Chapter 8

BIOADHESIVE HYDROGELS

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TABLE OF CONTENTS

I. INTRODUCTION

A hydrogel is defined as a polymeric material which has the ability to swell in water without dissolving, and to retain water within its structure.[1] There are a variety of synthetic and natural polymers that can be included in this definition. In this chapter, attention will be focused on particular hydrogels possessing bioadhesive properties. It is appropriate to begin this discussion with definitions of bioadhesion and bioadhesive.

Adhesion is defined as the state in which two bodies, in the form of condensed phases, are held together for extended periods of time by interfacial forces.[2,3] These forces may range from valence forces to mechanical interactions, or some combination of chemical and physical interactions. Adhesion is referred to as bioadhesion, if one of the adherends or both are of a biological nature, e.g., proteins, cells, or tissues. A bioadhesive can therefore be defined as a substance which has the ability to interact with biological materials and is capable of being retained on the biological substrates for a period of time. The term "bioadhesion" has been traditionally employed to describe the adhesion phenomena occurring between biological and nonbiological materials rather than interactions occurring between biological objects. One distinctive feature of bioadhesion is that adhesion almost always occurs in the presence of water. In contrast to numerous studies on adhesion in artificial systems, where both adhesive and adherend are nonbiological materials, there are very few useful research papers dealing with bioadhesion, quite possibly due to our poor understanding of biological surfaces. For this reason, bioadhesion has been described from a phenomenological point of view, almost exclusively, rather than from a molecular perspective. Since various adhesion phenomena are commonly referred to as bioadhesion, it is necessary to distinguish different types of bioadhesion. Table 1 shows a classification of bioadhesion based mainly on phenomenological observation, and not on the mechanisms of bioadhesion.

Table 1
TYPES OF BIOADHESION

Type I:	Adhesion between biological objects Examples: cell fusion, platelet aggregation, wound healing
Type II:	Adhesion of biological objects to artificial substrates Examples: cell adhesion to culture dishes, platelet adhesion to biomaterials, microbial fouling, barnacle adhesion to ships
Type III:	Adhesion of artificial materials to biological substrates Examples: adhesion of synthetic hydrogels to soft tissues, adhesion of sealants to tooth surfaces

II. CLASSIFICATION OF BIOADHESION

A. Adhesion Between Biological Objects (Type I)

Type I bioadhesion refers to adhesion occurring between biological objects without involvement of artificial materials. This classification allows separation of natural biological events from artificial ones. If synthetic material is involved in bioadhesion, it will be classified as Type II or III as later described. A good example of Type I bioadhesion is cell-cell adhesion which has been extensively studied for a variety of reasons. Intercellular adhesion has been explained using a physical model which views adhesion of cells as a type of flocculation or coagulation. According to this physical model, cell adhesion results from a balance between nonspecific repulsive and attractive physical forces.[4] Interactions between cells, however, are not considered to be controlled solely by a balance of physical forces. Accumulating evidence suggests that there are cell surface-associated adhesive molecules which mediate specific interactions.[5] Cell adhesion is therefore thought to result from competition between nonspecific repulsion and specific macromolecular bridges.[6] The specific adhesive molecules identified thus far include tissue-specific adhesive molecules, such as cognins,[7] adherons[8] or cell adhesion molecules,[9] lectins,[10,11] glycosyltransferases,[12,13] and other glycoproteins, such as fibronectin,[14,15] laminin,[16] fibrinogen,[17] or von Willebrand factor.[18] Among these, fibronectin appears to be a universal cell-adhesive protein. It is involved in intercellular adhesion, adhesion of cells to culture substrates,[14] and the attachment of some bacteria to endothelial cells.[15] Intercellular adhesion can also be initiated by macromolecules which are not cell-specific. Dextrans and polylysine can aggregate red blood cells by macromolecular bridging.[19] Even a negatively charged natural macromolecule, such as heparin, can induce red blood cell aggregation.[20]

Another example of type I bioadhesion is adhesion between tissues, such as wound healing, pelvic adhesion following ovarian wedge resection,[21] sealing of blood vessels, or bone bonding. The adhesion between two tissues can be accelerated and strengthened by the use of bioadhesives, such as cyanoacrylates[22] and fibrin glue.[23] Adhesion of the mucus gel layer on epithelial cell surfaces in airways or the GI tract also belongs to this type of bioadhesion. Mucus gel is a naturally occurring hydrogel which is adhesive to the underlying epithelial cell surface. Fibrin tissue adhesive is also naturally occurring and adhesion of fibrin glue to biological substrates belongs to this class. Type I bioadhesion will be used as a model for types II and III bioadhesion.

B. Adhesion of Biological Objects to Artificial Substrates (Type II)

Type II bioadhesion is characterized by adhesion of biological materials to artificial substrates, such as synthetic polymers. Cell adhesion and spreading on culture dishes or other synthetic hydrogels are necessary steps for cell growth and proliferation in vitro. Most of the adhesive proteins for intercellular adhesion can also play an adhesive role for cell

adhesion to substrates. For example, fibronectin is highly effective as a cell-to-substrate adhesion molecule after it has been adsorbed to a substrate.[16,24] A region of fibronectin termed the "cell-binding" region, which interacts with the cell surface to mediate cell attachment and spreading on substrates, has been identified and localized to polypeptide fragments.[25,26] Even synthetic peptides can cause cell adhesion to substrates.[27] Thus, the cell attachment peptide, when attached to a substrate surface, can be used as a model adhesive for this type of bioadhesion. Platelet adhesion to blood contacting biomaterials is also known to be influenced by adsorbed protein molecules.[28] Adhesion of bacteria to tooth surfaces and attachment of marine bacteria[29] or barnacles[30] to submerged surfaces, such as hulls of ships, are also mediated by adhesive molecules released from the organisms. The adhesion is nonspecific and so tenacious that simple washing cannot detach them from the surfaces.

It appears that the adhesiveness of surfaces is determined by the adsorption of cell-adhesive proteins which precedes cell adhesion. Current understanding is that the surface energetics of the solid substrate defines the type of protein molecule or the conformation of the adsorbed protein layer, which in turn determines the adhesiveness of the substrate. Details of the interplay between surface energy and protein adsorption, however, are not well understood.

C. Adhesion of Artificial Materials to Biological Substrates (Type III)

Type III bioadhesion is distinguished from type II in that artificial adhesives adhere to biological substrates. This type of bioadhesion includes adhesion of soluble polymers or hydrogels to biological surfaces, such as the mucin/epithelial cell layer, skin, tooth, or bone.

Extensive reviews on intercellular adhesion (type I bioadhesion), cell adhesion to solid substrates (type II bioadhesion), and the role of protein molecules in cell adhesion are available.[31-33] Consequently, the thrust of this chapter will be primarily on type III bioadhesion.

III. THEORIES OF ADHESION

The range of adhesion extends from cell adhesion, which is of paramount importance in biotechnology, to adhesive tapes used in daily life. Compared to the wide range of adhesion phenomena we are dealing with, there are only a small number of theories. This small number does not imply that they are able to explain adhesion adequately or that they are in agreement with each other. A particular theory based on one concept usually explains adhesion only to a limited degree and commonly disagrees with other theories. The relative importance of each theory depends on the chemical nature of particular adhesive/adherend combinations. When one component of adhesion is isolated in a particular system, other molecular interactions which are also responsible for the unique properties of various substances are neglected.

The area of bioadhesion is relatively new and no comprehensive theory has been established or even proposed. This is simply because there are too many bioadhesion phenomena as described earlier, and no one single theory can fully explain each independent bioadhesion phenomenon. For this reason, development of bioadhesives has been empirical. A very brief review of adhesion theories will be useful in establishing preliminary theories of bioadhesion. The theories of adhesion have been classified into four principal subsets for both historic and geographic reasons.

A. Mechanical Theory

The mechanical theory is the oldest explanation for adhesion.[34] In this theory, the adhesive has to flow into the pores and interstices of the material to establish mechanical embedding.[35] The prime factor in mechanical adhesion is that embedded adhesive solidifies and becomes inextractable. As a result, the adhesive force is determined by the work to break adhesive extensions off the adhesive mass. Thus, the mechanical theory leans heavily on irregularities

of the surface, although specific adhesion is necessary for retention of adhesive within the pores.

This theory can be used to explain many cases of bioadhesion. Dental restorative materials are used to permanantly seal the filled cavity. Retention of the restorative material is improved by etching the cavity surface with acid.[36,37] Improved performance is thought to result from increased micromechanical attachment by better penetration of the adhesive into the pits of the enamel surface. Fibrinogen or cyanoacrylates polymerize and become solidified after filling all the porous areas of the tissue.

B. Electrostatic Theory

This theory states that an electrical double layer is produced at any interface and the consequent Coulombic attraction largely accounts for adhesion and resistance to separation. This theory was seriously contested by Voyutskii[38] who proposed the alternative diffusion theory.

C. Diffusion Theory

The basic tenet of this theory is that adhesion occurs through interdiffusion of the adhesive and adherend across an interface. This theory has been applied to adhesives involving polymeric materials. Since diffusion of polymer molecules can be considered as a form of molecular attraction, there must exist thermodynamic compatibility between the adhesive and the adherend.[39] In this theory, adhesion is treated as a three-dimensional volume process rather than a two-dimensional surface process. This is well suited for bioadhesion because physical entanglement between biomolecules and synthetic polymers is very common. The adhesion of polycarbophil (cross-linked polyacrylic acid) to the mucus layer of the GI tract is known to be mediated by physical entanglement.[40]

D. Adsorption Theory

The essence of this theory is that surface forces are involved in adhesion, and that polar molecules or groups, if these are used, are oriented in an ordered way so that surface molecules of adhesive and adherend are in contact.[41] The possibility of good adhesion can be correlated with wetting, which is the initial physical process occurring in interfacial bonding. Many attempts have been made to explain bioadhesion using surface energy analysis. Protein adhesion,[42] cell adhesion,[43] and cell spreading[44] have all been studied by this approach. If this theory is correct, the surface energy is expected to correlate with adhesive strength. However, correlations sufficient to support the theory have not been observed.[41]

IV. MODEL BIOADHESIVE

It is clear from the earlier discussions that bioadhesion is not a phenomenon which can be explained by any simple model or theory. Nevertheless, it is necessary to have a model system in order to study a particular bioadhesion phenomenon and subsequently to develop new bioadhesives. Considering the fact that all biological materials are negatively charged, polycations would appear to be the best bioadhesives. The interaction of polycations with cell surfaces, or mucin molecules which cover cell surfaces, is obviously magnitudes higher than polyanions or neutral polymers.[45] Polycations, however, tend to precipitate proteins and disrupt cell membranes. Thus, they are less desirable as model bioadhesives in this discussion where type III bioadhesion is of major interest. The mucus gel itself can be considered as a model bioadhesive hydrogel, since it has strong cohesive properties as well as adhesive properties to other molecules and firmly binds to the epithelial cell surface.[46]

Mucins are slimy viscoelastic glycoproteins that constitute a major part of mucus which contains more than 95% of water and coats all mucosal surfaces. The mucus is generally

heterogeneous in thickness and is present as a thin, continuous translucent gel cover adherent to the mucosal epithelial surface.[47] Multiple biological functions, requiring such physical properties as low solubility, high viscosity, elasticity, and adhesiveness, are thought to result from functional domains of the mucin molecule[48] and microheterogeneity in the size, composition, and charge of the oligosaccharide chains.[49] For a more comprehensive picture, the functions of the mucus layer are briefly described with associated examples.

