is highly speculative: if discrete molecular species such as "metcars" or exohedrally metallated carbon clusters exist, then surely their mass spectroscopic technique would already have provided direct evidence for them. As the authors themselves concede, such species are less likely to survive in air than their endohedral counterparts.

Based on both our initial study (*1*) and our more recent work on other metals, we still propose to model the technegas process with fundamental chemistry and physics. Simple reduction of a metal oxide in the presence of carbon, carbon sublimation, followed by cocondensation of two immiscible phases in a way that minimizes the overall surface energy, can produce a chemically inert, composite particle. None of these steps are revolutionary or new but, in combination, can form a unique encapsulated radiotracer.

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Interactive Compartmental Modeling

TO THE EDITOR: Burger and Buck (*1*) emphasize that their interactive compartmental modeling software package is a highly versatile tool for the analysis of time-activity curves from clinical PET and SPECT studies. They conclude that its main features are easy model configuration, evaluation and use after a short training session (*1*).

Mathematical models in nuclear medicine literature appear to be rather plain and straightforward (*1–4*), though they are not necessarily so simple (*5–8*). Relevant description of organ function in complex biological structures is difficult, particularly because the complexity is both geometrical and temporofunctional and data are based on external measurement of radioactivity distribution in space and time (*5,8*). Also, classical medical training often has not prepared physicians to use mathematical models properly, although image resolution (spatial and temporal), reconstruction errors, signal-to-noise ratio and other quantitation inaccuracies are well understood. Nuclear medicine physicians who begin to use quantitative models and software packages for describing and interpreting their data on tracer kinetics in situ, however, often find it difficult to get started. Here, I would like to emphasize that the suitable approach is often not to start with the direct formulation of the equations as suggested by Burger and Buck (*1*), but with (a) thorough consideration of the in vivo reactions during the study and (b) deep analysis of the basic and fundamental assumptions of the model.

Often the principal questions are the following:

- What is the reaction of interest (perfusion or metabolism or both) under study?
- How is this reaction related to local structure? (In most instances, structure and function are intimately inter-related because tracers distribute according to their substrate nature and to the anatomic distribution of the system features.)
- Do local functions affect global input?
- To what degree does fundamental nonlinearity of the systems exist?
- Are measured features common to all individuals and under all pathophysiological conditions?

It is most essential to make "correct" assumptions that are based wherever possible on previous physiological and anatomical observations. The biochemical fate of tracers has to be known completely. In addition, no fundamental chemical and physical laws can be broken. Only by thoroughly combining data from a particular nuclear medicine procedure with actual structure and function of the system under the study can a logical model be composed.

Next, there are several basic and fundamental assumptions underlying the compartmental model:

- The system is mathematically linear.
- Each compartment is wholly and instantaneously mixed so that the concentration within it is uniform at all times.
- The system is in a steady state with respect to mother substance (tracee) so that tracer exchange rates are first order.
- The volumes and exchange rates between compartments are constant.

The main problem with the compartmental, stirred tank model is its failure to meet the second condition. For example, it is obvious that the plasma is not an instantaneously mixed compartment although this is commonly assumed. A further condition is therefore appropriate: Time required for complete mixing in a volume (compartment) is very short compared to the time constant of the fastest exchange process. These are very restrictive assumptions. For example, the arteriovenous (A-V) difference of glucose across most organs is small (only a few percent). However, a steady-state A-V difference for the nontracer mother substance is not critical here, but it is the first-pass, instantaneous extraction of the tracer that counts (*8*). The first-pass extraction of fluorodeoxyglucose (FDG) is about 50%, a huge gradient, and so the estimates of the transfer rate constants (k_{ij}) by compartmental models tend to be too high, sometimes by a factor of 2 to 4 (*8*). Even in the brain, where the capillary network is a well-ordered, highly tortuous stereoscopic arrangement of capillaries (a well-mixed compartment), there is a relevant concentration gradient for the slowly diffusible tracers (such as FDG) that destroys the validity of the compartmental model, which assumes that each compartment is wholly and instantaneously mixed so that the concentration within it is uniform at all times.

Applied software packages are an essential part of the imaging system to analyze the data to provide clinically and scientifically relevant information. In particular, in-house programming, which certainly represents the developing edge of nuclear medicine, usually lacks proper quality assurance and testing (*9*). In short, with thorough consideration of the in vivo reactions during the study (under normal or pathophysiological conditions) and with the valid assumptions and testing of the model, the proposed software package (*1*) can be used to add diagnostic or scientific value to the nuclear medicine procedure.

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Is It Time for a Change?

TO THE EDITOR: I read with interest Dr. Henry N. Wagner's recent letter to the editor concerning merging the Society of Nuclear Medicine (SNM) and the American College of Nuclear Physicians (ACNP) (*1*). Dr. Wagner is a respected member of our community, and any time he voices an opinion we should give it due consideration. However, in terms of the material presented to support Dr. Wagner's point of view, there are a few confounding issues.

The American Society of Internal Medicine and the American College of Physicians are two organizations that permit only physicians to be members. To the best of my knowledge, they do not represent technologists, basic scientists or other medical professionals.