INTRODUCTION

Attachment of pharmacological agents to soluble macromolecules has two important consequences: firstly it alters the pharmacokinetics and secondly it provides the opportunity to target to those cell types where activity is required. In general, pharmaceuticals are of low molecular weight and readily pass across cell membranes; as a result the therapeutic potential of individual compounds rests with their ability to interfere selectively with the offending cell type. Cancer chemotherapy provides an obvious example where drugs currently available have limited ability to differentiate between target and normal host cells. Cell specific targeting would help to alleviate some of the problems associated with non-selective therapeutic agents.

Over the past decade, many soluble macromolecules have been examined as possible carriers of therapeutic agents, but in most cases these have been natural polymers (1). Formation of a macro-molecular conjugate restricts uptake of drug by cells to the process known as endocytosis. Endocytosis is a term than encompasses two distinguishable phenomena, those of phagocytosis and pinocytosis (2). Phagocytosis involves the engulfment of large (> 1 μM diameter), usually particulate, material and is triggered by interaction of the particle with the surface of certain specialized cells known as phagocytes. In contrast, pinocytosis is a process thought to be common to all cell types and involves the continuous internalization of plasma membrane, extracellular fluid and the solutes dissolved therein. The discussion that follows is limited to pinocytosis, but it may be noted that material ingested by phagocytosis generally has the same intracellular fate.
A brief description of the pinocytic pathway and discussion of the relevance to drug delivery follows. During pinocytosis the cell membrane invaginates to form a membrane-bound vesicle that contains extracellular fluid, substances in solution, and sometimes substances adhering to the cell surface. After "pinching-off" from the plasma membrane, the pinocytic vesicle migrates into the cytoplasm, fusing with other incoming vesicles and ultimately fusing with lysosomes to form what is known as a secondary lysosome. Lysosomes are vesicles of intracellular origin and they contain many hydrolytic enzymes. Normally all natural macromolecules entering the secondary lysosome are susceptible to their degradative activity. The monomeric constituents liberated during hydrolysis are usually able to pass through the lysosomal membrane for reutilization in anabolic metabolism or alternatively are lost from the cell.

Macromolecule-drug conjugates cannot pass through cell membranes and therefore only enter the cell by pinocytosis. They are then transferred to the lysosomes and, providing either the carrier molecule itself, or the drug-carrier linkage, is degradable by the lysosomal enzymes, free drug will be delivered to the cell from an intracellular location (Fig. 1). Drug conjugates that accumulate in lysosomes are termed "lysosomotropic" (3). Coupling to a macromolecule automatically alters the body distribution of a drug. If the conjugate is captured solely as a solute (fluid-phase pinocytosis (4)), the body distribution will depend on the rate of pinocytosis of individual cell types and the accessibility of the conjugate to each cell type. However, in instances where the conjugate has affinity for cell surfaces and is therefore captured by adsorptive pinocytosis (4), the

Figure 1. Intracellular fate of macromolecular-drug conjugates.