STRUCTURE AND PROPERTIES OF PHARMACOLOGICALLY ACTIVE POLYMERS

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SYNOPSIS

Although the concept of using pharmacologically active macromolecular compounds as drugs is still regarded with much skepticism for both theoretical and practical reasons, interest in this field has grown in recent years because of the opportunity to take advantage of the specific properties of polymeric materials. For low molecular weight drugs, changes in structure often lead to a loss of specific activity. On the other hand, the properties of macromolecular drugs depend on the structure of the polymer used and this can be varied over a wide range by the incorporation of comonomer units, by the application of polymer-analogous reactions, or by related structural changes. A new model is presented for pharmacologically active polymers which incorporates the possibility for continuous variation in (a) solubility and toxicity, (b) fixation and removal of active material, and (c) body distribution. Using the new model as a guide, examples of the synthesis and study of the biological activity of various macromolecular drugs are presented in order to emphasize the importance of this cooperative effort between polymer research and therapeutic problems.

INTRODUCTION

The investigation of biomaterials is one of the newest and most exciting areas of polymer chemistry. Especially interesting are investigations of pharmacologically active polymers representing macromolecules which by themselves may be active as drugs or alternatively may be used as carriers for normal pharmaceutical agents.

Although polymers are already widely used in the area of biomedical engineering, e.g., to construct artificial replacements for human organs [1] or to provide biochemical functions [2], the field of polymeric drugs is still subject to considerable skepticism. More points have been raised against the use of pharmacologically active polymers than in their favor. Nevertheless, much has been accomplished in recent years as shown by the growing number of papers and reviews articles in this area [3–7].

Originally, one of the main ideas behind the possible use of pharmacologically active polymers was the hope that one might achieve depot effects with such drugs based on previous experience with synthetic

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polymeric blood substitutes [8]. However, considering the many possibilities for specific chemical and physical interaction between synthetic or natural polymers and body membranes or involvement with various biochemical processes in the body, this depot effect is only one facet of the new horizons which are evolving in chemotherapy by the switch from low to high molecular weight drug systems. In the present survey, no attempt will be made to discuss the many types of drugs which have already been fixed to polymeric carriers or the biological activity of these materials [3, 4, 7]. Instead, on the basis of a rather simple model for the medical use of polymeric drugs, the structure and properties of pharmacologically active macromolecules will be discussed for the purpose of demonstrating the potential importance of this new field.

PROBLEMS IN DRUG DESIGN

After the application of a drug, a series of events normally takes place before the drug finally reaches the site of action. A schematic summary of such drug pathways is presented in Figure 1.

Between the application and excretion of a drug it will be subject to many physiological systems which will influence both its concentration and its reactions in the body. Upon entering the blood plasma the drug molecules may be free or bound to transport proteins. The free drug molecules may undergo biotransformations or may form tissue depots. Eventually the drug will enter the site of action where, for example, by a drug-receptor interaction the biological event will take place. Because of
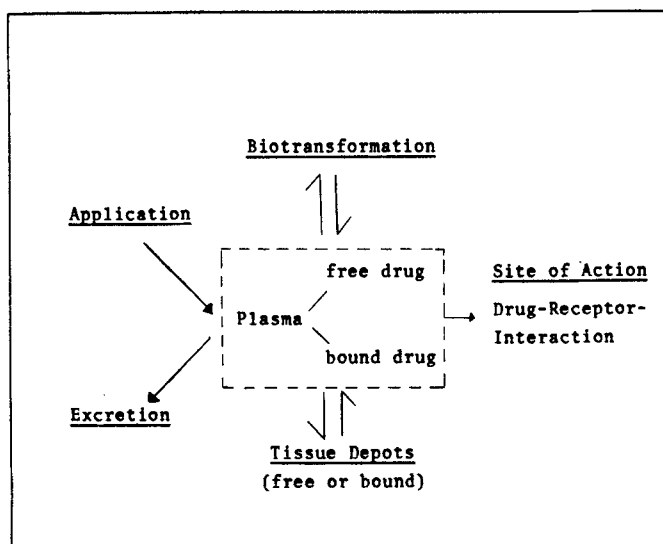

FIG. 1. Drug pathways in biological systems.

these different metabolic pathways the drug is distributed throughout the body rather than solely at the site of action, and therefore the therapeutic concentration must be greatly exceeded with low molecular weight drugs. It would be extremely important to be able to synthesize drugs which would act cell-specifically and only at the desired site.

Considering the various factors to which a drug is subject, it is clear that in attempting to effect their combination in order to develop an ideal drug, there is a possibility that the original biological activity of the low molecular weight compound may be lost. A very interesting example of this difficulty was described by Connors and co-workers who studied the influence of substituents on the cell-specific uptake of sulfadiazines by malignant tissue [9], as shown in Figure 2. On the left-hand side of Figure 2 it can be seen that sulfadiazine is more rapidly incorporated into Walker carcinoma tissue than into liver tissue. These findings are of considerable interest, since tumors generally take up injected materials to a lesser extent than the liver. Based on this result, Connors and co-workers synthesized a sulfadiazine mustard (compound II in Fig. 2) in order to combine the ability of the sulfonamide to concentrate in tumor cells with the cytotoxic effect of the lost system. Compound II was, in fact, shown to be an antitumor agent, although by combination with the lost system the sulfadiazine unit lost its ability to act as a homing device for tumor tissue. As can be seen in Figure 2, uptake of the sulfadiazine mustard (II) into liver tissue is higher than its uptake into malignant tissue.

