

AN EMPIRICAL CONSTITUTIVE EQUATION
FOR ANTI-COAGULATED HUMAN BLOOD

by

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Thesis submitted to the Graduate Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Engineering Science and Mechanics

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ACKNOWLEDGMENTS

My first wish is to express my deepest appreciation to Dr. Daniel J. Schneck of the Engineering Science and Mechanics Department, Virginia Polytechnic Institute and State University for his guidance, encouragement, and most of all, introducing to me a fascinating field of study. I wish to thank Dr. J. E. Kaiser, Dr. H. F. Brinson, and Dr. D. Frederick of the same department and Dr. J. C. Osborne of the Veterinary Science Department for serving as members of my graduate committee. I am also grateful for the assistance provided by my aunt, Miss Marjorie Walburn and the statistical advice of Ms. Agnes Heller is appreciated. I wish to thank all connected with the Montgomery County Hospital, especially Jim Mitchell and all others who work in the hematology lab, for the donation of the blood samples used in this study. Thanks also go to Dr. William Gutstein of New York Medical College for providing the total lipid determinations. I wish to thank Willie Mae Hylton for an excellent job of typing this thesis. Finally I wish to express my appreciation to my parents, Mr. and Mrs. James H. Walburn, for their financial and spiritual assistance and I dedicate this thesis to them.

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CHAPTER I

Introduction

Blood has always aroused wonder and curiosity in the mind of man. Long ago on the ancient battlefields of Greece and Persia, men marveled and wrote about this dark red fluid that oozed from some wounds and spurted from others. In each case, death came to those who had lost too much of this fluid, and so ancient scholars called it The Fluid of Life, declaring that it was of the utmost importance to the health of an individual. Galen, who lived from approximately 130 A.D. to 200 A.D., believed that all substances which entered the body (food, air, etc.) were changed into blood, which then flowed to different parts of the body where it was transformed into bones, skin, hair, etc. This theory lasted for nearly fifteen hundred years [1].

Through the ages many noted scholars have studied blood [2], among them Hippocrates (460-375 B.C.), Aristotle (384-322 B.C.), Leonardo da Vinci (1452-1519 A.D.), Sir William Harvey (1578-1657 A.D.), Reverend Steven Hales (1733 A.D.), and a name familiar to many engineers, Jean L. M. Poiseuille (1828 A.D.). This interest has continued, and today many investigators are studying the complex role of blood in the cardiovascular system of man and animals. Yet, even with the modern sophisticated research methods available today, there is still much that is not known about this extremely complicated life-giving fluid. Recently, investigators in both the medical and engineering fields have found evidence which suggests that the

dynamics of blood flow in the cardiovascular system may be related to arteriosclerosis. Commonly known as "hardening of the artery," arteriosclerosis is the number one killer in this country. Current medical treatment of a heart attack or stroke, the most common consequence of hardening of the arteries, is limited to saving the life and then rehabilitating the patient. Until recently all really significant advances have been concerned with the individual who already has a discernible arteriosclerotic condition. Very little is known about the specific causes of the disease. In order to uncover information concerning the etiology of arteriosclerosis as related to hemodynamics, two approaches could be utilized. The first is experimental, where either an in vitro model of the in vivo flow situation is constructed, and relevant information is obtained from the model, or where the information is obtained directly from an animal.

The second approach is to develop a mathematical model of the in vivo flow situation. Such a model for an incompressible fluid consists of an equation of continuity (conservation of mass), three generalized momentum equations, and a constitutive equation. When the constitutive equation is introduced into the generalized momentum equations, they become specific for the particular fluid involved in the flow situation. With appropriate simplifications and boundary conditions, the equation of continuity and the specific momentum equations can be solved to yield information about the flow: stresses, strain rates, etc. In accordance with the second approach, this thesis offers an empirical constitutive equation for use in describing the behavior of blood.

CHAPTER II

Review of Literature

A. Early Work

Interest in the viscosity of blood began in the early part of this century when Hess [3] developed a simple convenient viscometer. Of the many papers published during this period, however, it is difficult to determine whether the investigator used whole blood, plasma, or serum (see appendix A for definitions of physiologic terms). Where whole blood was used, it is often further uncertain as to the kind and quantity of anticoagulant that was used. Moreover, viscometers were of crude design and virtually every investigator used a viscometer that was different from many others. Although it is difficult to draw conclusions from this early work, some gross observations may be of value.