A. Proposed Roles of the Mucus Gel Layer

Mucus gel plays a number of very important roles in maintaining homeostasis of epithelial cells. The various functions of the mucus layer can be collectively summarized as either protective or barrier.

1. Protection

One of the major functions of the mucus layer is protection of the underlying mucosa from mechanical damage, such as shear forces during blinking in the eye, exogenous insults to the oral cavity, or the passage of food in the intestine, by lubricating the surface of the epithelial cells. Mucus glycoproteins are negatively charged due to the presence of ester sulfate and/or sialic acid groups on the mucin molecule. Water molecules become organized in multiple interacting layers around these charges and consequently the mucus layer can hold large volumes of water. This can provide epithelial cells with a constant aqueous environment and an appropriate milieu for the movement of cilia which line most of the epithelial cells.[50] The optimum mucin concentration for the lubrication effect on ciliary propulsion in tubes was found to range between 1.7 and 4.1% mucin.[51] Thus, it is expected that mucin concentration in vivo is in about the same range. In the stomach and duodenum, epithelial cells are protected from acid and pepsin in gastric juice by virtue of this mucus layer.[52] In addition, the mucus layer has been postulated as the "first line of defense".[53] It is expected that the thicker the mucus layer, the greater the protective effect. However, it has been suggested that the cytoprotective role of the mucus layer is not by virtue of an increase in thickness of the gel layer adherent to the gastric mucosa.[54]

2. Selective Permeability Barrier

Mucin secreted by the goblet cells appears to be the decisive luminal barrier to passage of a compound through the gut wall.[55] The mucus layer can influence the concentration of substances in the immediate vicinity of the cell membrane through filtration of solute or foreign particles by its gel network.[50] Macromolecular compounds and microorganisms can be easily filtered. The mucus gel, however, is composed mostly of water and diffusion of small ions should not be affected more than by an unstirred water layer.[46] The upper limit on the size of the molecule that can penetrate the mucus gel has not yet been determined. Mucin can protect tissues by favoring attachment and subsequent proliferation of certain microorganisms and/or by promoting the clearance of others.[48] Later in this chapter, structural requirement as to bioadhesive polymers will be discussed. In this context, it is helpful to summarize the possible reasons for the adhesive properties of mucus.

B. Analysis of Rheological Properties

Some of the biologically important proteins, such as fibronectin,[56] immunoglobulins[57] or collagen[58] have been extensively studied to assign definite functions to the various structural domains of each molecule. However, the structure of mucin is not well understood and its relationship to functional domains has yet to be determined. The propensity of mucins to form homotypic and heterotypic complexes is thought to result from various interactions.

1. Interaction Between Mucin Molecules

Interchain disulfide bridges have been observed in porcine gastric mucin,[59] human bronchial mucin,[60] and monkey saliva mucin.[61] Mucus glycoproteins exist as a multimer through formation of disulfide bonds between monomer units, and this polymeric structure maintains its viscious and gel-forming properties. The cleavage of disulfide bonds results in an irreversible loss of viscosity and gelling properties.[48] There might be other cross-linking agents, such as lectins, which can form a mucus network or gel.[62]

The nature of the noncovalent interactions that lead to self-association is unknown, but association must involve carbohydrate-carbohydrate, carbohydrate-protein or protein-protein interactions, or all three.[63] When mucin is hydrated and swells, long oligosaccharide chains can form carbohydrate-carbohydrate cooperative "junction zones", like agar gels.[64] Hydrophobic interactions are also believed to play a role in stabilizing the structure of hen egg white ovomucin.[65] This hydrophobic interaction may occur between sugar residues[66] or nonglycosylated protein regions which contain hydrophobic amino acids.[67] The high content of glycine and proline of the peptide core[63] provides mucin with a self-aggregating ability as a result of high flexibility which favors physical entanglement.

Mucin molecules will form a gel at a solution concentration of approximately 20 mg/mℓ. Mucin gel, at a concentration of about 50 mg/mℓ, possesses characteristics of the native mucus gel taken directly from the gastric mucosal surface.[68] It has been estimated that mucin molecules start to interpenetrate at approximately 0.5 mg/mℓ, with a degree of entanglement which is a function of the size and shape of the molecule.[69] Although physical entanglement alone may not be sufficient to explain the properties of mucus, it must be an important factor in formation of the mucus gel.

Ionic interactions between amino groups and carboxyl groups can also mediate complex formation[63] and thus influence the physical properties of mucin. Small amounts of calcium are reported to increase viscosity of canine tracheal mucin[70] and rat goblet cell mucin.[71] Whether binding of calcium to sialic acid is responsible for these observations remains to be determined.

2. Interaction with Other Macromolecules

Mucin forms heterotypic complexes with other biopolymers, such as albumin,[72] IgA,[73] and lysozyme.[74] Albumin dramatically enhanced the viscosity of hog gastric mucin.[72] Such complexes might reduce or enhance specific biological functions.[48] The effect of biopolymers on the viscoelastic properties and mucociliary transport rates of mucus gels was measured by Marriott et al.[75] It was shown that all of the biopolymers tested, i.e., DNA, IgG, IgA, and albumin, thickened the mucus gel with an order of effectiveness which was directly related to the molecular weight of the added species. The presence of cross-linking factors was proposed to explain the physical properties of the gel.[66,76] This proposal, however, was not proven.

Many of the effects of mucin can be imitated by sulfated carbohydrates such as heparin[77] and sodium pentosanpolysulfate,[78] thus suggesting the importance of polysaccharides with a high charge density.

As discussed above, the best bioadhesive candidates which can be used in vivo and which minimize undesirable side effects, would appear to be mucomimetic hydrogels. In this sense, the search for bioadhesive polymers is essentially the same as determining the structural features of mucin which are responsible for their physicochemical and biological properties. Although the nature of the mucus gel is still not well understood, some observed properties and structural features of suggested mucin models can be used as a starting point to study bioadhesive hydrogels.

V. TYPE III BIOADHESION

The lack of a universal method to measure the adhesive strength of a synthetic polymer to a biological surface in an unambiguous manner has hindered quantitative evaluation of

various bioadhesives. Even for a given method, a small change in variables such as applied force, the rate of removal of the adhesive, contact area, impurities, or characteristics of biological adherends, results in completely different values so that the measured bioadhesiveness tends to be subjective. In addition, there is more than one type of stress which can be important in assessing adhesive strength. Various tests are carried out in shear, tension, peel, and cleavage experiments. Resistance to tensile stress may be much greater than to shear stress or vice versa depending on the system. As a result, the absolute value of adhesion strength depends on the nature of the experiment and it is not possible to assign an absolute value representing bioadhesiveness for a particular bioadhesive. When a bioadhesive for a specific application is selected by screening various candidate materials, appropriate experimental techniques, the required strength, and the type of biological adherend should be considered first. Once a test method is established, the best way to characterize bioadhesive properties of various polymers is to have a comparative measure of adhesive performance. In this regard, no attempt will be made in this chapter to defend absolute numbers describing bioadhesiveness for a variety of polymers. Numerical values will be used on a comparative basis to establish adhesive properties measured by a certain method. The following test methods have been used to provide quantitative or qualitative measurements of bioadhesion. Since there are no standard test methods and testing conditions, these methods can be modified and/or improved for specific applications.

A. Test of Bioadhesion

1. Methods for Insoluble Polymers

a. Adhesion Test Using Two Tissue Layers

The bioadhesive ability of candidate materials is often tested in vitro by using biological substrates as adherends. A bioadhesive polymer is placed between two tissue layers in an appropriate buffer solution and the force to detach them measured (Figure 1A). The advantage of this method is that attachment of the test polymer to another solid support is unnecessary. This technique is particularly useful for testing of synthetic hydrogels. Under well-controlled conditions, i.e., constant apparent surface area, applied force, and pulling speed, reproducible results can be obtained. This tensile test has been employed to measure adhesiveness of various hydrogels to soft tissues, like mucosal surfaces[40] of the GI tract, and to lung or muscle tissues.[22] Small pieces of tissue samples sandwiching an adhesive polymer were pressed together for a preset period of time and with predetermined force. The tensile strength of the adhesive was measured by determining the force to detach the two tissue layers.

b. Adhesion Test Using One Tissue Layer

This method is useful when tissue is not available in large quantity. In contrast to the above test, the bioadhesive to be tested should be attached to a solid support (Figure 1B), although this can be avoided if the hydrogel or test adhesive is large enough (Figure 1C). The adhesive strength between the bioadhesive and solid support should be greater than that between the bioadhesive and tissue layer. The adhesiveness of various synthetic adhesives to skin,[79] parenchymal tissue,[80] and dental enamel[81] were evaluated with this simple tensile test. Recently, adhesion forces were measured between various hydrogels and the rabbit corneal endothelial cell surface which were submerged in an aqueous saline solution.[82] Shear testing has also been used to measure adhesiveness of dental restoratives to enamel surfaces.[83]

c. Measurement of Intrinsic Adhesiveness

Adhesive force is a function of many variables, such as applied pressure, contact time, and type of tissue. To minimize artifacts due to such factors, it is useful to measure intrinsic adhesive strength. Thus the adhesive strength is measured as a function of one variable and the adhesiveness is extrapolated back to zero influence of the variable. An example is shown