This example demonstrates a problem in drug design and shows that the alteration of a low molecular weight drug to enhance its biological activity or to incorporate a specific property may be difficult or even impossible.
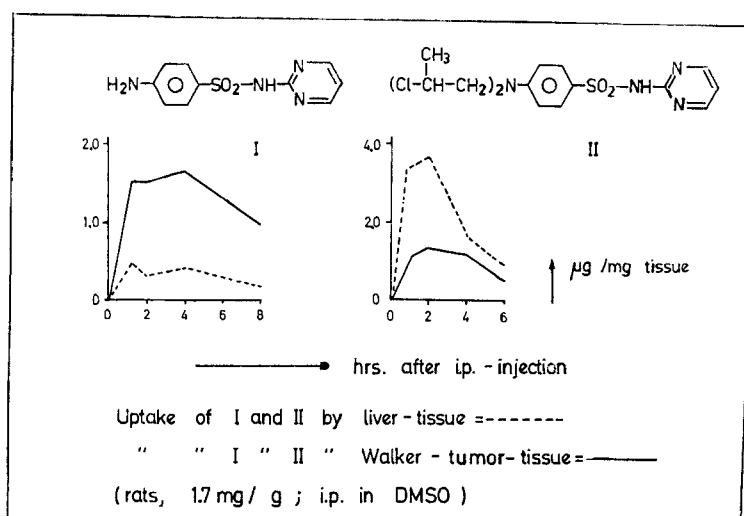

FIG.2. Influence of substituents on the cell-specific uptake of sulfadiazines [9].

MODEL FOR PHARMACOLOGICALLY ACTIVE POLYMERS

From the standpoint of polymer chemistry, one can consider the possibility of devising a polymeric drug with which one can separate the different necessary requirements by using discrete areas along the polymer chain to accomplish specific effects. The principle is shown schematically in Figure 3. In this schematic representation of a pharmacologically active polymer, the biostable or biodegradable backbone is used as carrier for at least three different units. One area of the polymer is used to make the whole macromolecule soluble and nontoxic; the second area is the region where the pharmacon is fixed; and the third area incorporates a transport system, the crucial property of which is represented by its ability to carry the whole polymer to the target cells. The separation of the different areas along the polymer chain may be accomplished by statistical terpolymerization or by block copolymerization.

In addition, unusual and polymer-specific properties of pharmacologically active polymers may be induced by certain polymer-specific structural characteristics such as high molecular weight, coil structure, copolymer composition, unusual binding capabilities, variable polyelectrolyte charges, and tacticity. All three phases of drug action [10] will be influenced by the structure of biologically active macromolecules: (a) the pharmaceutical phase, e.g., by disintegration of dosage forms; (b) the pharmacodynamic phase, e.g., by unusual absorption and distribution, variations in metabolism or retarded excretion; and (c) the pharmacodynamic phase, e.g., by variations in drug-receptor interactions and possible cell-specific effects.

From the model and these considerations, one can predict some important properties to be expected of polymeric drugs as compared with their low molecular weight analogs:

1. Depot effects $\begin{cases} \text{retarded absorption} \\ \text{retarded excretion} \end{cases}$

2. Widely variable toxicity and solubility.

3. Pharmacokinetic variation:
    a) variable release of the active component;
    b) different metabolic pathways;
    c) influence of the structure of the polymer, of molecular weight and of comonomer units incorporated.

4. Different body distribution with regard to:
    a) protein binding;
    b) resorption;
    c) cell-specific interaction and uptake.

5. Polymer-specific effects.

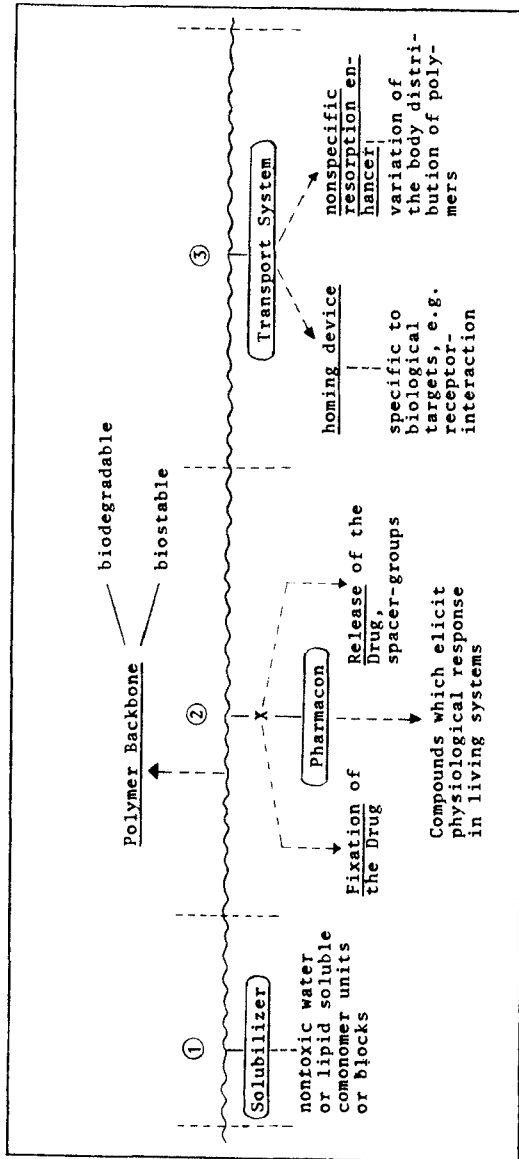6. Drug combination along the polymer chain.

FIG. 3. Model for pharmacologically active polymers.