Fahraeus [4-6], Holker [7], and others [8-17] reported that the viscosity of serum was increased in certain diseases. This proved to be important, since serum or plasma viscosity could then be used to measure the severity of a disease. In 1940, for example, T'ang and Wang [18] found a good correlation between the increase in plasma viscosity and the severity of a tuberculosis condition. Whittington [19] and others [20-23] extended this work to other physiologic disorders. Although much was done by these early investigators, the crudeness and uncertainties cited above make their observations useful only in a very general and qualitative way.

B. Modern Developments

For the most part, beginning in 1828 when the physiologist Jean L. M. Pouiseuille [2] examined the steady laminar flow of water, interest in the viscosity of whole blood, plasma, and serum centered primarily around its relation to disease conditions. Investigators simply accepted the fluid as being essentially Newtonian for their purposes [24-34]. Inasmuch as the validity of using Stokes' Viscosity Law for flow conditions characteristic of the cardiovascular system has been seriously questioned [27], only recently has interest surfaced in actually determining a constitutive equation (see appendix B) for the fluid.

The dependence of the viscosity of blood upon strain rate has been thoroughly investigated, and it is universally agreed that the viscosity of whole blood decreases as the strain rate increases. A fluid which exhibits this type of behavior is called pseudoplastic [35]. In addition to its pseudoplastic behavior, whole blood also exhibits a yield stress--that is, a certain minimum force is necessary in order to initiate flow [36-38]. A fluid exhibiting such a yield stress is called a Bingham Plastic [35]. An equation which attempts to describe both Bingham Plastic and pseudoplastic behavior was proposed in 1959 by Casson [39] who at the time was working with pigment-oil suspensions of printing ink. The equation has the form:

$$\tau^{1/2} = k_c \dot{\gamma} + \tau_y^{1/2} \quad (2.1)$$

where

$$\begin{aligned}\tau &\equiv \text{shear stress,} \\ \dot{\gamma} &\equiv \text{shear rate} \\ k_c &\equiv \text{Casson viscosity, and} \\ \tau_y &\equiv \text{yield stress.}\end{aligned}$$

Merrill, et al. [36], and other investigators [37,40-43] have used this equation with a reasonable degree of success to model the behavior of whole blood. However, when the Casson equation is introduced into the generalized momentum equations, the equations obtained are much too complicated to be of any practical value.

Other investigators [40,42,44-47] have chosen a different functional form for the constitutive equation for blood, namely, a power law equation of the form:

$$\tau = k\dot{\gamma}^n \text{ dynes/cm}^2 \quad (2.2)$$

where

$$\begin{aligned}\tau &\equiv \text{shear stress,} \\ \dot{\gamma} &\equiv \text{shear rate,} \\ k &\equiv \text{consistency index, and} \\ n &\equiv \text{non-Newtonian index.}\end{aligned}$$

The parameters k and n are assumed to be constant for a given hematocrit level and a given chemical composition. Notice that the yield stress τ_y , does not appear in the power law equation. The yield stress for blood is extremely small, and it is due mainly to interactions between the protein fibrinogen and the erythrocytes. The

addition of an anticoagulant either reduces these interactions or eliminates them completely [48]. Thus, the power law equation is considered valid even though whole blood does exhibit a slight yield stress (for further details, see Chapter III).

A few investigators have studied the relationship between the hematocrit level and the parameters k and n . Sacks [49] found that the non-Newtonian index, n , is a decreasing function of hematocrit. He gives an equation of the form:

$$n(H) = 1.00 - C_1 H \quad (2.3)$$

where C_1 , an empirical constant depending upon the animal species, is reported to be:

$$C_1 = 4.5 \times 10^{-3} \text{ for human and canine blood, and}$$

$$C_1 = 1.7 \times 10^{-3} \text{ for bovine blood.}$$

In addition, Sacks found the consistency index, k , to increase exponentially with increasing hematocrit levels:

$$k(H) = C_2 e^{C_3 H} \quad (2.4)$$

where

$$C_2 = 1.05 \times 10^{-2}, \text{ and}$$

$$C_3 = 5.4 \times 10^{-3}$$

for human, canine, and bovine blood. Waller [50], using blood samples taken from domestic pigs, has confirmed the functional form of

equations (2.3) and (2.4). He obtained the following constants:

$$C_1 = 2.19 \times 10^{-3},$$

$$C_2 = 2.95 \times 10^{-2}, \text{ and}$$

$$C_3 = 3.62 \times 10^{-3}.$$

A search of the literature reveals that no studies have been attempted to relate k and n to the chemical composition of the fluid, or, at least no results have been published on this topic.