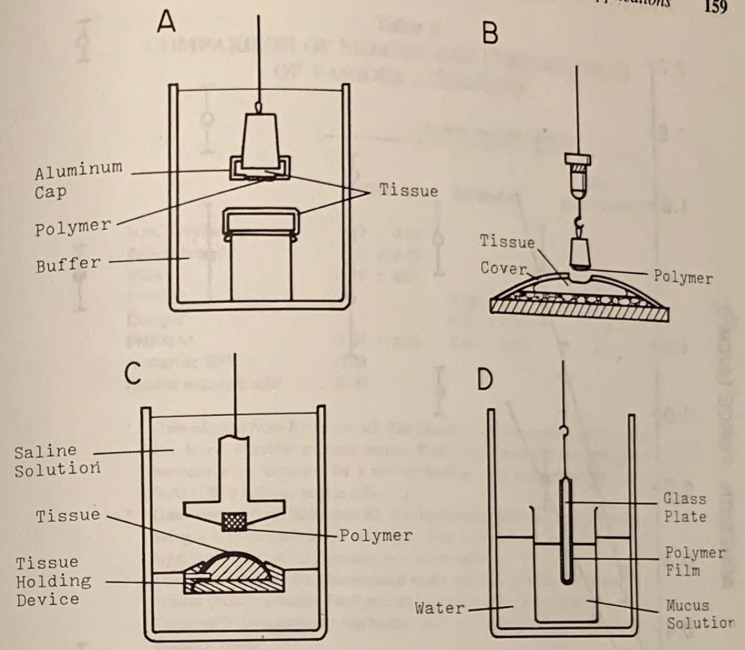

FIGURE 1. Examples of bioadhesion tests. (A to C) Adhesion tests for hydrogels using one[80,82] or two[40] tissue layers. Test hydrogel is placed between two tissue layers (A) or attached to a solid support (B). (D) Adhesion test for soluble polymers using glass plate.[85]

in Figure 2. The adhesive force for detachment was measured as a function of the applied force which was varied from 500 mg to 4 g, while other variables were kept constant. The plot of adhesiveness vs. applied force was then extrapolated to zero applied force.[40] Although intrinsic values can be obtained and reproduced, caution should be exercised with regard to its interpretation as a true adhesion force. It should be borne in mind that surface irregularities and minute protuberances prevent perfect contact between adhesive and tissue, which results in an imperfect interface. Thus, the effective area of contact is uncertain and difficult to determine, and the force required to separate the surfaces gives no clue to the true strength of the bonding at the points where contact does occur.[84]

2. Methods for Soluble Polymers

a. Adhesion Test Using Mucus Solution or Tissue Layer

For soluble polymers, direct measurement of bioadhesiveness to a tissue surface by a tensile test is difficult. Smart et al.[85] measured interaction of soluble polymers with mucus molecules by coating a glass plate with soluble polymers and measuring the force to move it through a mucus solution using a tensiometer (Figure 1D). Obviously, there are a number of uncertainties in the method. It is not clear to what extent soluble polymers adsorb and cover the glass surface. In addition, it is not possible to know whether the measured force is due to adhesion failure between mucus and polymer molecules or cohesion failure between polymer molecules. It would be more informative if a whole tissue is cut into appropriate sizes and immersed in a solution of test bioadhesive polymers and the force for detachment measured. The result obtained by the glass plate method, however, agreed fairly well with those measured by other techniques.

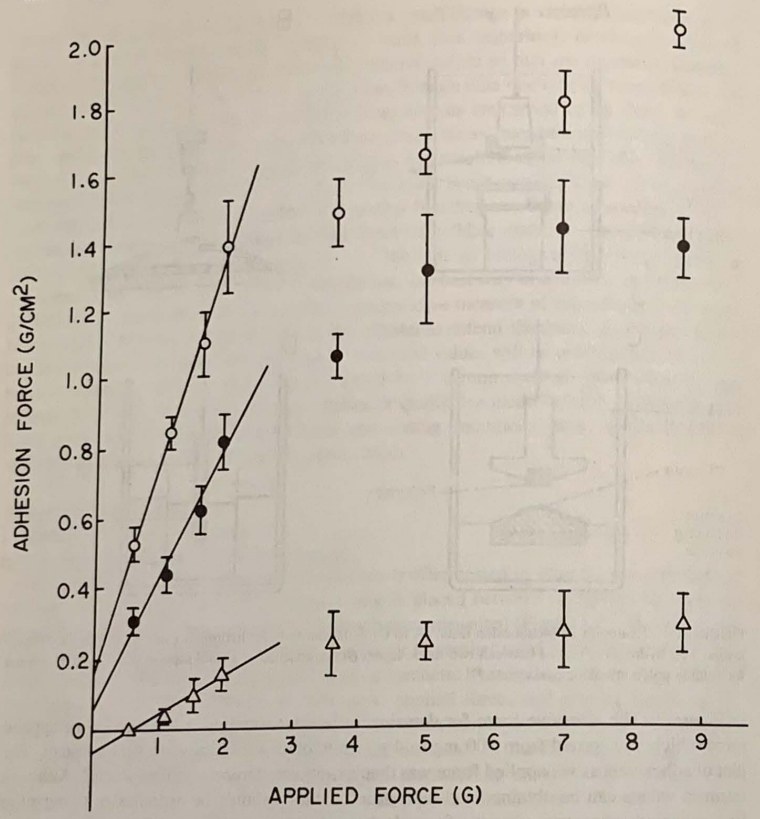

FIGURE 2. Measurement of intrinsic bioadhesiveness of hydrogels. Adhesion force was measured after placing polycarbophil (○), cross-linked polymethacrylic acid (●), and polyhydroxyethyl methacrylate (△) between two layers of rabbit stomach tissue in the simulated gastric fluid and applying force for 1 min.

b. Fluorescent Probe Method Using a Cell Suspension

Recently, a new technique employing a fluorescent probe was developed to measure the bioadhesion of various soluble polymers to a cell membrane.[87] The adhesiveness of test polymer molecules to the cell surface was quantified by the change in membrane viscosity. An alteration in membrane viscosity after polymer binding was measured from the change in fluorescent spectra of pyrene which was incorporated into the lipid bilayer of the cell membrane. A number of charged and neutral polymers were tested and compared in a quantitative manner.

B. Bioadhesive Hydrogels

Hydrogels adapted for contact lenses or introcular lenses demand a minimum bioadhesive ability. In this case adhesion between hydrogels and epithelial cells, endothelial cells, or protein is undesirable. On the other hand, hydrogels for drug delivery systems need to stay on tissue surfaces for a long period of time and thus require maximum bioadhesion. The

Table 2
COMPARISON OF BIOADHESIVE PERFORMANCES OF VARIOUS HYDROGELS

	Tensile strength (g/cm²)		
	Method A[a]	Method B[b]	Rel. performance
NAC/polycarbophil[c]	1.49 ± 0.07		37.3
Polycarbophil	1.09 ± 0.07		27.3
PMA[d]	0.39 ± 0.07		9.8
PMMA[e]		0.66 ± 0.11	7.3
Duragel[f]		0.14 ± 0.05	1.6
PHEMA[g]	0.04 ± 0.01	0.09 ± 0.02	1.0
Amberlite 200[h]	0.00		
Gelatin microcapsule[i]	0.00		

[a] Data adapted from Reference 40. The bioadhesiveness was measured by using two layers of rabbit stomach tissues. Two tissue layers with test hydrogel in between were contacted for 1 min by loading 1.8 g in the simulated gastric fluid (USP) without pepsin (pH 1.2).
[b] Data adapted from Reference 82. The bioadhesive performance was tested by using a corneal endothelial cell layer. Test hydrogel was placed on the cell layer for 30 sec at 16 g loading in a saline solution.
[c] The mucosal side of rabbit stomach tissue was treated with 20% *N*-acetyl-L-cystein (NAC) solution for 5 min and polycarbophil (polyacrylic acid cross-linked with divinylglycol) was tested. NAC is a mucolytic agent which breaks disulfide bonds.
[d] Polymethacrylic acid cross-linked with divinyl benzene.
[e] Polymethylmethacrylate.
[f] A soft lens hydrogel based on an amino-polyamide polymer.[82]
[g] Polyhydroxyethyl methacrylate.
[h] Cation-exchange resin (Rohm-Haas).
[i] Cross-linked with formaldehyde.

bioadhesive properties of a number of synthetic hydrogels were measured by a simple tensile test using either one or two tissue layers.[22,40,79,82] For reasons mentioned earlier, the absolute values for bioadhesiveness obtained from different laboratories cannot be compared, but a relative comparison can be made. As shown in Table 2, it is possible to compare bioadhesive performances observed under different experimental conditions, if there is at least one common test material. One interesting observation is that polycarbophil has a superior bioadhesive property compared to other hydrogels. Polycarbophil binds tenaciously to mucin/epithelial cell surfaces, cultured cell monolayer, or skin, while other hydrogels are easily washed off.[88] When tested in an animal, gastric half emptying of polycarbophil was about 5 hr in a dog[89] and 12 hr in a rat,[40] which is approximately twice as long as that of polymethacrylic acid. Polyacrylic acid is also known to be superior to polymethyl methacrylate as a dental cement.[81] The general tendency observed is that bioadhesiveness increases as the charge density increases and the structure of polymer becomes simpler. When hydrogels become more hydrophobic as with polyhydroxyethyl methacrylate, they tend to interact with each other, thus reducing interaction with mucus layers. The absence of bioadhesive properties of Amberlite® resin and cross-linked gelatin microcapsules is thought to be due to the lack of chain flexibility which is required for physical entanglement with the mucin molecules.

One of the critical factors affecting overall bioadhesive performance is the pressure applied to contact the tissue layer and hydrogel. To find out the interaction force when no pressure is applied to contact adhesive and adherend, the intrinsic bioadhesiveness was measured, as shown in Figures 2 and 3. There are four aspects worthy of notice. The first is that the

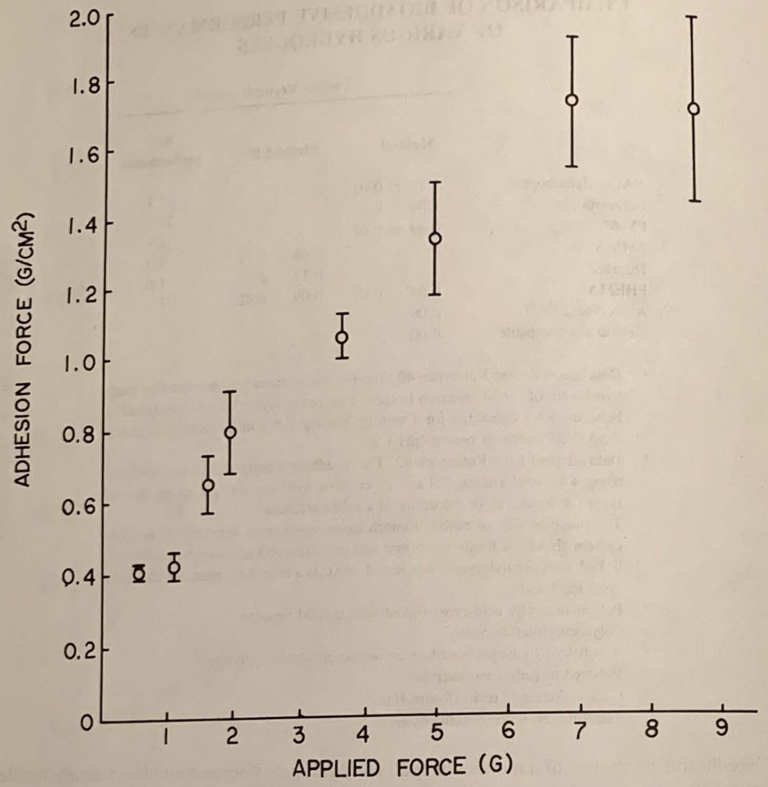

FIGURE 3. Measurement of intrinsic bioadhesiveness of mucus layers. Two layers of rabbit stomach tissue were contacted for 1 min in the simulated gastric fluid and adhesion force was measured.

