# Liposomes and Vesicles: A New Class of Radiopharmaceuticals?

For the past several years liposomes and vesicles have been employed as models for research on biologic membranes. Currently, they are being evaluated as carriers of radioactivity with the expectation that in this role they may serve as a new class of radiopharmaceuticals. In this issue of the *Journal of Nuclear Medicine*, two articles report current efforts towards this goal (*1,2*).

A liposome is a colloidal droplet (also termed a spherule or a micelle) in which a bimolecular layer of fat and fat-soluble substances surrounds one or more aqueous inner droplets, diagrammatically illustrated in Fig. 1A. A liposome may contain several layers of oil and water phases, which give it an onion-like character. A vesicle, the most elemental of liposomes, is composed of simple lipid bilayers which enclose a single aqueous-phase microdroplet (Fig. 1B).

At least two general methods exist for tagging these lipid micelles with radioactivity. The micelles may be prepared in the presence of a labeled water-soluble substance, such as diethylenetriaminepentaacetic acid tagged with technetium-99m ($^{99m}$Tc-DTPA), and the enclosed aqueous phase will contain the radiolabel. This method has been used by Caride et al. (*1*). Alternatively, the micelles may be prepared with a radiolabeled molecule that is incorporated into the lipid bilayer, the method of Dunnick et al. (*2*). The first method is inherently inefficient since the percent labeling is equal to the percentage of the aqueous phase incorporated into the liposomes. Caride et al. (*1*) achieved 14% labeling, which is probably close to maximum. The advantage of this method, however, is that almost any aqueous solution can be used as a label. Since such compounds as $^{99m}$Tc-DTPA are inexpensive and easy to prepare, the low labeling efficiency is not an important limitation. On the other hand, the second method offers the possibility of approaching 100% labeling efficiency but restricts the labeling to those substances that can be incorporated into the lipid layer.

The concept of the radiopharmaceutical design is to produce bifunctional substances. One end of the substance would have a specific biochemical property which would be the functional group of a hormone or hormone receptor, an antibody or antigen, or an enzyme poison (a substance which irreversibly couples with a specific enzyme). On the other end of the substance there would be a site for attaching the radioactive label. Ideally, the two functions, biochemical specificity and radioactive tagging, would not interfere with each other. This same concept is used for the production of the bifunctional chelates as radiopharmaceuticals. To date only a few such substances have been prepared. One example is $^{99m}$Tc-N-(2,6-dimethylphenylcarbamoylmethyl)iminodiacetic acid ($^{99m}$Tc-HIDA), an analog of lidocaine in which the tagging end is the chelating group iminodiacetic acid, which binds reduced technetium-99m. This particular bifunctional molecule concentrates in the bile, rather than in the heart as originally proposed (*3*), i.e., the chelate group did influence the function of the other group. Castronovo et al. (*4*) have synthesized phosphonates for this purpose. Figure 2 diagrammatically compares

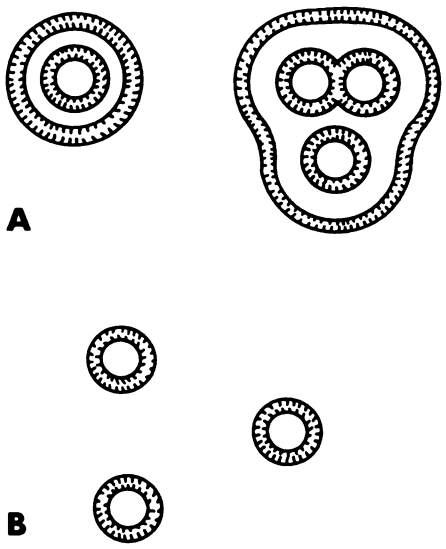


**FIG. 1.** (A) Drawings of liposomes showing aqueous-phase droplets and layers enclosed in bimolecular layers of lipids. (B) Drawings of vesicles showing their simple single-droplet structure.

the bifunctional chelates (A) to vesicles (B). An advantage of vesicles or liposomes over the chelates is that more than one radioactive atom can be attached to each biochemically specific group, i.e., theoretically the specific activity is not limited when vesicles or liposomes are employed as the carrier.