Some studies have been made relating the chemical composition to viscosity. Rohrer [51,52] and Naegeli [53] report that the non-protein constituents of serum play a minor role in determining the viscosity of the fluid. The protein fractions have been found to contribute in varying degrees. Rohrer [51,52] and Naegeli [53] found that when equal amounts of globulin and albumin molecules are separately introduced into equal amounts of serum, it is the globulin sample which shows a higher value of viscosity. Studies that have correlated plasma viscosity with its protein fractions have repeatedly shown that the larger the protein molecule and the more its shape differs from a sphere, the larger the effect on viscosity [54-61]. Arranged in the order of decreasing effects on viscosity at equal concentration, the three major proteins are: fibrinogen, globulin, and albumin. Lawrence [55] reports that although albumin, globulin, and fibrinogen have concentration ratios of 4.0 : 2.5 : 0.3, respectively, their contributions to viscosity increases are in the ratio 36 : 41 : 22. Since the albumin solutions exhibit a lower viscosity than fibrinogen

and globulin solutions, Harkness [62] and Wells [63] suggest that albumin may actually decrease the viscosity of plasma. In fact, the viscosity of albumin solutions is lower than that of serum, and the viscosity of fibrinogen and globulin solutions is higher than that of serum. Merrill, et al. [41], show that a correlation exists between viscosity and fibrinogen and the various types of globulins, but there is no mention of albumin.

To the best of this author's knowledge, information relating the plasma lipids to the viscosity of whole blood is not available in the literature.

However, other investigators have studied numerous other variables and their effect on the viscosity of blood. Isogai, et al. [61], have studied the erythrocyte sedimentation rate (E.S.R.); Giombi and Burnard [64] have looked at osmolality and pH; Gregersen, et al. [43], have reported on the volume concentration and the size of the red cells; and Hershko and Carmeli [65] have investigated packed cell volume, hemoglobin content, and the red cell count.

C. Summary

It has been well documented that blood behaves as a combination of a Bingham Plastic and a pseudoplastic fluid. When an anticoagulant has been added, the Bingham Plastic behavior is no longer present to any significant degree. Investigators have determined constitutive equations for blood as a function of the shear rate and hematocrit level. Studies have also been made relating plasma proteins to viscosity, but this information has not been included in a constitutive

equation. Additionally, several investigators have considered the E.S.R., osmolality, pH, hemoglobin content, size of the red cells, and the red cell count.

CHAPTER III

The Present Problem

The present problem is to develop a practical and realistic constitutive equation for whole human blood. When it is introduced into the generalized momentum equations, this equation should be of a form that they may be readily solved. Since the non-Newtonian behavior of blood is primarily pseudoplastic, a general power law, such as equation (2.2), will be examined. The Bingham Plastic behavior will not be incorporated into this constitutive equation. This is justified on the basis of two observations; first, the yield stress exhibited by blood is extremely small and virtually constant; and, second, the power law constitutive equation may be easily modified to allow for the presence of a yield stress, i.e., it may be written as follows:

$$\tau = k\dot{\gamma}^n + \tau_y \text{ dynes/cm}^2. \quad (3.1)$$

This merely shifts the ordinate values by an amount τ_y as shown in figure 8.

The scope of this investigation is, first, to determine the dependence of the consistency index, k , and the non-Newtonian index, n , on the hematocrit level in an effort to verify equations (2.3) and (2.4). The parameters k and n will also be examined as functions of the plasma lipids and proteins. In each case the level of significance of these equations will be determined.