order of intrinsic bioadhesiveness is the same in the presence and absence of applied pressure. The second is that all three hydrogels tested show a break in adhesiveness with the exception of mucin (Figure 3). The slope observed above 2 g of initial applied pressure is greater than that below 2 g. The interactions of hydrogels with the mucus layer are schematically shown in Figure 4. For a good bioadhesive such as polycarbophil, the penetration of a hydrogel into the mucus layer is dependent on the initial applied pressure. A poor bioadhesive hydrogel, like polyhydroxyethyl methacrylate (PHEMA), shows little pentration into the mucus layer. Thus, adhesion is a function of the applied pressure only to a certain level. A moderately bioadhesive hydrogel, like cross-linked polymethacrylate, shows a capability to entangle with the mucus layer, although the depth of penetration is shorter than that of polycarbophil. The break happens to occur at the initial applied pressure of 2 g, but its significance is different for each hydrogel. The break observed with polycarbophil may imply that the mucus layer consists of at least two distinct layers of which the bottom layer is less adhesive to hydrogels. The less adhesiveness of the bottom layer is expected to result from a denser packing of mucin molecules which prevents mucin molecules from free rotation and high flexibility. To test this assumption, the mucus layer was briefly treated with a mucolytic

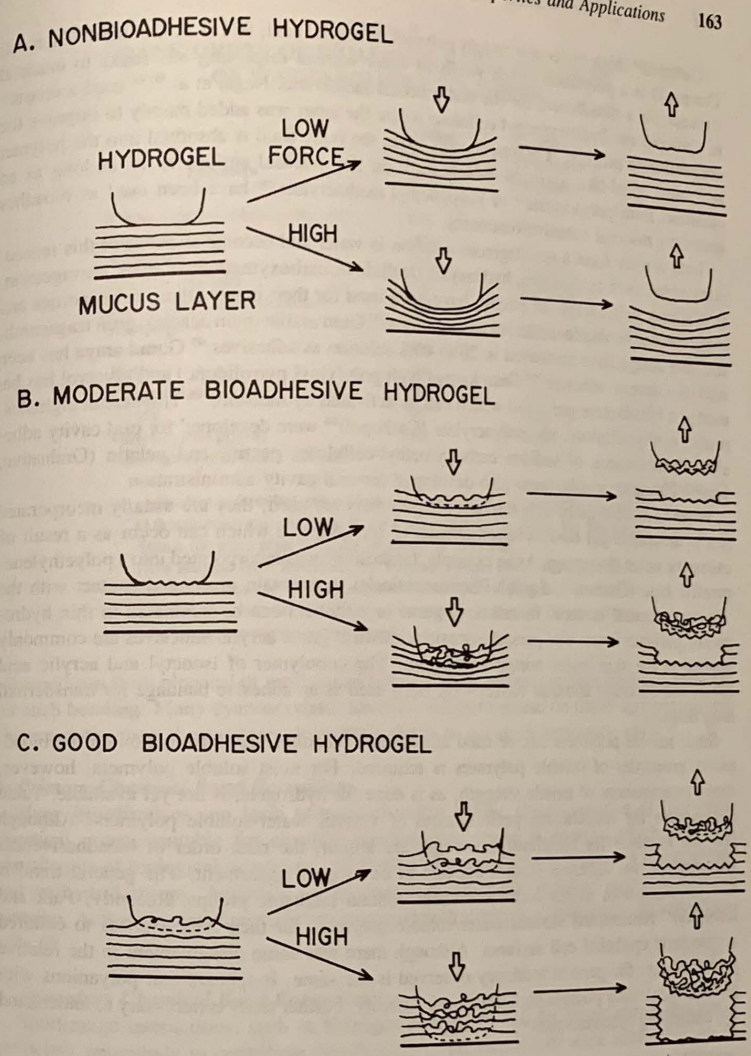

FIGURE 4. The interaction between mucus layer and hydrogels. Interactions of the mucus layer with poor, moderate, and good bioadhesives at low and high applied forces are shown.

agent. As shown in Table 2, the adhesiveness of polycarbophil was increased about 40%. Partial mucolysis can increase the flexibility of mucin molecules which improves their interaction or entanglement with hydrogels. The third important aspect is that the intrinsic adhesiveness of PHEMA is negative (Figure 2). In other words, if external force is not applied, PHEMA will repel mucin molecules. This supports the concept that adhesion occurs through physical entanglement. The fourth observation is that the mucin-mucin interaction is greater than the intrinsic adhesiveness of polycarbophil to mucin. This is reasonable because the mucin-mucin interaction should be spontaneous to form a thick mucus gel.

Carbopol® (high molecular weight polymer of acrylic acid, 934 B.F. Goodrich Chemical Company) is a polyanion which swells in water without dispersing and sticks to mucosal surfaces. As a bioadhesive for the oral mucosal membrane, Nagai et al.[90,91] used a mixture of Carbopol and hydroxypropyl cellulose where the latter was added mainly to improve the drug-releasing property. Carbopol swells when the body fluid is absorbed into the polymer and forms a gel-like aggregate which stays on the mucosal surface twice as long as an ointment. Both polyacrylate[97] or poly(methyl methacrylate)[96] have been used as bioadhesive agents for mucosal adhesive ointments.

Gums usually form a mucilaginous solution in water and become sticky. For this reason, many gums, such as alginates, hydroxyalkylcellulose, carboxymethylcellulose, carrageenan, gum arabic, gum karaya, or pectin, have been used for their innate adhesive properties and to provide thickening for adhesive formulations.[92] Gum arabic (gum acacia), gum tragacanth, and gum karaya have been used in 20 to 40% solution as adhesives.[93] Gum karaya has been used as a denture adhesive.[94] Gum karaya with poly(vinyl pyrrolidone) and glycerol has been used as a bioadhesive precursor which can be activated by moisture.[95] Tragacanth alginates, pectin, methylcellulose, and polyacrylate (Carbopol)[96] were developed for oral cavity adhesion. Combinations of sodium carboxymethyl-cellulose, pectin, and gelatin (Orahesive, Squibb Pharmaceuticals) were also developed for oral cavity administration.

When vegetable gums or water-soluble polymers are used, they are usually incorporated in a hydrophobic gel base to retard erosion of the adhesive which can occur as a result of excessive water absorption. As an example, Orahesive® was incorporated into a polyethylene-paraffin base (Orabase®, Squibb Pharmaceuticals) to maintain prolonged contact with the wet oral mucosal surface. Bioadhesive gums or polymers can be laminated to thin hydrophobic polymer films. The pressure-sensitive medical grade acrylic adhesives are commonly applied to the skin under normal conditions. The copolymer of isooctyl and acrylic acid (94:6) and dimethyl siloxane rubber have been used as an adhesive bandage for transdermal drug delivery.[98]

Since soluble polymers can be used as effective bioadhesives, information on the bioadhesive properties of soluble polymers is required. For most soluble polymers, however, direct measurement of tensile strength, as is done for hydrogels, is not yet available. Table 3 compares the bioadhesive performances of various water-soluble polymers. Although absolute numbers for bioadhesive strength are absent, the rank order of bioadhesiveness measured in two different studies appears to be in good agreement. The general trend is that polymers with higher bioadhesiveness contain ionizable groups. Recently, Park and Robinson[87] reexamined various water-soluble polymers for their adhesiveness to cultured conjunctival epithelial cell surfaces. Although there was some disagreement in the relative performances, the general tendency observed is the same. It appears that polyanions with high charge density possess high bioadhesive ability. Further study is necessary to understand the underlying mechanism(s).

VI. MECHANISM OF BIOADHESION

The major problem in the field of bioadhesion has been the lack of an appropriate theoretical model and adequate experimental techniques to characterize bioadhesives and biological substrates. Proposed mechanisms remain conjectural and listed requirements for bioadhesion are derived purely from observations of many different systems. We will begin this section by considering the possible types of interactions occurring in bioadhesion.

A. Interactions Involved in Bioadhesion

1. Nonspecific Adhesion

a. Physical or Mechanical Bond Formation

Highly fluid adhesives which are able to penetrate into the cracks and crevices of the

Table 3
RANK ORDER OF BIOADHESIVE PERFORMANCES OF WATER-SOLUBLE POLYMERS

Polymers	Relative mucoadhesive force[a]	Qualitative bioadhesive property[b]
Carboxymethylcellulose (Na salt)	193	Excellent
Carbopol	185	
Tragacanth	154	Excellent
Alginate (Na salt)	126	Excellent
Hydroxypropylmethylcellulose	125	
Karaya gum		Satisfactory
Gelatin	116	Fair
Pectin	100	Poor
Poly(vinylpyrrolidone)	98	Poor
Acacia	98	Poor
Poly(ethylene glycol)	96	Poor
Carboxymethylcellulose (Ca salt)		Poor

[a] Data adapted from Reference 85. A glass plate dip coated by soluble polymer (1% solution) was immersed in the mucus solution for 7 min. The force to detach the glass plate from the solution was measured.

[b] Data adapted from Reference 86. Polymer powder (60%) was mixed with polyisobutylene (40%) and laminated to a thin polyethylene film. The bandage was pressed with a finger onto the anterior gingiva for 30 sec and the adhesiveness qualitatively measured.

adherend can form physical or mechanical bonds. Tissue surfaces present large opportunities for such bonding. Many cyanoacrylates have the ability to spread on tissue surfaces and this characteristic gives the cyanoacrylates their ability to act as an hemostatic agent.[99]

b. Primary Chemical Bond Formation

Many bioadhesives can form primary chemical bonds, since a number of functional-chemical groups suitable for covalent bonding are present in proteins which are major constituents of biological substrates. Alkylating agents can readily react with amino groups and sulfhydryl groups. Acylating agents react with amino and hydroxyl groups of serine or tyrosine. Amino groups of proteins can also react with aldehydes, isocyanates, and diazonium salts.[100]

c. Secondary Chemical Bond Formation

Short-range interactions, such as hydrogen bonding or van der Waals attractions, are of sufficient magnitude to contribute significantly to the strength of some adhesive joints.[100] Adhesive and adherend should be in close proximity for such interactions to be effective. Even relatively simple polymers can effect extremely high adhesion, through very weak but numerous secondary interactions.

2. Specific Adhesion

As discussed in types I and II bioadhesion, there can be specific interactions mediated by protein molecules. Specific adhesion is expected to be more common on living surfaces than inanimate surfaces. It is clear that specific interactions depend on the nature of adhesive and adherend.

