Drug Design

Volume VII

DRUG DESIGN

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Preface

As indicated in the preceding volumes of this treatise on "Drug Design," due to or, perhaps, thanks to the universality of biochemical theory, there is, in general, a good deal of similarity among the principles underlying the action of drugs and bioactive agents. Consequently, for investigators working on the design of drugs, "excursions" into the workshops of investigators involved in the development of other bioactive agents, such as pesticides, may lead to fruitful cross-fertilization.

This volume stresses the design of agents such as blood substitutes, pesticides derived from insect pheromones, and herbicides related to the auxin-type plant hormones. The other chapters deal with recent developments in the use of substituent parameters and computer technology in drug design, both advanced and promising approaches to this field.

I hope this volume, as the others, will achieve its goal: to provide investigators involved in the development of bioactive agents with new data, new views, and new speculations in their field.

E. J. ARIËNS

Contents of Other Volumes

VOLUME I

VOLUME II

VOLUME III

VOLUME IV

Contents

Chapter 1 The Design of Artificial Blood Substitutes

Robert P. Geyer

I. Introduction

Alternatives to blood have been long sought for a variety of purposes in medicine and biology. However, by its very complex nature, blood has presented formidable obstacles to attempts to replace it. Indeed, even the

substitution of one blood for another in the same species has indicated the problems to be encountered. It is likely that no two bloods are alike and that even in a given individual, significant long- and short-term variations occur. Furthermore, blood is a responsive tissue in that it is affected by many factors, such as disease, diet, and environment. It is clear, then, that when one sets out to replace blood *in vivo* and *in vitro* with artificial materials, there is no particular "standard" blood which serves to guide such attempts. Rather, it is the well-being of the recipient, whether human or lower animal, that must be used as the final evaluation of failure or success of any preparation. Even in the case of organ perfusions, the "normality" of function and metabolism of the organ serves as the gauge of success. Because there are so many roles blood plays, it is obvious that as a minimum, an artificial whole blood substitute must satisfy the absolutely essential ones. To do less would jeopardize the survival of the organism or organ. On the other hand, to attempt to meet all functions artificially would unnecessarily complicate an already difficult task at its initiation. For the present, at least, most investigators have chosen a less ambitious goal.

TABLE I

SOME FUNCTIONS OF NORMAL BLOOD

Component	Function
Red cells	Carry hemoglobin; furnish DPG and carbonic anhydrase; (mechanical effects)
Hemoglobin	Carries oxygen and carbon dioxide
Leukocytes	Combat infections; produce antibodies; generate superoxide
Platelets	Furnish clotting factors
Plasma	Suspension medium for cellular elements; and solvent for proteins and other soluble components
Plasma proteins	Furnish oncotic pressure; carry free fatty acids, vitamins, hormones, etc.; clotting reactants; antibody activity; act as buffer
Nutrients	Feed tissue cells
Waste products	Transported to kidney and liver for elimination
Electrolytes	Maintain osmotic pressure; furnish necessary ions
Bicarbonate	Buffer; furnish bicarbonate to cells, if necessary
Water	Solvent and hydration agent

Of the long list of functions carried out by blood components certain ones appear more critical than others (Table I). Transporting adequate quantities of oxygen and carbon dioxide, as well as other materials that need to be transported, maintaining the correct blood volume, assuring the proper osmolality and pH, and perfusing all areas of the tissues would have to be

given high priorities. Yet others, such as clotting and antibacterial defense, could hardly be less important. Which blood functions, then, should a blood substitute fulfill at the present time? Clearly they must be functions for which artificial alternatives exist. Several of the major functions of normal blood must be temporarily neglected, since no rational means of substituting for them are available. Such elimination by nonavailability allows other aspects of the overall problem to be pursued and helps to define an attainable target.

Several of the areas that can be relegated to a later stage of the development of artificial blood substitutes are clotting, antibody reactions, and hormonal considerations. These have in common the fact that they all involve proteins in some way. Except for some protein hormones that have been synthesized, no artificial substitutes for the compounds that participate in these functions have been made. To add naturally occurring materials would not be in keeping with the basic concept that all ingredients of the artificial preparations must be themselves artificial, or at least modified in form or structure if initially derived from natural sources. Thus, erythrocytes would be unacceptable since they are a natural commodity. Free hemoglobin would represent an "unpackaged" form of this protein and might be considered sufficiently different to qualify as an ingredient for artificial blood substitutes. If chemically modified, hemoglobin would certainly be considered a candidate for the artificial substitute. Last, a synthetic heme would obviously qualify for such a classification. On the basis of such reasoning, clotting factors, antibodies, and most protein hormones and hormone transport proteins would have to be omitted from the substitute mixtures at present. Reference will again be made to these substances late in this chapter, for as various artificial blood substitutes become realities, it may become necessary in some instances to incorporate some of these natural materials into the preparations. Where such necessity does not exist, however, it is also important to examine reasons for their nonessentiality. In this manner not only a better understanding of the artificial system but also basic information about the natural processes themselves may be acquired.