The diagnostic problems which might be solved by means of this type of radiopharmaceutical are not obvious. Neither the studies published in this issue nor the previous reports of those authors have provided clear-cut answers to this question. Apparently, they are seeking tissue-specific targeting of radionuclides, i.e., developing guided nuclear missiles instead of magic nuclear bullets. Although there has been criticism of this approach (*5*), it still has the attention of many investigators who believe it to be a promising method.

An examination of the behavior of radiolabeled liposomes and vesicles suggests some possible uses. Like other colloids, they are removed by the liver, spleen, and bone marrow and, when aggregated, they are removed by the lungs. Could they be used to measure RES capacity by measuring clearance as a function of the administered dose? Could they be used to measure liver enzyme activity by measuring the release of encapsulated $^{99m}$Tc-DTPA? Could they be used to measure body pools of antibodies by quantitating the lung uptake that results from aggregation of circulating droplets, as illustrated in Fig. 3A, or by measuring the release of encapsulated $^{99m}$Tc-DTPA, as illustrated in Fig. 3B?

The reports in this issue of the *Journal* show that liposomes and vesicles can be made to carry radioactive labels. The next step is to define a specific diagnostic problem and design a radiopharmaceutical of this type as a key component to the solution of this problem. Perhaps it is permissible to make the cart before the horse as long as somewhere along the line the need to get the horse is recognized.

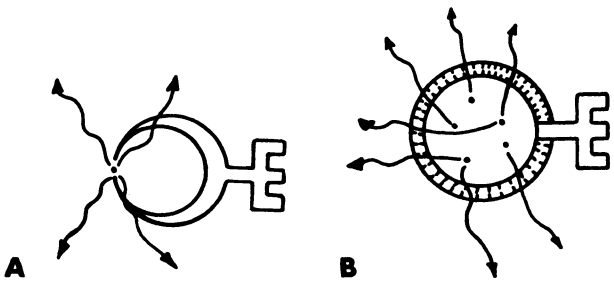


**FIG. 2.** (A) Bifunctional chelate showing attachment of radionuclide by chelation to biochemically specific group. (B) Same biochemically specific group is attached to vesicle containing radionuclides as solute in enclosed aqueous-phase droplet.

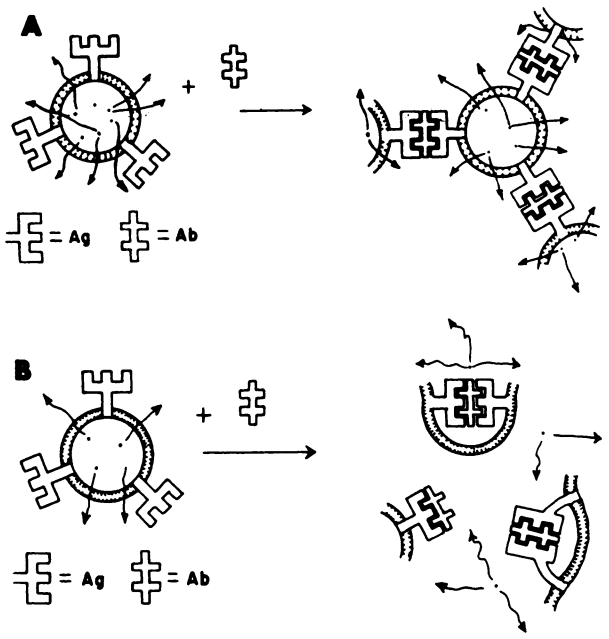


**FIG. 3.** (A) Agglutination of radiolabeled vesicles containing antigens in membranes by reaction with antibodies. This reaction increases lung uptake of radioactivity. (B) Cytolysis of radiolabeled vesicles containing antigens by reaction with antibodies. This reaction releases encapsulated water-soluble tracer.

BUCK A. RHODES, Ph.D.
University of New Mexico
Albuquerque, New Mexico

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