A potentially significant aspect of the use of a polymeric drug which has been discussed even in the older review literature [3] is the question of a depot effect which might be brought about by either reduced absorption or reduced excretion of the drug. More important is the possibility of varying drastically the pharmacodynamics of drug systems by the use of polymeric substrates. This is due not only to the fact that one may effect variable release of an active component, but also because the toxicity of a drug may be diminished drastically and, in addition, completely different metabolic pathways may result. Conceivably, this could influence the amount of drug one has to inject in order to reach the therapeutic dose level, and consequently may provide a good opportunity to keep the dosage level very low over a long period of time. Another very important consideration is the possibility of effecting a different body distribution of the polymeric drug relative to its low molecular weight analog. This might be brought about by varying protein binding of the polymer, the high endocytotic rate of polymers [11] or a possible selective endocytotic uptake by target cells for the acheivement of cell-specific effects [12]. Last but not least, one should consider the possibility of discovering drugs which show specific effects not exhibited by their low molecular weight analogs. An interesting example comes from the work of Schlipköter and co-workers [13–15], who found that poly(vinylpyridine)-N-oxides are active against silicosis although the low molecular weight models such as isopropylpyridine-N-oxides showed no activity. The polymer-specific effect of these N-oxides in protecting macrophages against silica injury can be explained by the fact that the polymer coats silica particles and thus prevents them from interacting with lysosomal membranes, thereby causing their rupture [13, 16, 17].

Finally, it is not unreasonable to speculate that systematic studies on the synthesis and pharmacological activity of polymeric drugs might lead to new methods of drug design.

DISCUSSION OF THE MODEL FOR PHARMACOLOGICALLY ACTIVE POLYMERS

To consider further the model depicted in Figure 3 we may first briefly discuss the area of the solubilizer. The comonomer units introduced to render the resulting polymer water soluble must satisfy some fundamental requirements, e.g., lack of toxicity and immunogenicity. For polyvinyl derivatives such nontoxic, water-solubilizing units have generally been introduced via vinylpyrrolidone [8], β-hydroxyethyl acrylates and acrylamides [18], vinylpyridine-N-oxides [19], and sulfoxide-containing acrylates [20]. Because of their pronounced lack of acute toxicity we have been especially interested in polymeric systems containing sulfoxide and N-oxide units [21]. Homopolymers as well as a number of copolymers
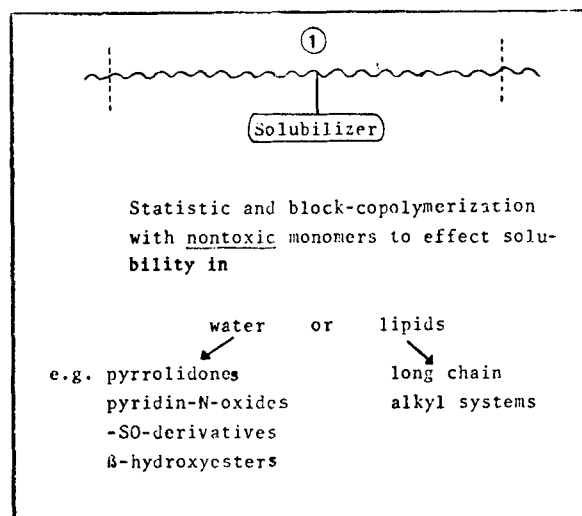
FIG. 4. Solubility system for pharmacologically active polymers (see model in Fig. 3).

containing these solubilizer units did not show any immunogenicity. In order to make polymeric drugs lipid-soluble one can use comonomer units bearing long alkyl chains which serve to increase possible absorption at lipid phases and cell membranes.

In addition to the lack of toxicity and antigenicity of specific macromolecular units, the overall molecular weight of the polymers used and their normal body distribution should be of significance. It may be mentioned that excretion via the highly porous glomerular membrane of the kidneys is limited for most synthetic polymers, since those with molecular weights above 80,000–100,000 cannot pass the tubular epithelium. On the other hand, such polymers can be slowly excreted via the liver and its biliary system into the intestine. Synthetic polymers as well as oligomers with molecular weights even lower than 1000 cannot pass the so-called "blood-brain barrier" and thus are not able to enter the brain and cerebrospinal fluid.

Clearly, molecular weight and its influence on total excretion is one of the crucial problems in connection with the use of nondegradable polymeric drugs. Many examples could be given showing that molecular weight is one of the important parameters influencing the biological activity of polymers [23, 43]. So far, the most detailed investigations concerning the influence of molecular weight have been made with polyvinylpyrrolidone [8], fractions of which having a narrow distribution and an average molecular weight of 10,000–40,000 are still used as plasma expanders [22].

The second area schematically represented in the model (Fig. 3) is that where the pharmacon is fixed to the polymer chain. (Fig. 5). Three points are of interest in this connection: (a) the question of how to fix the
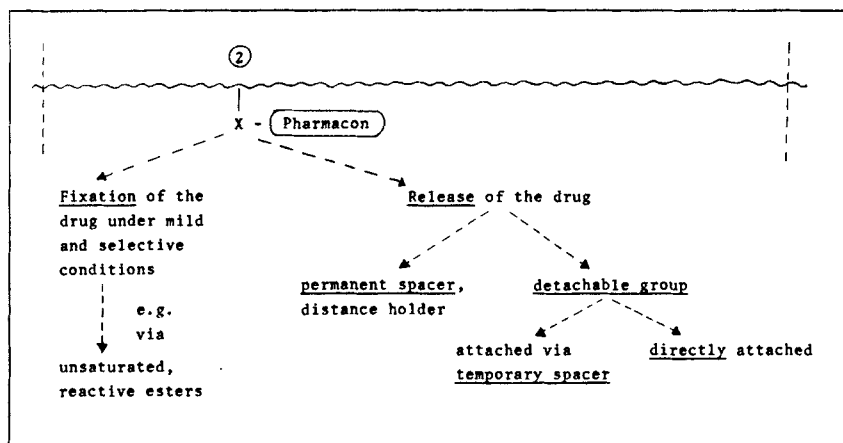
FIG. 5. Area of drug fixation and drug release (see model in Fig. 3).

pharmacon to the polymer chain under conditions mild enough not to affect its biological activity, (b) the nature of the group used to fix the polymer to the chain, and (c) the nature of the pharmacon itself.