CHAPTER IV

Method of Analysis

A. Materials

Over a period of five months beginning in March, 1974, exactly 200 human blood samples of 10 milliliters each were obtained from the hematology laboratory of the Montgomery County Hospital. These human blood samples, anticoagulated with EDTA, were mixed well by careful shaking, and two 1.2 milliliter aliquots were drawn from each 10 milliliter test tube. Viscosity measurements at strain rates of 23.28, 46.56, 116.40, and 232.80 reciprocal seconds were recorded for each aliquot, and the results at each shear rate were averaged. This reduces the chance for an error due to incomplete mixing, inasmuch as the pairs of viscosity values may be compared and if large discrepancies are noted, more viscosity measurements can be made.

A Wells-Brookfield Micro Cone and Plate Viscometer was used, along with a Brookfield Model N recirculating constant temperature water bath. The latter has an accuracy of ± 0.01 degrees centigrade, and the entire apparatus has been used with extreme accuracy by many investigators. The most important feature of a cone and plate viscometer is that it produces a constant strain rate in the fluid (see appendix C for details). In addition, the optimum sample volume for the viscometer is 1.2 milliliters, which is important when the fluid being examined cannot be easily obtained in large quantities.

The chemical analysis (S.M.A. 10) of each blood sample was also generously supplied by the Montgomery County Hospital. Total lipid determinations were performed under the supervision of Dr. William Gutstein at the New York Medical College in Valhalla, New York [73].

B. Variables

The dependence of the viscosity of blood upon the shear rate and hematocrit level is well documented and will be included in the constitutive model. The chemical parameters that will be investigated include total lipids, albumin, and total protein minus albumin (TPMA). TPMA is composed of fibrinogen and the globulin. These chemical variables were chosen because they are composed of long chain asymmetric molecules which exist in large numbers and interact more than do symmetric particles. Thus, it is probable that they contribute most to the rheologic properties of the fluid. Albumin, TPMA, total lipid, hematocrit, and the strain rate will be treated as independent variables, with the viscosity being considered dependent. A multiple regression computer procedure will then be used to determine the variables of greatest significance.

C. Statistical Analysis

Equation (2.2) is the basic functional form that will be selected for developing the constitutive equation. Since the viscosity of blood varies for different shear rates, we introduce a new quantity called apparent viscosity (μ_a), which is defined as the

viscosity of the fluid at a given shear rate:

$$\mu_a = \tau / \dot{\gamma} \text{ poise.} \quad (4.1)$$

When equation (4.1) is substituted onto equation (2.2), an equation relating the apparent viscosity to the shear rate results:

$$\mu_a = k \dot{\gamma}^{n-1} \text{ poise.} \quad (4.2)$$

Equation (4.2) is nonlinear, making it extremely complicated from the point of view of least squares regression analysis. Therefore, it is more convenient to linearize the equation by taking logarithms to the base e yielding:

$$\log_e \mu_a = \log_e k + (n-1) \log_e \dot{\gamma}. \quad (4.3)$$

Equation (4.3) is of the form:

$$Y = mX + b \quad (4.4)$$

where

Y = dependent variable,

X = independent variable,

m = slope of the line, and

b = the Y intercept.

With respect to equation (4.3), these become:

$\log_e \mu_a$ = dependent variable,

$\log_e \dot{\gamma}$ = independent variable,

$(n-1)$ = slope of the curve, and

$\log_e k$ = the intercept.

An equation which can be transformed in the manner just described is called an intrinsically linear equation [66].

The parameters $(n-1)$, $\log_e k$, and $\log_e \mu_a$ shall be examined in the regression analysis as functions of albumin, TPMA, total lipid, hematocrit, their squares, their inverses, the squares of their inverses, and all interaction terms (albumin x TPMA, albumin x $\log_e \dot{\gamma}$, albumin x 1/hematocrit, and so forth). $\log_e \mu_a$ is the basic dependent variable.

With respect to the inclusion of interaction terms such as $(1/\text{hematocrit}) \times \log_e \dot{\gamma}$ and $(1/\text{hematocrit}^2) \times \log_e \dot{\gamma}$, we note the following:

Given a regression equation of the form:

$$\log_e \mu_a = C_1 + C_2 Y_1, \quad (4.6)$$

if a variable such as

$$Y_1 = (1/\text{hematocrit}) \times \log_e \dot{\gamma} \quad (4.7)$$

is introduced, it suggests, for a constant shear rate, that an increase in hematocrit will decrease the apparent viscosity. This is physically unrealistic since the apparent viscosity of blood actually shows an increase as the percentage by volume of erythrocytes increases. Terms of the form $(1/\text{hematocrit}) \times \log_e \dot{\gamma}$ and $(1/\text{hematocrit}^2) \times \log_e \dot{\gamma}$, therefore, are unrealistic and will not be allowed to appear in the model.

