bypass graft, valve repair) or the response to drug therapy. Also, a ^{99m}Tc ejection fraction study can be performed to assess the benefits of heart medications, such as digoxin.

Radiopharmaceuticals also find utility to help monitor drug therapy, including toxicity. For example, the ability of doxorubicin to cause irreversible heart failure is well known, and the cumulative dose of this drug should not exceed 550 mg/m^2. Because there is much variation in the individual response to this drug, serial determinations of left ventricular ejection fraction using ^{99m}Tc are useful to determine the risk of developing doxorubicin-induced heart failure on an individual basis.

THERAPEUTIC USE OF RADIOPHARMACEUTICALS

Therapeutic radiopharmaceuticals are radiolabeled molecules designed to deliver therapeutic doses of ionizing radiation to specific disease sites, such as cancerous tumors, with high specificity in the body. The design of each radiotherapeutic agent requires optimizing the balance between specific targeting of the disease, such as a cancerous tumor, and the clearance of radioactivity from nontarget radiosensitive tissues; it is also necessary to consider the physical radioactive decay properties of the radionuclide. As mentioned earlier, difficulties in the design and development of a highly selective radiolabeled drug carrier include drug delivery, maximizing the residence time of radioactivity at target sites, in vivo catabolism and metabolism of the drug, and optimization of relative rates of the radiolabeled drug or metabolite clearance from nontarget sites, among others.

Unsealed source radiolabeled agents have been used for treatment of cancers for more than five decades. Thyroid disease has been treated with sodium iodide, ^{131}I; polycythemia vera can be treated with sodium phosphate, ^{32}P; peritoneal effusions can be treated with chromic phosphate, ^{32}P; and ^{89}Sr-chloride, ^{153}Sm-EDTMP, and ^{186}Re-HEDP are used for pain relief associated with metastatic bone lesions. The intent is to use beta radiation to destroy diseased tissue selectively. Thus, a minimum sufficient dosage must be administered although this dose can be much larger than doses for diagnostics. In the case of ^{131}I, the therapeutic dose is 5 to 10,000 times the dose used to assess organ function. The major indications for radioiodine therapy include hyperthyroidism (diffuse toxic goiter or Graves disease and toxic multinodular goiter) and eradication of metastatic disease (thyroid cancer).

A major focus of current research is to enhance drug targeting to internal target sites (e.g., solid tumors, specific organs). The objective is to enhance the drug by concentrating it at the target site and minimize its effect in healthy sites. This approach is being investigated for cancer chemotherapy and radioimmunotherapy (RIT). RIT uses antigen-specific monoclonal antibodies (MABs) or their derived reagents to deliver therapeutic radionuclides to tumorous tissue (2). Improved bioengineered delivery vehicles (e.g., humanized and chimeric whole antibodies, Fv fragments, and hypervariable domain region peptides) have reinvigorated RIT, and more and more pretargeting protocols are becoming available (2).

Most chemotherapeutic drugs and radiotherapeutic peptides are small molecules. Consequently, low concentration of drug is obtainable at the target site, largely because of rapid excretion and metabolism by the kidneys and liver. This limits the amount of drug available for localization in the target site from the bloodstream. Increasing the dosage of drug is not an option because of the toxicologic implications for one or more body organ systems. Covalent conjugates of MABs were the first generation of drug-targeting agents that were employed to attain the concentrating effect in tumors (7).

In 1996, the FDA granted licenses to three manufacturers to market four radiolabeled antibodies for diagnostic imaging. CEA-Scan was a murine MAB fragment linked to ^{99m}Tc. It was reactive with carcinoembryonic antigen, a tumor marker for cancer of the colon and rectum and indicated with other standard diagnostic modalities for the detection of recurrent and/or metastatic colorectal cancer. Cytogen Corporation developed a