For fixation of the pharmacon to the polymer chain, conditions must be mild enough to allow attachment without any adverse effect on the biological activity of the pharmacon. For this purpose, various coupling methods which are well known in the field of peptide synthesis can be applied [24]. To this end, several polymerizable active esters and amides covering a wide spectrum of reactivity have been used in order to allow for selectivity depending on the nature of the nucleophilic center being used to fix the drug to the polymer chain [25]. Systems examined included esters of trichlorophenol, N-hydroxysuccinimide, N-hydroxybenztriazole, and imidazole derivatives. In the case of hydroxysuccinimide and hydroxy-benzotriazole derivatives it was easy to discriminate between hydroxyl and amino groups with only the latter reacting under mild conditions [25]. For example, the N-hydroxysuccinimide derivative of poly(methacrylic acid) reacts selectively with the amino group of ethanolamine at room temperature to give completely soluble noncrosslinked polymers. On the
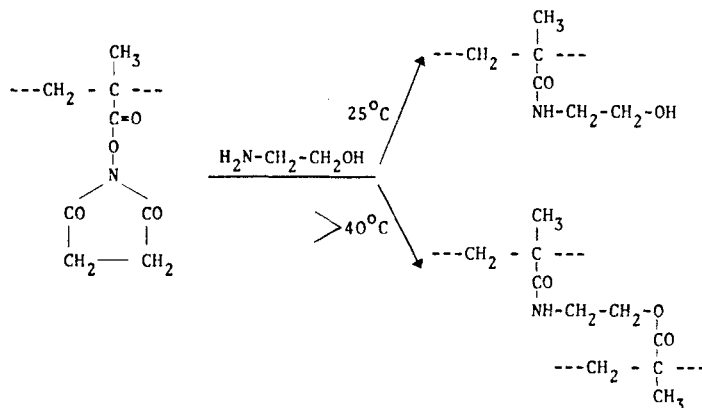
other hand, at temperatures above 40°C reaction occurs with both the amino and hydroxyl substituents as shown by the formation of insoluble crosslinked polymers.

The question of the eventual release of the drug in the body is as important as the problem of its initial fixation to the polymer chain. For some purposes it might be necessary to prepare polymers in which the pharmacon is firmly attached to the polymer by means of a linkage which is completely stable under all normal body conditions. Alternatively one may wish to use a linkage from which the drug can be released rapidly in the body either by hydrolysis or via an enzymatic process. For these purposes permanent or temporary spacer groups may be used.

A permanent spacer group merely separates the active drug from the polymeric backbone or coil so that the latter do not interfere with the biological activity of the bound material. Such effects are common in the field of polymer-bound enzymes. In some such cases, direct fixation leads to loss of enzymatic activity, possibly because of interference with the normal conformation of the enzyme, whereas attachment via a distance holder such as a long alkyl group restores the normal activity. Recently, Kaplan and Venter and their co-workers have shown that catecholamines fixed to glass beads or polystyrene matrices by permanent spacers were able to induce muscle contractions and affect the heartbeat rates of experimental animals in a manner comparable to the effect of the low molecular weight compounds themselves [26–28].
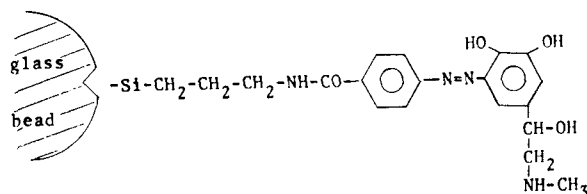
Direct fixation of such catecholamines to poly(acrylic acid) was ineffective [29]. These very interesting results demonstrate a true membrane response in which the effect sensed by the drug receptor is transmitted without prior detachment of the pharmacon from the solid support.

A temporary spacer group is one from which the active material can be readily released. One of the first examples of the use of such a temporary or detachable spacer group was described by Jatzkewitz as early as 1954 [30, 31] (Fig. 6). Copolymers of N-vinylpyrrolidone and amides formed from mescaline and acrylic acid in which the mescaline was bound directly to the main chain were found not to release the psychotic agent in the body over a period of a few weeks. On the other hand, when mescaline was bound, again as the amide, via the terminal carboxyl group of the dipeptide glycyl leucine, which was itself bound to the polymeric acid via the terminal amino group, Jatzkewitz was able to demonstrate the continuous excretion of mescaline over a period of 17 days. Mescaline itself was completely excreted after only 20 hr. Recently, polymerizable reactive
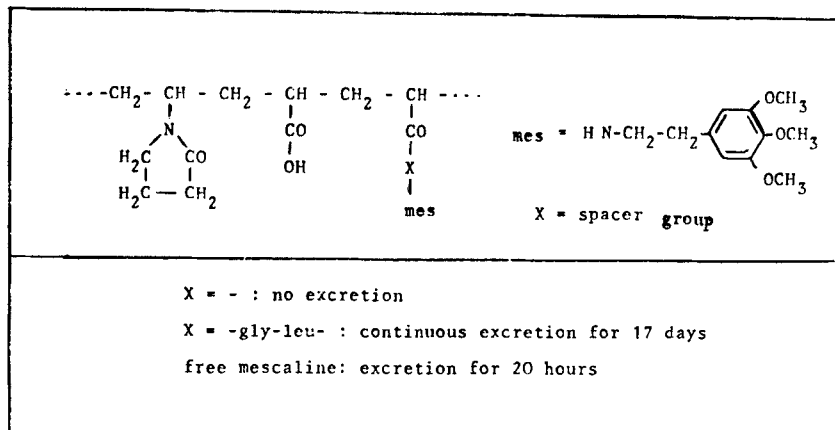
FIG. 6. Influence of a temporary spacer group on the release of polymer-bound mescaline [30, 31].

esters bearing temporary spacer groups have been prepared by Franzmann [29] (Fig. 7).