An artificial blood substitute must assume the functions of both plasma and blood cells. Materials chosen as constituents of such substitutes must be compatible with each other in the concentration ranges needed. This means that developing a replacement for red cells separately from plasma protein substitutes, for example, may lead to an impasse when the two are eventually brought together. It is likely that during the evolutionary process red cells and plasma developed in an interdependent way, since anything else would have led to extinction. Investigators have often used the term "artificial blood substitute" to mean "red cell substitute" or "plasma protein substitute." Strictly speaking, the term "artificial blood substitute" should be reserved for

those preparations that can substitute for both red cells and plasma proteins. As used in this chapter on artificial blood, plasma or red cell substitute is a preparation consisting of synthetic components and/or physically or chemically modified natural materials that is capable, for a reasonable period of time, of supporting life *in vivo* and viability of organs *in vitro*. The wide scope such a definition entails can be seen from the list of subjects included in a recent symposium on artificial blood substitutes (*1*).

Historically, the emphasis on substitutes for blood has actually been directed toward maintaining the blood volume or replacing the plasma proteins. This was not accidental but due to two main factors. One was the recognition that following blood loss, restoration of blood volume was essential to sustain adequate pressure and tissue perfusion. The other was the practical matter that no alternatives to red cells (and hemoglobin) were available. As a consequence of these influences, a very one-sided development took place which resulted in several plasma volume expanders reaching the market, but no products which could be termed red cell substitutes, let alone blood substitutes. To an extent, the same situation existed with organ perfusion. Because there were no substitutes for erythrocytes, the expediency was to use oxygenated plasma or plasma substitutes and chill the organ to lower oxygen demand. Such compromising is not apt to be conducive to long-term preservation of the organs. What has been clearly needed are good artificial substitutes for red cells, plasma, and whole blood. This chapter deals with their design and use.

II. Constituents

A. Substitutes for Plasma

1. *Electrolyte Solutions*

Blood plasma is composed of many compounds, some of which have probably not yet been identified. Thus, to reconstitute a true artificial plasma would be an almost endless undertaking. The approximately 80% of plasma that is water and the various electrolytes present no particular problem except for the binding to protein of some of the elements. To achieve nondialyzable forms of the elements or reversibly bound forms of some such as calcium, an artificial blood substitute would have to be formulated that provided the proper type of binding molecules. No convincing data are as yet available to show such bound forms are essential in partial or total blood replacement. No doubt this problem will receive considerable attention in the future as more intensive studies with artificial blood substitutes are carried out.

Many electrolyte solutions that have been formulated for use in place of plasma or serum have been patterned after the electrolyte spectrum of the latter, but may or may not contain buffers. Krebs–Ringer bicarbonate solution (*2*) and Eagle's tissue culture salts solution (*3*) are widely used and are examples of such formulations. Obviously, the complexity needed depends upon the intended use. Partial replacement might be effectively carried out with substitutes having a fairly simple electrolyte composition. This may involve only sodium chloride, potassium chloride, calcium lactate, and sodium bicarbonate at a total concentration isotonic with 0.9% sodium chloride. The proper osmotic pressure is essential, especially when the percent of blood replacement is relatively high. Preparations with low osmotic pressure will cause water to enter tissues, and the blood volume may decrease somewhat. Hyperosmotic solutions, on the other hand, will draw water from the tissues causing blood volume expansion. Such solutions have been shown to be effective in removing pulmonary edema even *in vitro* (*4*). It is important to bear in mind that the effects of moderately high or low osmolarities are ordinarily relatively short-lived and probably not of great concern. However, as the extent of blood replacement with such solutions increases, the effects may well be more lasting and serious. In experiments involving complete blood replacement, neither hypertonic nor hypotonic blood substitutes were capable of sustaining the animals properly (*5*). Except in some unusual circumstances, the overall osmotic pressure of the substitute should be kept close to that of the blood plasma of the recipient species. It should be made clear that those emergency situations in which hypertonic solutions are given would usually have to be followed by administration of blood or artificial blood substitutes to obtain more lasting beneficial effects.

2. *Artificial Plasma Substitutes*

Quantitatively, the primary constituents of plasma and serum are the proteins. Human blood plasma contains 5.2 g albumin and 2.0 g globulins per 100 ml (*6*). The total protein concentration is extremely important, since it determines the colloid osmotic pressure of the plasma. Ordinarily, the quantity present is sufficient to furnish a colloid osmotic pressure of approximately 22 mm Hg. When the concentration of protein drops, water leaves circulation and blood volume decreases. If this movement of water continues, edema occurs, often with undesirable results. When excess protein is present, water moves into the circulatory system, expanding the blood volume and dehydrating the tissues. Obviously, this, too, is to be avoided. Under ordinary circumstances the concentrations of proteins are carefully controlled even though new molecules of proteins enter circulation