B. Requirements for Bioadhesives

1. Flexibility

Flexibility of the adhesive is important to permit the adhesive to conform to the adherend. The flexibility of a polymer backbone is influenced by the steric effect of substituent side groups. As the size of the substituent side group becomes larger, chain flexibility is considerably impaired. London dispersion forces, which are significant in forming secondary chemical bonds, act at a distance of approximately 4 Å and require intimate contact. Thus, it is understandable that adhesiveness is influenced by flexibility of the adhesive molecule. The importance of chain flexibility is well reflected in the proposed mechanism of wet adhesion by Chen and Cyr[86] which will be discussed later. If side chains are flexible, they then confer internal plasticization to the whole polymer structure. When a high degree of internal plasticization is achieved, the product becomes tacky and suitable as an adhesive.[101] Increased cross-linking obviously reduces chain flexibility and a decreased bioadhesive performance is expected. However, a thorough systematic study is lacking.

2. Molecular Weight

Higher molecular weight leads to higher cohesive strength and reduces creep due to the greater degree of chain entanglement resulting from longer chains. It has been observed that adhesive force increases as polymer molecular weight increases until a plateau value is reached.[85] At higher than optimum molecular weight, adhesion may be reduced due to reduced penetration of the adherend surface by adhesive polymers owing to their low mobility. This can be explained by using the diffusion theory of adhesion as discussed earlier.[101] Within a molecular type, chain length may be a determinant of adhesive strength.[86] The general observation is that the longer the chain length, the better the bioadhesion.

Side-chain length also influences bioadhesive abilities. As an example, polyglutamic acid showed higher cell adhesive behavior than polyaspartic acid.[87]

3. Functional Groups

Effective adhesives usually contain numerous hydrogen bond forming functional groups and hydrogen bonding appears to play a major role in wet adhesion.[86] The excellent performance of adhesives containing phenolic or aliphatic hydroxyl groups with polar substrates can be explained by formation of hydrogen bonds. Hydrophilicity of adhesive formulations permit good adhesion by overcoming the destructive actions resulting from normal secretions of body fluids or mechanical movements.[86] The hydrophilic nature may enhance the cohesive properties of the adhesive by minimizing slippage of the polymer chains. By comparing the amino acid content of bioadhesives from various sources, Wake[93] pointed out that amino acid compositional differences between biological adhesives do not appear important provided that the free carboxylic acid groups from aspartic and glutamic acids, the hydroxyl groups from threonine, serine, and hydroxyproline, and the strongly basic arginine are present.

4. Charge Density

The reason for the excellent bioadhesive property of polycarbophil or Carbopol is not yet clear, but it is observed that they are both polyanions with high charge density. It was also concluded from a study of polymer interactions with cell membranes that high charge density was an important element for bioadhesion.[87] The immediate question to this observation should be the mechanism whereby negatively charged polymers can bind in such an effective way to a mucus surface of the same sign. When the bioadhesiveness of polycarbophil to the rabbit stomach was tested by a tensiometer as a function of pH, the following result was observed as shown in Figure 5.[40] As the pH was increased, charge repulsion between two

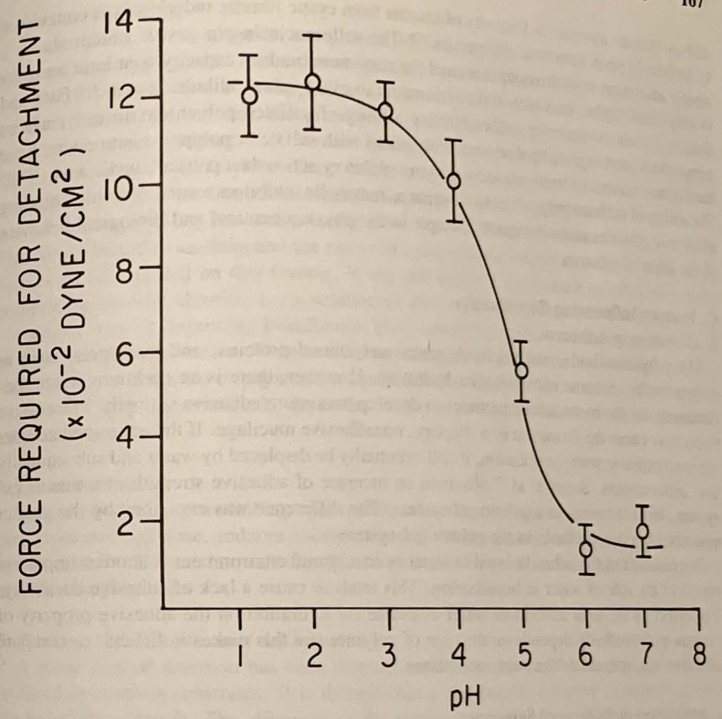

FIGURE 5. The effect of pH on adhesion force. The adhesion force of polycarbophil to rabbit stomach tissue was measured in the simulated gastric fluid after placing the hydrogel between two tissue layers and loading 1.8 g for 1 min.

negatively charged polymers, i.e., polycarbophil and the mucus layer, was also expected to increase, and reduced adhesion of polycarbophil to the stomach mucosal surface was anticipated. The interaction, as expected, decreased as the pH was increased. The maximum interaction was observed at pH lower than 3. Above pH 4, a dramatic decrease in the interaction was observed. The interaction of polycarbophil with intestinal tissue was negligible compared to that with stomach tissue and this observation was explained by the difference in pH between stomach and intestinal tissues. It might be proposed that hydrogen bonding is responsible for polycarbophil adhesion to the mucous layer at acidic pH. However, more experiments are necessary to reach such a conclusion.

Charge density also contributes to improving cell attachment in type II bioadhesion. The extent of platelet adhesion was markedly enhanced with an increase in the number of carboxyl or sulfonate groups on the surface.[102,103] In type II bioadhesion, increased adhesiveness by anionic groups was explained by an increased wettability due to the presence of such groups.[104]

5. Negative Charge Type

The biological roles of anionic polyelectrolytes are significantly influenced by the type of anionic groups and there appears to be a physiological control which regulates microheterogeneity relative to the levels of carboxyl and sulfate groups.[48] It was observed that mucins from cystic fibrosis patients were more highly sulfated than those of normal subjects[105]

and an extreme increase in viscosity of mucins from cystic fibrotic individuals is considered to be due to such structural differences.[106] The sulfomucin in pig gastric mucin shows a strong adsorption to hydroxylapatite, and the maximum binding capacity is at least an order of magnitude higher than that of the sialomucin in ovine submandibular mucin.[107] Park and Robinson[87] also observed a higher binding affinity of sulfated polyanions to cell surfaces compared to carboxylated polyanions. Polyanions with sulfate or polyphosphate esters, have been more frequently found to possess enzyme inhibitory action than polycarboxylic acids.[108,109] The ability of sulfated polyanions to function as metabolic inhibitors results from high binding affinity to proteins and subsequent changes in the physicochemical and biological behavior of the latter substances.

C. Factors Influencing Bioadhesion

1. Hydration of Adhesives

Many hydrocolloids, like vegetable gums and animal proteins, and hydrogels, such as polycarbophil, become adhesive after hydration. However, there is an optimum water concentration for the hydrocolloid particles to develop maximum adhesive strength.[86] Excessive water may cause the formation of a slippery, nonadhesive mucilage. If the adhesive becomes too susceptible to water permeation, it will eventually be displaced by water and subsequently lose adhesiveness. Smart et al.[85] observed an increase of adhesive strength in a mucus gel system, but a decrease in a gelatin gel system. The difference was explained by the greater quantity of water available in the gelatin gel system.

Degradation of the adhesive bond in water or in a humid environment is another important aspect of the role of water in bioadhesion. This tends to cause a lack of adhesive durability. The effect of the total amount of water available for hydration on the adhesive property of various hydrocolloids depends on the type of polymer and this makes it difficult to compare adhesive strength under the same conditions.[86]

2. Hydration of Biological Substrates

Effective adhesion can only occur when an adhesive and adherend are brought into molecular contact. Such interfacial contact is the first requirement for good adhesion. The presence of water and other fluids on the surface of adherend may prevent full effective interplay of possible interactions at appropriate interfaces. If adhesive bonds cannot displace surface contaminants, adhesion failure can occur due to a weak boundary layer. Matsumoto[22] reported that materials such as poly(acrylic acid) behave poorly as surgical adhesives as contrasted with findings of other investigators, and attributed this poor adhesion to the unavailability of binding sites due to the presence of water. The acrylic adhesive did not adhere measurably to wet skin.[79] The greatest disruptive effect of water in adhesive bonds is likely to occur with those polymer systems which rely primarily on hydrogen bonding for adhesive forces.[110]

Baier et al.[104] discussed the role of water on adhesion in some detail. They suggested that addition of water-displacing agents, such as alcohols, glycols, or other hydrophilic organic liquids to adhesives can accomplish good wetting which results in good adhesion. The displacement of water is also important for organic liquid adhesives which polymerize to form adhesive bonds. If they are not compatible with water or cannot displace water molecules which are adsorbed on the adherend, the formed adhesive bond will be weak. In addition to the effect of water, the influence of blood should be considered in practical applications. When a homologous series of alkyl 2-cyanoacrylates were tested for their ability to polymerize on water, the lower homologs (methyl to butyl) polymerized faster than the higher homologs.[99] On blood, however, the higher homologs polymerized instantaneously while the lower homologs polymerized considerably slower. The change in spreadability and polymerization rate on blood was called the "blood effect". This blood effect was also observed on tissue substrates and the higher homologs formed stronger tissue bonds.[99]

3. Surface-Modifying Agents

As the blood effect suggests, some tissue surfaces appear to be hydrophobic and it is expected that hydrophobic interaction might contribute to adhesive bond formation. When a polyurethane prepolymer was applied to a wound on rat skin, further reaction was initiated by the moisture present and the prepolymer solidified. The adhesion to tissue surface, however, was insignificant.[111] Adhesion, however, was improved considerably by priming the tissue surface with tolylene diisocyanate or *n*-hexyl isocyanate. It was suggested that the condensation of hydrophobic *n*-hexyl isocyanate with receptors on the tissue surface promotes compatibility between polymer adhesive and the tissue surface at the interface. The formation of cross-links and the nature of tissue surface components do not seem to be critical factors. Based on this finding, Wang and Evans[112] formulated an adhesive system comprising benzoyl chloride and a solution of silicone in methylene chloride.

Another way of improving bioadhesion is by adsorbing multifunctional molecules, such as epoxyacrylate derivatives,[113] onto adherend surfaces so that interaction with adhesives is facilitated by a chemical or physical process.[83] Ideal adhesion promoters should adsorb onto the surface as a monomolecular layer that will prevent contamination of the adherend by other substances.[114]

4. Divalent Cations

The addition of a cross-linking agent, such as calcium, to anionic hydrocolloids, such as carboxymethylcellulose, reduces solubility and decreases the wet adhesive property of the hydrocolloid.[86] The calcium salt of polycarbophil does not swell in water and does not exhibit bioadhesive properties.