Morawetz and co-workers recently studied the enzymatic cleavage of polymeric nitrophenyl esters and its dependence on the spacer groups which were used to link the ester to the polymer chain [32].

Regarding the types of biologically active materials which have been studied so far, there is to date hardly any type of drug which has not been fixed to some type of polymer [3–7]. Besides the examples given above in connection with the discussion of the proposed model, only a few additional polymers which show typical structural effects will be discussed.

An important area for the potential application of pharmacologically active polymers is the development of macromolecules with carcinolytic activity [12, 33–36]. The field of polymeric antitumor agents has been reviewed recently [37]. In this connection cyclophosphamide- and hor-
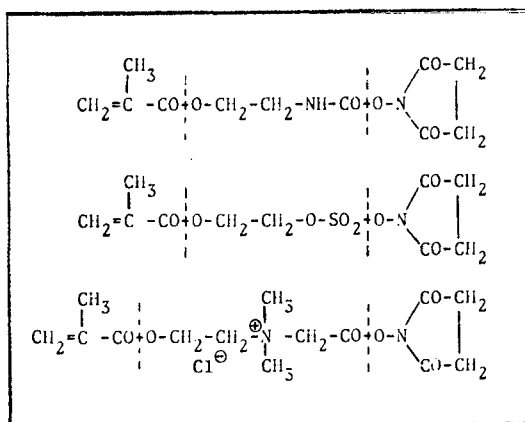

FIG. 7. Polymerizable reactive esters bearing temporary spacer groups [29].

mone-containing polymers have been prepared and tested [35]. Studies of
the androgenic effect of testosterone-containing polymers (Fig. 8) demon-
strated the influence of spacer groups [38]. While testosterone directly fixed
to the polymer chain (1) does not show any effect, the activity of the
polymer with a temporary spacer group (2) is as effective as the low
molecular weight model.

A recent example of a typical polymeric depot effect comes from the
area of anti-radiation prophylactics. The great disadvantage of practically
all known chemical radioprotective agents is their limited period of activity
due to their low molecular weight [41]. They are effective only if injected
15–30 min before irradiation. Since macromolecules are only slowly ex-
creted by the body, polymers containing potentially radioprotective func-
tions were investigated for possible long-lasting effects by Overberger and
co-workers [39–42]. Recently a water-soluble terpolymer (S_3) prepared
from vinylpyrrolidone, acrylic acid and acryloyl thiazolidine was tested
[43]. In Figure 9 the effectiveness of the terpolymer is compared with its
low molecular weight model (mercaptoethylamine, MEA). The Dose Re-
duction Factor

$$DRF = \frac{LD_{50/30} \text{ (protected animals)}}{LD_{50/30} \text{ (controlled animals)}}$$

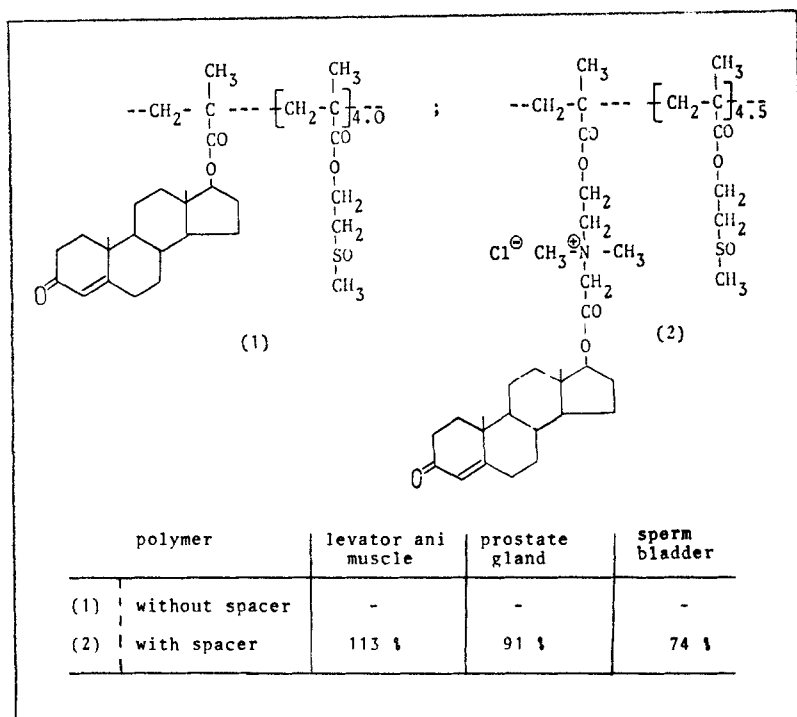| polymer		levator ani muscle	prostate gland	sperm bladder
(1)	without spacer	-	-	-
(2)	with spacer	113 %	91 %	74 %

