TEACHING EDITORIAL

The Classification of Radiotracers

Classifications of radiopharmaceuticals have been proposed in a number of publications; however, rarely has the classification been based on the concentration mechanism of the agent in the target organ. The uptake mode of most current clinically useful radiopharmaceuticals can be classified as "substrate nonspecific." For example, regional blood flow can be measured by capillary blockade, but the agent need not be a specific substrate; in fact, a number of different radiolabeled particles, if of the appropriate size, can be used. Colloids are trapped by reticuloendothelial cells, but the liver phagocytes do not discriminate among the types of colloids—sulfur colloid, gold colloid, etc.

The use of substrate nonspecific radiopharmaceuticals makes possible the study of certain physiological processes, such as regional perfusion of the lung or distribution of phagocytic function *(1)*, and they represent an important class of radiopharmaceutical. To acquire further information from the concentration or distribution of radioactivity in the lung, liver or kidneys, however, this approach, i.e., the use of substrate honspecific, is not likely to be of additional diagnostic benefit. Thus, many researchers believe that further advances in the use of radiotracers can be accomplished only through the development of radiopharmaceuticals that follow specific biochemical or pharmacologic processes.

To contrast the characterization of the present clinical radiopharmaceuticals (which we term "substrate nonspecific"), we propose a new category to be grouped under the general title of "substrate specific." Although the initial tracer experiments with P-32 and I-131 described specific biochemical pathways *(2)*, and a number of similar tracers have been developed through the years, the need for classification has only recently been emphasized. In this issue of the *Journal,* Gallagher et al. discuss metabolic trapping as one tracer mechanism whereby a certain portion of a specific biochemical pathway can be assessed *(3)*. They state, "the use of 2-deoxy-D-glucose. . . as a substrate for the enzyme hexokinase isolates the hexokinase reaction." Similarly, 2-deoxy-2-fluoro-D-glucose is "trapped," and [^{75}Se] selenomethionine *(4)* and [^{131}I] 6-iodomethyl-19-norcholesterol *(5)* probably should be included in this class, although the analogous studies have not been reported for these two radiotracers.

The most obvious class of biochemical radiotracers are those compounds that contain an isotopic substitution in the native biochemical. Examples of these are [^{11}C] palmitic acid *(6)* and [^{11}C] glucose *(7)*. Also, the radioiodide (for iodide) and radiophosphorus (in phosphate) used in early experiments belong to this category *(2)*.

A number of biochemicals and drugs cause highly specific reactions in the body when given in relatively low doses. Evidence from a variety of sources suggests that the primary event in the action of many peptide and steroid hormones and drugs is the binding to a specific site, a receptor, on the plasma membrane or in the cytosol. This receptor initiates the biochemical action, and the response is controlled by the amount of unchanged substrate in the biophase surrounding the receptor. An equilibrium is established depending on the concentration of receptor, the concentration of the substrate in the biophase, and the affinity constant between the two. Since receptors are involved in the action of the drug or biochemical, one might expect changes in

the concentration of receptor as a function of disease state. Radiotracers labeled with gamma-emitting isotopes can quantitate these changes by noninvasive means. Of the various receptor systems available, those binding estrogens and those binding adrenergic and muscarinic blocking agents have been suggested (*8, 9*) as extensions of the earlier proposals by Counsell to study the steroid hormones (*10*). These receptor-binding radiopharmaceuticals represent a third type of substrate-specific mechanism.

Beierwaltes and coworkers at Michigan have long been interested in enzyme inhibitors. A number of specific substrates that block a particular enzyme necessary for the conversion of progesterone to cortisol and aldosterone have been radiolabeled and evaluated as adrenal imaging agents (*11*). This approach may be mechanistically similar to the active process described in this issue (*3*) or to an interaction with a specific protein, the enzyme, under equilibrium conditions. From the studies with one enzyme inhibitor, [^{14}C] isoxazole, it appears that the latter mechanism is operative (*12*), but complete classification of all inhibitors has not been published.

Another example of localization by a substrate-specific mechanism is the reaction of radiolabeled antibodies with a tumor-associated antigen. The recent publication of Goldenberg et al. using radioiodinated CEA antibody reveals the rapid advancement made in this area *(13).*

In general, the classification of radiotracers has not been possible in many instances because the substantiating in vitro and in vivo data are not available. Our classification is presented to promote further discussion toward refinement of this concept and to emphasize the importance of a mechanistic approach to further radiopharmaceutical development (Appendix A). Defining the precise mechanism of action and the portion of the pathway studied by the radiosubstrate should lead to better understanding of the specific information obtained so that precise diagnostic interpretation is possible. Classification is also important because it permits us to judge how general a particular mechanism actually is, since it may well be that anecdotal examples will not lead to substantial use of that particular mechanism. If the emphasis in radiopharmaceutical chemistry is to be directed toward the study of biochemical and pharmacological pathways, each new radiopharmaceutical must be examined so that the extent of its ability to trace a particular interaction is well documented. The characterization of [^{18}F] 2-deoxy-2-fluoro-D-glucose by the group at Brookhaven National Laboratories is an encouraging start.

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Appendix A: Mechanism of Localization

A. Substrate Nonspecific. The compound does not participate in a specific chemical reaction.
   1. Diffusion
      (a). [^{99m} Tc]-TcO_4^- for Brain Tumor Imaging
      (b) Xe-133 and Kr-81m for Lung Ventilation Studies
   2. Compartmental Space
      (a) Tc-99m DTPA for ECF measurements
      (b) Tc-99m RBC for red cell volume
      (c) I-131 HSA for plasma volume
   3. Capillary Blockade and Cell Sequestration
      (a) Tc-99m MAA for regional perfusion studies
      (b) Damaged Tc-99m RBC for splenic sequestration studies
   4. Phagocytosis
      (a) Tc-99m Sulfur Colloid for phagocytic function measurements
      (b) Tc-99m Antimony Sulfur Colloid for lymphoscintigraphy

B. Substrate Specific. The substrate must participate in a definite chemical reaction or take part in a specific ligand-substrate interaction.
   1. Isotopically Substituted Biochemical
      (a) [^{11}C]-labeled palmitic acid
      (b) [^{11}C]-labeled glucose
   2. Metabolic Trapping
      (a) [^{18}F]-2-Deoxy-2-Fluoro-D-Glucose
   3. Enzyme Inhibitor or Enzyme Substrate
      (a) [^{14}C] isoxazole
      (b) [^{131}I] 6-iodomethyl-19 norcholesterol (?)
      (c) [^{75}Se] Selenomethionine (?)
   4. Receptor-Binding Biochemical or Drug
      (a) Steroids
      (b) Adrenergic Blocking Agents
      (c) Cholinergic Blocking Agents
   5. Antibodies to Tumor-Associated Antigens
      (a) CEA Antibody