A maximum R-square improvement regression procedure, contained in the Statistical Analysis System (S.A.S.) [67] of the VPI&SU 370 IBM digital computer, was used to analyze the data. This procedure finds, first, the "best" one variable model that produces the highest R-square statistic (see appendix D). That is, of the independent variables chosen for analysis, the program selects one and uses the linear least squares method to determine an equation of the form (4.6). It then computes an associated R-square statistic for this equation. Going through this procedure separately for each independent variable, the computer finally chooses the model with the largest R-square statistic as the best one variable model.

To determine the best two variable model, the statistical program now adds one of the remaining variables to the best one variable model. The linear regression analysis is used to determine an equation of the form:

$$\log_e \mu_a = C_1 + C_2 Y_1 + C_3 Y_2 \quad (4.8)$$

and the associated R-square statistic for this equation is computed. A different variable is then added to the best one variable model, and again the R-square statistic is computed. This procedure is followed for all remaining variables to determine which one, when added to Y_1 , will produce the greatest increase in R-square.

At this point, it is realized that the Y_1 variable which produced the best one variable model may not necessarily be one of the two which produces the best two variable model. Thus, the program

goes back to check each of the variables, both Y_1 and Y_2 , in the model it has just obtained. That is, it determines whether there will be a further increase in the R-square value if either of the presently included variables is replaced by one which was excluded. After all possible comparisons are made, the combination of two variables which produces the greatest increase in R-square over the previous two variable model is isolated. The procedure continues cycling until no increase in R-square is found. The result is the best two variable model. Essentially, this procedure determines whether or not the variable Y_1 in the best one variable model is also significant in the best two variable model. For higher order models, the entire procedure is repeated.

Since this study seeks a practical as well as realistic constitutive equation, the best three variable model will be the highest order model investigated. Furthermore, the model will be restricted to the normal physiologic range of hematocrit, i.e., 35-50%.

CHAPTER V

RESULTS AND DISCUSSION

A. Preliminary Remarks

It has been well documented that the behavior of whole blood is primarily pseudoplastic. That is, the viscosity decreases as the shear rate increases. Therefore, it should not be too surprising to find that the best one variable rheologic model shows the shear rate to be the single most significant independent variable. This equation is:

$$\mu_a = k\dot{\gamma}^{n-1} \text{ poise} \quad (5.1)$$

with

$$k = 0.134, \text{ and}$$

$$n = 0.785 \text{ both constant.}$$

Equation (5.1) has an R-square value of 0.6187 and a mean square error of 0.0218, so the fit of this equation to the data is not good enough. Also, notice that n , the non-Newtonian index, is constant in this model for all hematocrit levels and chemical compositions. Physically, this is unrealistic, since the non-Newtonian properties of blood arise from the interactions of red blood cells with each other and with the long chain molecules present in the plasma. When the number of red blood cells increase so does the non-Newtonian behavior. A plot of equation (5.1) is shown in figure 13 along with two experimental

curves. It is not hard to see that an equation involving only the shear rate is not a very good approximation of the true behavior of blood. It would seem, therefore, that the hematocrit level should be the next likely candidate for inclusion in the constitutive model.

B. Dependence on Hematocrit

The best two variable model (BTVM) found by the multiple regression procedure shows the shear rate and hematocrit level to be the most significant independent variables. The equation has the same form as equation (5.1) except that k and n now depend on the hematocrit level as follows:

$$k = C_1 e^{C_2(\text{Hematocrit})}, \text{ and} \quad (5.2)$$

$$n = 1.0 - C_3(\text{Hematocrit}), \quad (5.3)$$

where

$$C_1 = 0.0148,$$

$$C_2 = 0.0512, \text{ and}$$

$$C_3 = 0.00499.$$

The R-square value for this model is 0.8789, while the mean square error is 0.0069. Each coefficient, C_i ($i = 1, 2, 3$), has a T value of 0.0001. The T value of the coefficient is a measure of the probability that a variable is not statistically significant in the model. Thus a T value of 0.0001 means that the probability of a variable being statistically significant is 99.99%.