FIG. 8. Androgenic effects of testosterone-containing polymers on castrated rats
[38]: S.C.-application; equimolar doses of polymer-fixed testosterone and free testos-
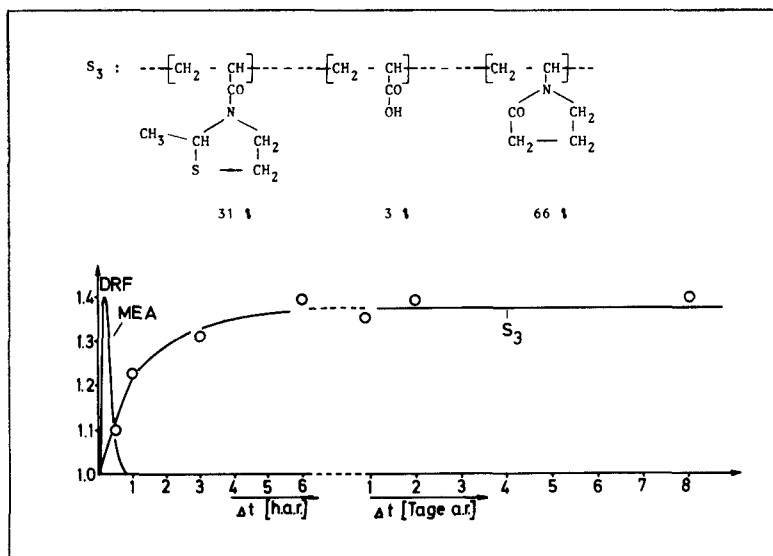terone in control experiments. (Effect of free testosterone = 100%).

FIG. 9. DRF values for S_3 after administration of 15 mg i.v. to rats and various time differences between injection and irradiation [43] (Δt, a.r.). Values for mercaptoethylamin (MEA) are given for comparison. The DRF values for the different times were taken from the corresponding dose-effect curves (see Fig. 10).

is plotted against the time difference (Δt) between the i.v. injection of the drugs and the onset of irradiation. While the low molecular weight model (MEA) is only active if injected about 30 min before irradiation, the polymer (S_3) shows the same activity up to a period of 8 days. In this special case it could be shown that the molecular weight of the polymers used did not influence their effectiveness as radioprotectants. Carefully fractionated terpolymers (S_3) with M_n values between 3,000 and 80,000 were examined at two Δt values. The results are given in Figure 10.

The results vary only if the time difference is not in the range of hours, as in Figure 10, but in the range of days. Preliminary experiments showed that in this case only the highest molecular weight fraction yields a DRF-value of 1.4 as shown in Figure 9. The lower molecular weight fractions are less effective as expected on the basis of a higher rate of excretion with a consequent smaller cell concentration of the radiation prophylactic.

To return to the schematic diagram depicted in Figure 3, the third area of general importance for pharmacologically active polymers is that of the transport system (Fig. 11). Such transport systems may induce specific or nonspecific resorption or be capable of fixing the polymeric drug in the target area via a reaction such as that involving an active ester side chain with nucleophilic cell-wall or tissue component, e.g., an amino or sulfhydryl group.

It should also be pointed out that pharmacologically active polymers, simply because of their high molecular weights, will be capable of inducing some cell-specific uptake without regard to other factors. As will be dis-
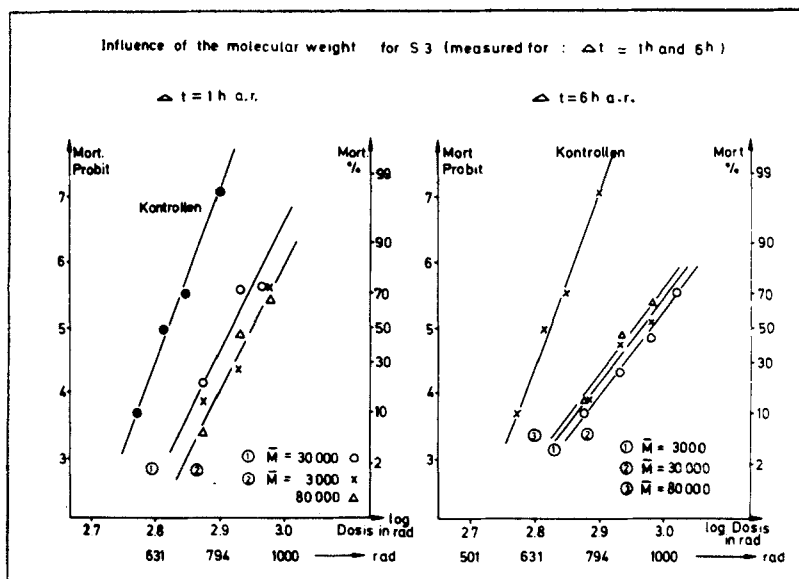
FIG. 10. Dose effect curve for S_3 with various molecular weights (M_n) [43]: rats (50 animals per point); dose 15 mg i.v., $\Delta t = 1$ hr a.r. and $\Delta t = 6$ hr a.r.

cussed later, the intracellular penetration of polymers is restricted to the endocytotic route [44–46] (see Fig. 14), and one can therefore use the high endocytotic activity of certain cells to increase preferentially their polymer drug load. This concept is the basis of recent attempts to apply polymers in cancer chemotherapy [12, 35–57] by taking advantage of the high endocytotic activity of many tumor cells [47–49]. This is also the case for all types of diseases of the reticuloendothelial system which is, in fact, the main target for polymeric drugs.