5. Turnover of Adhesive and Adherend

A great deal of attention has been focused on the attachment of barnacles and molusca to fixed or moving substrates. It is thought that a polypeptide adhesive is pulled out into the liquid like threads. The efficiency of the adhesion mechanism is related to the fact that the adhesive is continuously, though very slowly, renewed in the area covered by the animal and is exuded.[93] The continuous renewal of the adhesive allows maintenance of strong adhesion to foreign surfaces in water. However, if the surface of the adherend is continuously renewed, a strong adhesive bond cannot be formed. This has significant implication in soft tissue bioadhesives. Mucus covering epithelial cells in the GI tract or eye is continuously secreted and eliminated. Bioadhesives which bind to this mucus layer are expected to be removed at the same time when mucin turnover occurs regardless of the adhesive strength. Thus, the study of mucin turnover is necessary.

D. Proposed Mechanisms of Bioadhesion

Although it is not easy to explain various bioadhesion phenomena by any one mechanism, an attempt has been made to generalize the bioadhesion phenomenon. Bioadhesion occurring in the presence of water (wet adhesion) is distinguished from adhesion to dry surfaces in that bioadhesion maintains a dynamic state. A mechanism of wet adhesion was proposed based on the empirical relationship between properties of soluble polymers and adhesion performance.[86] Hydrated polymer chains are free to move and stretch and thus become entangled or twisted when brought into close contact with the substrate. Once entangled, they are able to match their active adhesive sites with those on the substrate to form an adhesive bond or the entangled molecules are also free to form cohesive bonds. In this process, the amount of water at the interface controls adhesive performance. Excessive hydration may overextend polymer chains to make them stiffer and more difficult to interact or entangle. This suggested mechanism can explain many of the observed bioadhesive phenomena. The role of physical entanglement between polymer chains is most prominent

in polycarbophil adhesion to the gastric mucus gel. When polycarbophil is separated from the mucus gel layer, some mucin molecules are detached from the tissue surface and stay inside the hydrogel (Figure 4). A direct relationship was observed between physical entanglement and bioadhesiveness.

Dried hydrogels display extremely aggresive adhesion to moist soft tissues. They may function by dehydrating moist tissue surfaces, swelling, and penetrating surface depressions[115] as in wet adhesion.

The adhesion of dental adhesives, such as polyacrylic acid, to enamel was explained by the ability of free carboxyl groups to ensure excellent wetting.[116] It was suggested that polyanion chains of the adhesive actually penetrate into the enamel apatite, and that carboxyl groups displace phosphate ions from the apatite matrix to ensure intimate contact between adhesive and adherend.[117] The adhesion of glass-ionomer cements to tooth surfaces was attributed to ionic forces operating across the interface.[116,118]

VII. APPLICATIONS

A. Drug Delivery Systems

The various mucus coated routes of drug administration includes ocular, nasal, buccal, respiratory, GI, rectal, and vaginal. In each of these routes of drug delivery it is possible to optimize either local or systemic drug delivery by the use of bioadhesive polymers. There are three major categories of bioadhesive application in the area of drug delivery.

1. Extension of Residence Time

For oral drug delivery, one can minimize GI transit by using bioadhesive polymers and prepare a once-a-day controlled drug delivery system. In the case of ocular drug delivery, following instillation of a drug solution to the eye, there is only approximately 90 sec for drug absorption to occur before the drug solution is removed by loss pathways such as solution drainage and tear turnover. The ability to prolong contact time of an ocular drug delivery system in the front of the eye would significantly improve drug therapy.

2. Localization of Drug Delivery System

In the case of a large bowel inflammation, it would be desirable to have the drug delivery system localize in the large bowel and release the drug to this region only. An alternate example is in those cases where a drug is preferentially absorbed in a specified region of the GI tract, the so-called ''window for absorption''. A number of drugs are reported to have a ''window for absorption'', e.g., iron, riboflavin, chlorothiazide, etc. Assuming that considerable specificity of mucins exist in the GI tract under normal circumstances, it should be possible, provided structural specificity of the bioadhesive is available, to achieve site specific localization.

3. Intimate Contact with an Absorbing Membrane

A high drug concentration and hence high drug flux through the absorbing membrane can be achieved by maintaining intimate contact of a drug delivery system with the absorbing tissue. In addition, for high molecular weight compounds such as polypeptides and proteins, it may be necessary to modify the local permeability of the absorbing membrane in order to achieve therapeutic levels of drug. To accomplish this requires localization and intimate contact of the drug delivery system.

There are a variety of ways in which bioadhesive polymers can be utilized to accomplish the above objectives. The most primitive form is to simply coat the bioadhesive on existing drug delivery systems, such as tablets, osmotic devices, or ion-exchange resins. Covalent linkage of drug to a suitable bioadhesive polymer is also possible and represents a prodrug strategy with site specificity.

B. Medical Applications

Bioadhesives have been used as hemostatic and wound healing agents. Drug incorporated bioadhesive dressings were applied to skin loss wounds,[119,120] and periodontal surgical procedures.[121] Fibrinogen and cyanoacrylates are effective in face-to-face sealing of tissues, or wound healing. The major aim is to eliminate cumbersome immobilization by suturing. Surgeons use aerosol adhesives to stop bleeding of blood vessels and capillaries. Applying cyanoacrylate adhesives by aerosol is the best method of dispensing the glue as a hemostatic agent. Hemostasis of liver, kidney, pancreas, and spleen can be readily accomplished. The surgical areas should be dried by temporarily clamping the blood supply to the organ. A bioadhesive for surgical use should have high adhesive strength, undergo rapid polymerization or curing within seconds with minimal volume change, and be nontoxic and nonirritating to the tissue. In addition, the presence of the adhesive should not interfere with normal progress of the natural repair process.[122] Methyl-2-cyanoacrylate bioadhesive caused a significant soft tissue response adjacent to the implants under the conditions used while epoxy resin-resin amine compounds and a butyl acetate cement did not.[123] A polyurethane adhesive was also used as a fast-setting adhesive.[124]

Adhesive foam (Reston, 3M Company) was used in a skin grafting technique. Adhesive foam was attached to a skin template and cut to shape. The skin-foam composite was then positioned on the defect to be grafted. This procedure eliminated the discomfort of subsequent suture or staple removal.[125]

A bioadhesive strip composed of gelatin, pectin, sodium carboxymethylcellulose, and polyisobutylene was used to attach the contraceptive sheath of a urinary drainage device under the name of Urihesive®.[126]

C. Dental Applications

High incidence of failure results when the restoration of dental cements in teeth rely principally on mechanical interlocking. Improved durability can be obtained with dental cements which also display adhesion to the enamel and dentin of the tooth.[81] However, the production of true adhesion to a tooth substance is difficult because the surface is not usually smooth and the external enamel is coated with an organic proteinaceous cuticle derived mainly from saliva. Materials which show adhesion to calcified tissues were found to be those which form a biologically stable chelate with calcium.[81] One such agent which has been used as an adhesive material is poly(acrylic acid).

The adhesion of dentures to supporting tissues is accomplished using a high viscosity fluid. Solutions, such as karaya and tragacanth gums and sodium carboxymethylcellulose, are tacky and stick to denture bases while having little effect on the oral mucosa.[127] Karaya gum has no local adverse effect in the mouth, but due to the low pH (4.7 to 5.0), it can decalcificate dental enamel.[128] Some denture adhesives which contain constituents capable of forming aqueous solutions of pH below that at which hydroxyapatite dissolves can cause a small, though measurable degree of enamel decalcification.[128]

REFERENCES

1. **Ratner, B. D. and Hoffman, A. S.,** Synthetic hydrogels for biomedical applications, in *Hydrogels for Medical and Related Applications*, ACS Symp. Ser. 31, Andrade, J. D., Ed., American Chemical Society, Washington, D.C., 1976, 1.
2. **Skeist, I.,** *Handbook of Adhesives*, Van Nostrand Reinhold, New York, 1977, xi.
3. **Good, R. J.,** On the definition of adhesion, *J. Adhes.*, 8, 1, 1976.
4. **Curtis, A. S. G.,** *The Cell Surface: its Molecular Role in Morphogenesis*, Logos Press, London, 1967, chap. 3.