Equations (5.2) and (5.3) are in the same form as reported by Sacks [49]. The differences appear in the coefficients C_1 , C_2 , and C_3 , as shown in Table I. Observe that the values for C_3 are of the same order of magnitude. In fact, the coefficient from the best two variable model is only 0.00049 larger than Sacks' value. Off hand, one might attempt to attribute this small difference to experimental and statistical errors. However, it may be argued that the difference, though small, is still meaningful because the very small mean square error (a measure of the average distance each data point falls off the regression line) and the very low T values indicate that the coefficients in this best two variable model are statistically quite significant. Thus the BTVM predicts a higher degree of non-Newtonian behavior than does the model reported by Sacks. Figure 14 shows equation (5.3) with the C_3 value from both Sacks' model and the BTVM. Clearly, the slope of the BTVM line is greater than the slope of Sacks' line. Furthermore, by observing the experimental data which are plotted on the same graph, we see that most of the points fall much closer to the BTVM line. This tends to confirm that the difference between C_3 (Sacks) and C_3 (BTVM) is, in fact, significant and not mainly due to experimental or statistical errors.

Table I shows that the two values of C_1 are again of the same order of magnitude, but the values of C_2 differ by a full order of magnitude. These coefficients appear in the equation for k . Sacks' curve and the BTVM curve for k are plotted in figure 15, and a significant difference is immediately visible. Some experimental

data points are plotted to show the variance about the BTVM line. The difference between the two lines is composed of a linear term and a nonlinear term. The linear difference is the increase by 0.00436 of C_1 (BTVM) over C_1 (Sacks). The nonlinear difference arises from the difference in the C_2 values, the C_2 (BTVM) value being 0.0458 larger. Thus, the BTVM consistently predicts a higher value of apparent viscosity and this increase is nonlinear.

C. Dependence on Plasma Proteins

The first variable examined was total protein, hereafter referred to as TP. TP is composed of fibrinogen, albumin, and globulin. The normal physiologic ranges for these quantities are: (1) fibrinogen, 0.2 to 0.6 gram/100 ml., (2) albumin, 3.5 to 5.5 gram/100 ml., and (3) globulin, 1.5 to 3.0 gram/100 ml. When TP was added to the variables already under consideration in the BTVM, the resulting best three variable model produced an R-square of 0.8836 which is an increase of only 0.00468 over the BTVM. This implies that TP does not have much of an effect on the viscosity of blood, which is an unexpected finding when one considers that the plasma proteins are very long chain asymmetric molecules which interact strongly with each other and with the red blood cells.

Pursuing this point further, the author discovered articles by Harkness [62] and Wells [63], in which it was reported that saline solutions of albumin have significantly lower viscosities than do equivalent solutions of globulin. Therefore, it would seem likely

that, since albumin and globulin are two of the primary constituents of total protein, they could have cancelling effects when introduced as a single variable. Thus, the single variable, total protein, was separated into albumin and total protein minus albumin (or TPMA). TPMA is composed of globulin and fibrinogen, these two being combined into a single variable for two reasons: (1) globulin saline solutions and fibrinogen saline solutions each have higher viscosities than albumin solutions; and (2) no specific information concerning the fibrinogen concentration was available for the blood samples used in this study.

A three variable model including albumin was not generated by the regression analysis, but there was a model developed containing TPMA. Thus, it may be inferred that albumin does not affect viscosity at the same level as does TPMA. This can be partially explained by noting that albumin has a molecular weight of 66,000 and an axial length-width ratio of 3 : 1, while TPMA is composed of molecules having molecular weights ranging from 35,000 to 1,000,000 with axial length-width ratios of 12 : 1 and greater. Studies [54-61] have shown that the larger the molecule and the more its shape differs from a sphere, the greater the effect on viscosity. Thus, it is not surprising to find that TPMA enters into the constitutive model before albumin, although it is not immediately obvious why this finding should be masked when albumin is lumped with the other proteins in the model. Perhaps the observation that rouleaux formations (aggregations of red blood cells), caused by fibrinogen and other fibrous proteins, were

found to be dispersed by serum albumin could play a role in explaining the latter observation.