More specific transport of soluble polymers to target cells will be possible only by the use of homing devices, e.g., receptor-active components of pH-sensitive groups. The first attempts to make use of these two effects have been published recently. Tumor-specific antibodies as homing devices were linked to polyglumatic acid which carried a p-phenylenediamine mustard unit as an antitumor agent. This "terpolymer" is more active than a mixture of the antibody (unlinked) with glutamic acid carrying a mustard group as a side chain [50]. The increased activity provides evidence that a homing mechanism and not a normal drug-antibody effect is operating.

Based on the experiments of Connors et al. [9] as discussed above, attempts were made to use sulfonamide side chains in polymers as homing devices for tumor tissue [36, 51, 52] which shows a low pH-value after treatment with glucose. Figure 12 summarizes several polysulfonamides and their precipitation behavior in vitro. In vivo investigations of the body distribution of ^{14}C-labeled poly(acrylsulfadiazine) in tumor-bearing mice and rats are under way [53].
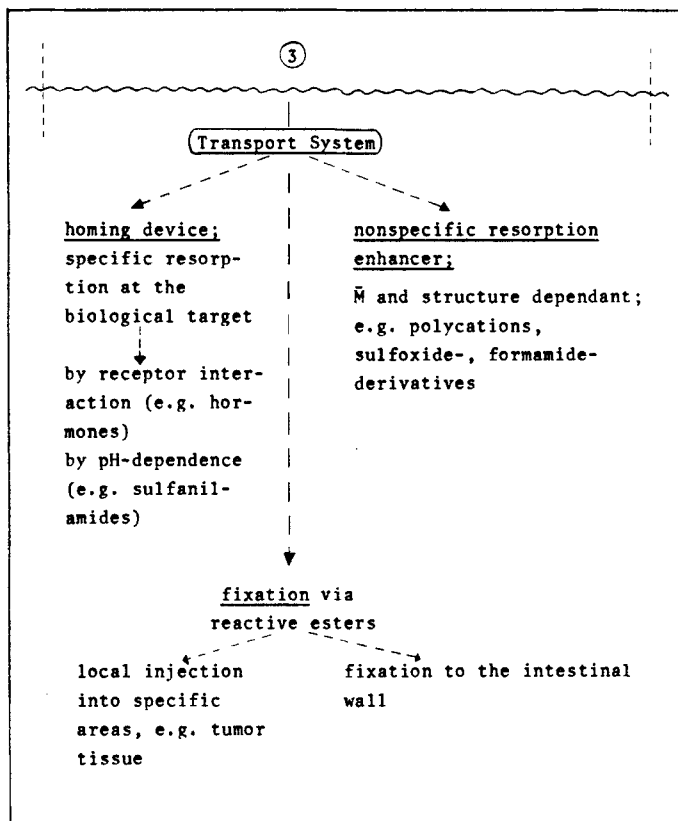
FIG. 11. Transport system for pharmacologically active polymers (see model in Fig. 3).

Transport systems which can act, according to Figure 11, as non-specific resorption enhancers by inducing variation in the normal body distribution of polymers can be expected of surface-, membrane- and skin-active systems, e.g., sulfoxides and formamides. Based on studies of dimethyl sulfoxide as a carrier for drugs through the skin and various membranes [54], a series of sulfoxide-containing polymers was prepared [20, 21] and their ability to enhance the uptake of certain drugs through the skin was successfully checked [21, 55]. The body distribution of these water-soluble and very nontoxic polymers after i.v. application was established by side-chain ^{14}C-labeling using rats with Walker muscle tumors [21, 56]. Some of the results are shown in Figure 13.

Although the average molecular weight ($\overline{M}_n$) of the polymeric sulfoxide was as high as 170,000, after 72 hr 41% of the material was excreted by the urine (37%) and feces (4%). These results are in contrast to those obtained in comparable investigations of poly(vinylpyrrolidone) fractions of the same molecular weight which were not found to be excreted at all via the kidneys. Even more remarkable is the fact that even after 72 hr the highest concentration of the polymer was found in the serum and

$$R-\overset{\overset{\displaystyle\ulcorner}{|}}{\underset{\underset{\displaystyle\llcorner}{|}}{C}}-CO-NH-\langle O\rangle-SO_2NH-R'$$
$$CH_2$$
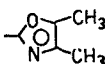
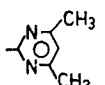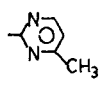| R	R'	pH of precipitation (± 0.3)	pKa
CH₃	H	10.0	10.6
"	(oxazole ring, CH₃, CH₃)	7.7	7.4
"	(thiazole ring, S)	7.3	7.0
"	(ring, N–CH₃, CH₃)	7.3	7.4
"	(ring, N, CH₃)	7.1	7.0
H	(ring)	6.6	6.5
CH₃	—CO—NH₂	3	5.4

FIG. 12. Poly-acryloyl- and methacryloyl-sulfonamides [51–53]; correlation between the pH of polymer precipitation from water and the pKₐ values of the corresponding sulfonamide units. Normal tissue: pH 7.2; Tumor tissue: pH 6.5–6.9 (after glucose treatment).

blood rather than in the liver. This may result from exceptionally high binding to transport proteins in the blood. The amount of polymer taken up by the liver, spleen and lungs was normal, whereas uptake in the muscle tumor was 181% compared with 28% in normal muscle tissue. The amount found in the brain (12.1% after 48 hr, 10.2% after 72 hr) suggests that part of the polymer must have been hydrolyzed with consequent appearance of low molecular weight β-hydroxyethyl sulfoxides in the brain area. The fact that the polymers themselves definitely cannot pass into the brain area has been checked more recently by working with fractions of the same polymer labeled in the main chain rather than the side chain [21, 56].