5. **Bell, G. I.,** Models for the specific adhesion of cells to cells, *Science*, 200, 618, 1978.
6. **Bell, G. I., Dembo, M., and Bongrand, P.,** Cell adhesion, *Biophys. J.*, 45, 1051, 1984.
7. **McClay, D. R. and Moscona, A. A.,** Purification of the specific cell aggregating factor from embryonic neural retina cells, *Exp. Cell Res.*, 87, 438, 1974.
8. **Schubert, D. and LaCorbiere, M.,** The adhesive specificity of extracellular glycoprotein complexes in mediating cellular adhesion, *J. Neurosci.*, 2, 82, 1982.
9. **Edelman, G. M.,** Cell-adhesion molecules: a molecular basis for animal form, *Sci. Am.*, 250, 118, 1984.
10. **Sharon, N.,** Lectins, *Sci. Am.*, 236, 108, 1977.
11. **Barondes, S. H.,** Soluble lectins: a new class of extracellular proteins, *Science*, 223, 1259, 1984.
12. **Shur, B. D. and Roth, S.,** Cell surface glycosyltransferases, *Biochim. Biophys. Acta*, 415, 473, 1975.
13. **Roseman, S.,** The synthesis of complex carbohydrates by multiglycosyltransferase systems and their potential function in intercellular adhesion, *Chem. Phys. Lipids*, 5, 270, 1970.
14. **Mautner, V. and Hynes, R. O.,** Surface distribution of LETS protein in relation to the cytoskeleton of normal and transformed cells, *J. Cell Biol.*, 75, 743, 1977.
15. **Vercellotti, G. M., Lussenhop, D., Peterson, P. K., Furcht, L. T., McCarthy, J. B., Jacob, H. S., and Moldow, C. F.,** Bacterial adherence to fibronectin and endothelial cells: a possible mechanism for bacterial tissue tropism, *J. Lab. Clin. Med.*, 103, 34, 1984.
16. **Yamada, K. M.,** Cell surface interactions with extracellular materials, *Ann. Rev. Biochem.*, 52, 761, 1983.
17. **McLean, J. R., Maxwell, R. E., and Hertler, D.,** Fibrinogen and adenosine diphosphate-induced aggregation of platelets, *Nature (London)*, 202, 605, 1964.
18. **Legrand, Y. J., Karniguian, A., Fauvel, F., and Gutman, N.,** The molecular interaction between platelet and vascular wall, *Blood Cells*, 9, 263, 1983.
19. **Chien, S.,** Aggregation of red blood cells: an electrochemical and colloid chemical problems, in *Biochemistry: Ions, Surfaces, Membranes*, Adv. Chem. Ser. 188, Blank, M., Ed., American Chemical Society, Washington, D.C., 1980, 3.
20. **Jan, K. M.,** Electrochemical basis of heparin-induced red blood cell aggregation, in *Biochemistry: Ions, Surfaces, Membranes*, Adv. Chem. Ser. 188, Blank, M., Ed., American Chemical Society, Washington, D.C., 1980, 143.
21. **Eddy, C. A., Asch, R. H., and Balmaceda, J. P.,** Pelvic adhesion following microsurgical and macrosurgical wedge resection of the ovaries, *Fertil. Steril.*, 33, 557, 1980.
22. **Matsumoto, T.,** *Tissue Adhesives*, Medical Examination Publishing, New York, 1972.
23. **Scheele, J., Gentsch, H. H., and Matteson, E.,** Splenic repair by fibrin tissue adhesive and collagen fleece, *Surgery*, 95, 6, 1984.
24. **Thom, D., Powell, A. J., and Rees, D. A.,** Mechanisms of cellular adhesion, *J. Cell Sci.*, 35, 281, 1979.
25. **Pierschbacher, M. D., Hayman, E. G., and Ruoslahti, E.,** Location of the cell attachment site in fibronectin with monoclonal antibodies and proteolytic fragments of the molecule, *Cell*, 26, 259, 1981.
26. **Hayashi, M. and Yamada, K. M.,** Domain structure of the carboxyl-terminal half of human plasma fibronectin, *J. Biol. Chem.*, 258, 3332, 1983.
27. **Ruoslahti, E., Pierschbacher, M. D., Oldberg, A., and Hayman, E. G.,** Synthetic peptide causing cellular adhesion to surfaces, *Bio Tech.*, 2, 38, 1984.
28. **Young, B. R., Lambrecht, L. K., Cooper, S. L., and Mosher, D. F.,** Plasma proteins: their role in initiating platelet and fibrin deposition on biomaterials, in *Biomaterials: Interfacial Phenomena and Applications*, Adv. Chem. Ser. 199, Cooper, S. L. and Peppas, N. A., Eds., American Chemical Society, Washington, D.C., 1982, 317.
29. **Corpe, W. A.,** Attachment of marine bacteria to solid surfaces, in *Adhesion in Biological Systems*, Manly, R. S., Ed., Academic Press, New York, 1970, 73.
30. **Walker, G.,** The adhesion of barnacles, *J. Adhes.*, 12, 51, 1981.
31. **Edwards, J. G.,** The biochemistry of cell adhesion, *Prog. Surf. Sci.*, 13, 125, 1983.
32. **Hubbe, M. A.,** Adhesion and detachment of biological cells in vitro, *Prog. Surf. Sci.*, 11, 65, 1981.
33. **Grinnell, F.,** Cellular adhesiveness and extracellular substrata, *Int. Rev. Cytol.*, 53, 65, 1978.
34. **Allen, K. W.,** Theories of adhesion surveyed, in *Aspects of Adhesion*, Vol. 5, Alner, D. J., Ed., University of London Press, London, 1969, 11.
35. **McBain, J. W. and Hopkins, D. G.,** On adhesives and adhesive action, *J. Phys. Chem.*, 29, 188, 1925.
36. **Buonocore, M. G.,** Bonding to hard dental tissues, in *Adhesion in Biological Systems*, Manly, R. S., Ed., Academic Press, New York, 1970, chap. 15.
37. **Oritz, R. F., Phillips, R. W., Swartz, M. L., and Osborne, J. W.,** Effect of composite resin bond agent on microleakage and bond strength, *J. Prosthet. Dent.*, 41, 51, 1979.
38. **Voyutskii, S. S.,** *Autohesion and Adhesion of High Polymers*, Wiley Interscience, New York, 1963.
39. **Wake, W. C.,** Theories of adhesion and uses of adhesives: a review, *Polymer*, 19, 291, 1978.
40. **Park, H.,** Synthesis and Evaluation of Some Bioadhesive Hydrogels, M.S. thesis, University of Wisconsin, Madison, 1984.
41. **Wake, W. C.,** *Adhesion and the Formulation of Adhesives*, Applied Science, London, 1976, 89.

42. **Kaelble, D. H.,** A surface energy analysis of bioadhesion, *Polymer*, 18, 475, 1977.
43. **Yasuda, H., Yamanashi, B. S., and Devito, D. P.,** The rate of adhesion of melanoma cells onto nonionic polymer surfaces, *J. Biomed. Mater. Res.*, 12, 701, 1978.
44. **van der Valk, P., van Pelt, A. W., Busscher, H. J., de Jong, H. P., Wildevuur, Ch. R. H., and Arends, J.,** Interaction of fibroblasts and polymer surfaces: relationship between surface free energy and fibroblast spreading, *J. Biomed. Mater. Res.*, 17, 807, 1983.
45. **Pitha, J.,** Polymer-cell surface interactions and drug targeting, in *Targeted Drugs*, Goldberg, E., Ed., John Wiley & Sons, New York, 1983, 113.
46. **Allen, A.,** Structure and function of gastrointestinal mucus, in *Physiology of the Gastrointestinal Tract*, Vol. 1, Johnson, L. R., Ed., Raven Press, New York, 1981, 617.
47. **Allen, A., Hutton, D., McQueen, S., and Garner, A.,** Dimensions of gastroduodenal surface pH gradients exceed those of adherent mucus gel layers, *Gastroenterology*, 85, 463, 1983.
48. **Tabak, L. A., Levine, M. J., Mandel, I. D., and Ellison, S. A.,** Role of salivary mucins in the protection of the oral cavity, *J. Oral Pathol.*, 11, 1, 1982.
49. **Gallager, J. T. and Corfield, A. P.,** Mucin-type glycoproteins — new perspectives on their structure and synthesis, *Trends Biochem. Sci.*, February, 38, 1978.
50. **Kaliner, M., Marom, Z., Patow, C., and Shelhamer, J.,** Human respiratory mucus, *J. Allergy Clin. Immunol.*, 73, 318, 1984.
51. **Winet, H.,** Ciliary propulsion of objects in tubes: wall drag on swimming tetrahymena (Ciliata) in the presence of mucin and other long-chain polymers, *J. Exp. Biol.*, 64, 283, 1976.
52. **Allen, A. and Garner, A.,** Gastric mucus and bicarbonate secretion and their possible role in mucosal protection, *Gut*, 21, 249, 1980.
53. **Hollander, F.,** The two component mucous barrier, *Arch. Int. Med.*, 93, 107, 1954.
54. **Robert, A., Bøttcher, W., Golanska, E., and Kauffman, G. L., Jr.,** Lack of correlation between mucus gel thickness and gastric cytoprotection in rats, *Gastroenterology*, 86, 670, 1984.
55. **Nimmerfall, F. and Rosenthaler, J.,** Significance of the goblet-cell mucin layer, the outermost luminal barrier to passage through the gut wall, *Biochem. Biophys. Res. Commun.*, 94, 960, 1980.
56. **Wagner, D. D. and Hynes, R. O.,** Topological arrangement of the major structural features of fibronectin, *J. Biol. Chem.*, 255, 4304, 1980.
57. **Padlan, E. A.,** Structural basis for the specificity of antibody-antigen reactions and structural mechanisms for the diversification of antigen-binding specificities, *Q. Rev. Biophys.*, 10, 35, 1977.
58. **Eyre, D. R.,** Collagen: molecular diversity in the body's protein scaffold, *Science*, 207, 1315, 1980.
59. **Pearson, J., Allen, A., and Venables, C.,** Gastric mucus: isolation and polymeric structure of the undegraded glycoproteins: its breakdown by pepsin, *Gastroenterology*, 78, 709, 1980.
60. **Roberts, G. P.,** The role of disulfide bonds in maintaining the gel structure of bronchial mucus, *Arch. Biochem. Biophys.*, 173, 528, 1976.
61. **Herzberg, M. C., Levine, M. J., Ellison, S. A., and Tabak, L. A.,** Purification and characterization of monkey saliva mucin, *J. Biol. Chem.*, 254, 1487, 1979.
62. **Lewis, R. W.,** Mucus globule membrane: a hypothesis concerning its role in determining the viscosity of mucus, *J. Theor. Biol.*, 61, 21, 1976.
63. **Hill, H. D., Reynolds, J. A., and Hill, R. L.,** Purification, composition, molecular weight, and subunit structure of ovine submaxillary mucin, *J. Biol. Chem.*, 252, 3791, 1977.
64. **Morris, E. R. and Rees, D. A.,** Principles of biopolymer gelation. Possible models for mucus gel structure, *Br. Med. Bull.*, 34, 49, 1978.
65. **Robinson, D. S. and Monsey, J. B.,** The composition and proposed subunit structure of egg white β-ovomucin, *Biochem. J.*, 147, 55, 1975.
66. **Clamp, J. R., Allen, A., Gibbons, R. A., and Roberts, G. P.,** Chemical aspects of mucus, *Br. Med. Bull.*, 34, 25, 1978.
67. **Sachdev, G. P., Zodrow, J. M., and Carubelli, R.,** Hydrophobic interaction of fluorescent probes with fetuin, ovine submaxillary mucin and canine tracheal mucins, *Biochim. Biophys. Acta*, 580, 85, 1979.
68. **Allen, A., Bell, A., Mantle, M., and Pearson, J. P.,** The structure and physiology of gastrointestinal mucus, *Adv. Exp. Mol. Biol.*, 144, 115, 1982.
69. **Sheehan, J. K. and Carlstedt, I.,** Hydrodynamic properties of human cervical-mucus glycoproteins in 6 M-guanidium chloride, *Biochem. J.*, 217, 93, 1984.
70. **Marriott, C., Shih, C. K., and Litt, M.,** Changes in the gel properties of tracheal mucus induced by divalent cations, *Biorheology*, 16, 331, 1979.
71. **Forstner, J. F. and Forstner, G. G.,** Effects of calcium on intestinal mucin: implications for cystic fibrosis, *Pediatr. Res.*, 10, 609, 1976.
72. **List, S. J., Findlay, B. P., Forstner, G. G., and Forstner, J. F.,** Enhancement of the viscosity of mucin by serum albumin, *Biochem. J.*, 175, 565, 1978.
73. **Spohn, M. and McColl, I.,** Studies on gastric mucosal IgA: separation of immunoglobulin rich fraction from gastric mucoproteins, *Biochem. Biophys. Res. Comm.*, 79, 837, 1977.