These various considerations concerning the body distribution of polymers and the specific or nonspecific effect of transport systems accord-

Organ	48 h	72 h
serum	650.2 %	434.7 %
blood	473.6 %	284.8 %
liver	107.9 %	85.4 %
spleen	106.3 %	100.5 %
lung	95.0 %	72.9 %
muscle	28.0 %	30.8 %
muscle-tumor	181.3 %	129.5 %
brain	12.1 %	10.2 %

FIG. 13. Body distribution of

$$[CH-CH]_n$$
$$|$$
$$CO-O-CH_2-CH_2-SO-^{14}CH_3$$
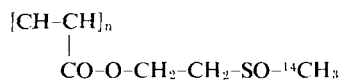
$[\eta] = 37.0$ (ml/g); 30°C, in H_2O in rats with Walker muscle tumor (50 mg i.v./ rat = 0.25 mg/g tissue; 0.25 mg polymer/g tissue = 100%).

ing to Figure 11 are ultimately dependent on the mechanism of uptake of polymers by mammalian cells as mentioned above. This problem will be discussed briefly as the last topic of this survey.

PIGGYBACK ENDOCYTOSIS AND LYSOSOMOTROPIC AGENTS

In 1968 H. J. P. Ryser considered the question of the uptake of polymers by mammalian cells an underdeveloped area of research [46]. As demonstrated recently in a review by DeDuve et al. [57] this field is not only no longer underdeveloped but has blossomed into one of the most fascinating areas of modern pharmacology. Synthetic polymers normally cannot enter cells by diffusion through a membrane or by active processes via membrane proteins. The normal mechanism whereby such a polymer passes the cell membrane is by the process of endocytosis [58–60]. This represents engulfment by an infolding of the plasma membrane with formation of a cytoplasmic vacuole (phagosome) (Fig. 14). Following uptake, fusion with the enzyme-containing lysosomes yields the digestive vacuole.

The endocytosis of polymers is initiated by their adsorption at the cell membrane. This adsorption process plays an important role in the cell uptake of large particles and is influenced by various factors such as molecular weight or charge effects [61, 62]. The higher the molecular weight, the higher the rate of endocytosis. Compounds which are taken up selectively into the lysosomes following formation of the phagosome are
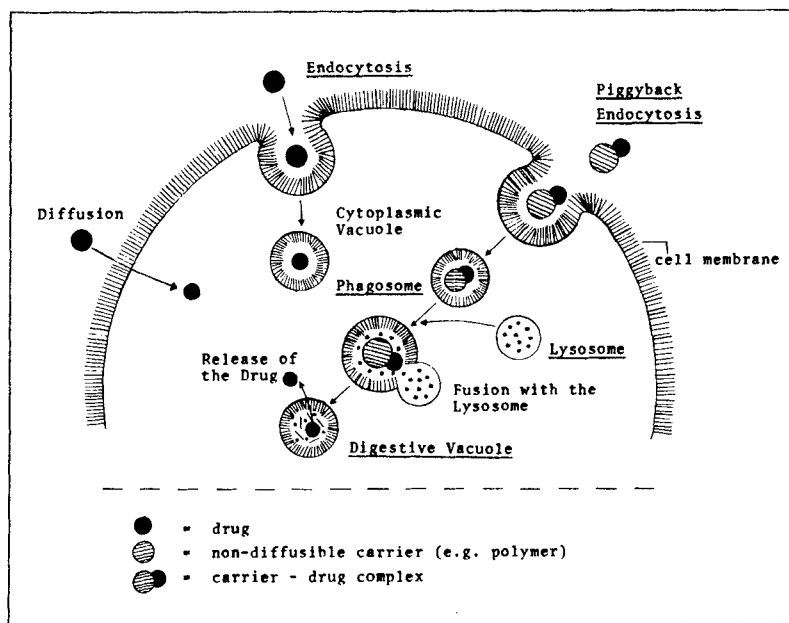
FIG. 14. Mechanism of endocytosis and piggyback endocytosis.

called lysosomotropic [57, 63]. The importance of lysosomotropic agents can be explained in connection with the process of piggyback endocytosis [64], which is also depicted in Figure 14. Piggyback endocytosis is the cell-uptake of a compound, e.g., a drug complexed with or fixed to carrier which is itself subject to endocytosis. Such drugs are released within the cell only after digestion of the carrier or cleavage of the detachable unit (temporary spacer, Fig. 5) by lysosomal enzymes. After their attachment to the carrier, the drug molecules can no longer diffuse freely with the consequence that their intracellular penetration is restricted to the endo-cytotic route, thus giving rise to specific uptake into those cells which display high endocytotic activity.

Recognition of the relevance of the process of endocytosis to the applicability of pharmacologically active polymers can point the way to the possible development of specifically designed polymeric drugs. By varia-tion of the transport system (Fig. 13), it is possible to enhance or inhibit the endocytotic process as well as the lysosomal fusion process.

There are a few examples in the literature showing that the concept of piggyback endocytosis of polymers not only offers wide scope for the design of new types of drugs but is already an established reality. Proteins [50], liposomes [66–69], dextrans [70], latex particles [71], and DNA [12, 57] have recently been used as carriers. Especially interesting are the investigations of Trouet, DeDuve, and Sokal et al., which have already reached the clinical stage [12, 57, 72]. This work involved the use of complexes between DNA and dannorubicin or adriannycin which are

potent cytotoxic agents. The complexes are nontoxic inducers of endocytosis and the carrier is easily degradable by lysosomes. The results so far obtained in the treatment of leukemia, lymphosarcoma, and solid tumors are encouraging.

The author is very much obliged to Dr. L. A. Carpino for intensive and detailed discussions of all the problems presented in this paper and especially of the terminology as given in the model.

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