74. **Creeth, J. M., Bridge, J. L. N., and Horton, J. R.,** An interaction between lysozyme and mucous glycoproteins, *Biochem. J.*, 181, 717, 1979.
75. **Marriott, C., Beeson, M. F., and Brown, D. T.,** Biopolymer induced changes in mucus viscoelasticity, *Adv. Exp. Med. Biol.*, 144, 89, 1982.
76. **Pearson, J. P., Allen, A., and Parry, S.,** A 70000-molecular-weight protein isolated from purified pig gastric mucus glycoprotein by reduction of disulphide bridges and its implication in the polymeric structure, *Biochem. J.*, 197, 155, 1981.
77. **Parsons, S. L., Mulholland, S. G., and Anwar, H.,** Antibacterial activity of bladder surface mucin duplicated by exogeneous glycosaminoglycan (heparin), *Infect. Immunol.*, 24, 552, 1979.
78. **Parson, C. L., Pollen, J. J., Anwar, H., Stauffer, C., and Schmidt, J. D.,** Antibacterial activity of bladder surface mucin duplicated in the rabbit bladder by exogenous glycosaminoglycan (sodium pentosanpolysulfate), *Infect. Immunol.*, 27, 876, 1980.
79. **Margules, G. S. and Harris, D. L.,** Adhesives for intact skin: a preliminary investigation, *Med. Biol. Eng. Comput.*, 18, 549, 1980.
80. **Wang, P. Y. and Forrester, D. H.,** Conditions for the induced adhesion of hydrophobic polymers to soft tissue, *Trans. Am. Soc. Artif. Int. Organs*, 20, 504, 1974.
81. **Smith, D. C.,** Medical and dental applications of cements, *J. Biomed. Mater. Res. Symp.*, 1, 189, 1971.
82. **Reich, S., Levy, M., Meshorer, A., Blumental, M., Yalon, M., Sheets, J. W., and Goldberg, E. P.,** Intraocular-lens-endothelial interface: adhesive force measurements, *J. Biomed. Mater. Res.*, 18, 737, 1984.
83. **Jedrychowski, J. R., Caputo, A. A., and Foliart, R.,** Effects of adhesion promoters on resin-enamel retention, *J. Dent. Res.*, 58, 1371, 1979.
84. **Weaver, C.,** The nature of adhesive forces, in *Aspects of Adhesion*, Vol. 5, Alner, D. J., Ed., University of London Press, London, 1969, 202.
85. **Smart, J. D., Kellaway, I. W., and Worthington, H. E. C.,** An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery, *J. Pharm. Pharmacol.*, 36, 295, 1984.
86. **Chen, J. L. and Cyr, G. N.,** Compositions producing adhesion through hydration, in *Adhesion in Biological Systems*, Manly, R. S., Ed., Academic Press, New York, 1970, chap. 10.
87. **Park, K. and Robinson, J. R.,** Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion, *Int. J. Pharm.*, 19, 107, 1984.
88. **Park, K., Ch'ng, H. S., and Robinson, J. R.,** Alternative approaches to oral controlled drug delivery: bioadhesives and in-situ systems, in *Recent Advances in Drug Delivery Systems*, Anderson, J. M. and Kim, S. W., Eds., Plenum Press, New York, 1984, 163.
89. **Bass, P. and Russell, J.,** Personal communication.
90. **Nagai, T.,** Some new dosage forms for better efficacy and safety of drugs, *Proc. Hoshi Inst. Pharm. Sci.*, 23, 29, 1981.
91. **Machida, Y., Masuda, H., Fujiyama, N., Ito, S., Iwata, M., and Nagai, T.,** Preparation and phase II clinical examination of topical dosage form for treatment of *Carcinoma coli* containing bleomycin with hydroxypropyl cellulose, *Chem. Pharm. Bull.*, 27, 93, 1979.
92. **Davidson, R. L., Ed.,** *Handbook of Water-Soluble Gums and Resins*, McGraw-Hill, New York, 1980.
93. **Wake, W. C.,** *Adhesion and the Formulation of Adhesives*, Applied Science, London, chap. 13.
94. **Meer, W.,** Gum karaya, in *Handbook of Water-Soluble Gums and Resins*, Davidson, R. L., Ed., McGraw-Hill, New York, 1980, chap. 10.
95. **Tsuk, A. G. and Martin, F. H.,** U.S. Patent 3,972,995, 1976.
96. **Bremecker, K. D., Strempel, H., and Klein, G.,** Novel concept for a mucosal adhesive ointment, *J. Pharm. Sci.*, 73: 548, 1984.
97. **Tanaka, W., Akito, E., Yoshida, K., Terada, T., and Ninomiya, H.,** U.S. Patent 4,059,686, 1977.
98. **Zaffaroni, A.,** U.S. Patent 3,797,494, 1974.
99. **Leonard, F.,** Hemostatic applications of alpha cyanoacrylates: Bonding mechanism and physiological degradation of bonds, in *Adhesion in Biological Systems*, Manly, R. S., Ed., Academic Press, New York, 1970, 185.
100. **Grode, G. A., Falb, R. D., Cooper, C. W., and Lynn, J.,** Chemical mechanisms suitable for bonding tissues, in *Adhesion in Biological Systems*, Manly, R. S., Ed., Academic Press, New York, 1970, 153.
101. **Reynolds, G. E. J.,** Polymer design in relation to adhesive properties, in *Aspects of Adhesion*, Alner, D. J., Ed., Vol. 6, University of London Press London, 1971, 96.
102. **Muramatsu, N. and Kondo, T.,** Platelet adhesion onto artificial red blood cells, *J. Biomed. Mater. Res.*, 14, 211, 1980.
103. **Muramatsu, N. and Kondo, T.,** Platelet adhesion onto sulfonated artificial red blood cells, *J. Biomed. Mater. Res.*, 15, 383, 1981.
104. **Baier, R. E., Shafrin, E. G., and Zisman, W. A.,** Adhesion: mechanisms that assist or impede it, *Science*, 162, 1360, 1968.

105. **Boat, T. F., Cheng, P. W., Iyer, R. N., Carlson, D. M., and Polony, I.** Human respiratory tract secretions. Mucous glycoproteins of nonpurulent tracheobronchial secretions and sputum of patients with bronchitis and cystic fibrosis, *Arch. Biochem. Biophys.*, 177, 95, 1976.
106. **Di Sant'agnese, P. A. and Davis, P. B.,** Research in cystic fibrosis, *N. Eng. J. Med.*, 295, 481, 1976.
107. **Amerongen, N., Roukema, P. A., Boerman, J. W., Valentijn-Benz, M., Oderkerk, C. H., and De Groot, K.,** The adsorption to calcium-hydroxylaptite of biopolymers, used to produce an artificial saliva, in *Proc. 10th Annu. Meet. Soc. Biomater.*, Washington, D.C., 1984, 261.
108. **Bernfeld, P.,** Polyanionic inhibitors, in *Metabolic Inhibitors*, Hochster, R. M. and Quastel, J. H., Eds., Academic Press, New York, 1963, chap. 30.
109. **Liebel, M. A. and White, A. A.,** Inhibition of the soluble guanylate cyclase from rat lung by sulfated polyanions, *Biochem. Biophys. Res. Commun.*, 104, 957, 1982.
110. **Macdonald, N. C.,** The effect of moisture on adhesive bonds, in *Aspects of Adhesion*, Vol. 5, Alner, D. J., Ed., University of London Press, London, 1969, 123.
111. **Wang, P. Y.,** Evidence of hydrophobic interaction in adhesion to tissue, *Nature (London)*, 249, 367, 1974.
112. **Wang, P. Y. and Evans, D. W.,** Adhesion of synthetic organic polyme to soft tissue IV. Evaluation of a silicone adhesive system, *Biomat. Med. Dev. Artif. Organs*, 5, 277, 1977.
113. **Bowen, R. L.,** Adhesive bonding of various materials to hard tooth tissues. XVIII. Synthesis of a polyfunctional surface-active comoner, *J. Dent. Res.*, 58, 1101, 1979.
114. **Brauer, G. M.,** Adhesion and adhesives, in *Scientific Aspects of Dental Materials*, Von Fraunhofer, Ed., Butterworths, London, 1975, 49.
115. **Coury, A. J., Cahalan, P. T., Jevne, A. H., Perrault, J. J., and Kallok, M. J.,** Recent development in hydrohilic polymers, *Med. Dev. Diag. Ind.*, 6, 28, 1984.
116. **Wilson, A. D.,** Alumino-silicate polyacrylate acid and related cements, *Br. Polym. J.*, 6, 165, 1974.
117. **Powis, D. R., Folleras, T., Merson, S. A., and Wilson, A. D.,** Improved adhesion of a glass ionomer cement to dentin and enamel, *J. Dent. Res.*, 61, 1416, 1982.
118. **Beech, D. R.,** A spectroscopic study of the interaction between human tooth enamel and polyacrylic acid (polycarboxylate cement), *Arch. Oral Biol.*, 17, 907, 1972.
119. **Buckley, C. J., Chambers, C. E., Kemmerer, W. T., Rawlings, C. A., Casey, H. W., and Hall, C. W.,** Evaluation of a synthetic bioadherent dressing as a temporary skin substitute, *Trans. Am. Soc. Artif. Intern. Organs*, 17, 416, 1971.
120. **Schwope, A. D., Wise, D. L., Sell, K. W., Skornik, W. A., and Dressler, D. P.,** Development of a synthetic burn covering, *Trans. Am. Soc. Artif. Intern. Organs*, 20, 103, 1974.
121. **Bhaskar, S. N., Frish, J., Margetis, P. M., and Leonard, F.,** Application of a new chemical adhesive in periodontics and oral surgery, *Oral Surg.*, 22, 526, 1966.
122. **Heiss, W. H.,** The use of synthetic polymeric materials as suture substitutes and their place in pediatric surgery, *Prog. Pediatr. Surg.*, 1, 99, 1970.
123. **Koudelka, B. M., Nelson, J. F., and Webb, J. G.,** Denture self-repair: experimental soft tissue response to selected commercial adhesives, *J. Prosthet. Dent.*, 43, 143, 1980.
124. **Lewellyn-Thomas, E., Wang, P. Y., and Cannon, J. S.,** Adhesion of synthetic organic polymer on soft tissue. I. A fast setting polyurethane adhesive, *J. Biomed. Mater. Res.*, 8, 35, 1974.
125. **Markison, R. E. and Colville, J.,** Adhesive foram technique for rapid simple skin grafting, *Surg. Gynecol. Obstet.*, 157, 276, 1983.
126. **De Leval J. and Louis, J. C.,** Urihesive: a new aid in the management of urinary incontinence in male paraplegic patients, *Paraplegia*, 16, 299, 1979.
127. **Ellis, B., Al-Nakash, S., and Lamb, D. J.,** The composition and rheology of denture adhesives, *J. Dent.*, 8, 109, 1980.
128. **Lamb, D. J.,** Denture adhesives — a side effect, *J. Dent.*, 8, 35, 1979.