The best three variable model is exactly the one which includes TPMA and this model has the form:

$$\mu_a = k \dot{\gamma}^{n-1} \quad \text{poise,} \quad (5.4)$$

where

$$k = C_1 e^{C_2(\text{Hematocrit}) + C_4 \left(\frac{\text{TPMA}}{\text{Hematocrit}^2} \right)}, \text{ and } (5.5)$$

$$n = 1.0 - C_3(\text{Hematocrit}). \quad (5.6)$$

The coefficients in equations (5.5) and (5.6) have the values:

$$C_1 = 0.00797,$$

$$C_2 = 0.0608,$$

$$C_3 = 0.00499, \text{ and}$$

$$C_4 = 145.85.$$

The R-square for this model is 0.9049, a significant increase of 0.0259 over the BTVM. The mean square error of 0.00546 is over 27% less than that for the BTVM and the T values for the coefficients are 0.0001 each. Thus, introducing TPMA into the model produces a statistically significant increase in fitting the data.

Table II shows a comparison of the BTVM and the best three variable model. Note that C_3 , the constant in the equation for n , is identical for both models. Therefore, this study shows that hematocrit is primarily responsible for the non-Newtonian index of

blood and that the plasma lipids and proteins have little or no effect on this index, n .

Also, observe in Table II, that the corresponding values of C_1 and C_2 are approximately of the same order of magnitude. The difference, therefore, between the two models arises primarily from the term in brackets, i.e.,

$$C_4 \left(\frac{\text{TPMA}}{\text{Hematocrit}^2} \right)$$

The range of values for this term at various hematocrit levels is shown in Table III for the two extreme values of TPMA considered in this study. Note that the value of X decreases with increasing hematocrit at constant values of TPMA, and vice-versa. Physically, this is reasonable, since when hematocrit, which has a first order effect on viscosity, is low, one would expect second order effects, such as the chemistry of the fluid, to become more important. This is exactly the behavior which equation (5.5) predicts. Mathematically, the limiting case is for an infinite hematocrit level, at which point X is equal to unity and thus has no effect on viscosity.

A comparison of the consistency index equations ((5.2) and (5.5)) for the BTVM and the best three variable model can be seen in figure 16. The highest and lowest values of TPMA used in this study are plotted along with the consistency index equation from the BTVM. The curves corresponding to other values of TPMA lie between the two extremes shown. Note that the best three variable model curve with

TPMA equal to 1.5 falls below the BTVM, while the curve for TPMA equal to 4.2 lies above the BTVM curve.

Similar behavior is shown in figures 17 through 22, which are plots of apparent viscosity versus shear rate for various hematocrit and TPMA levels. Several important results may be discerned from these figures.

First, it can be seen that TPMA has a significant effect on viscosity, a fact not revealed in the BTVM. Compared with the BTVM, the best three variable model shows that blood with relatively low levels of TPMA has a correspondingly lower apparent viscosity and the latter increases with TPMA. Thus, the best three variable model predicts either higher or lower fluid shear stresses (depending on the TPMA concentration) than does the BTVM.

Second, since the fluid viscosity is greatly dependent on hematocrit, note from figures 17-22 that the best three variable model curves converge around the BTVM as the hematocrit level progressively increases. This can be observed especially well at the lower shear rate ranges.

The increase in non-Newtonian behavior as the hematocrit level goes up, is also visible in figures 17-22. This behavior is illustrated even more clearly in figure 23, where curves of the best three variable model at various hematocrit levels are plotted with TPMA held constant.

Figure 24 shows a plot of the best three variable model for a low (1.5) and a high (3.8) TPMA level, with hematocrit held constant.

Experimental data points corresponding to these TPMA levels are also shown, as is a plot of the BTVM. This figure illustrates clearly that it is the high and low values of TPMA that produce a significant change from the BTVM. For example, figure 25 shows that for an intermediate value of TPMA (2.5) there is not much difference between the two models. Therefore, it may be concluded that if one is interested in examining fluid behavior at moderate levels of TPMA (2.5 ± 0.2) either a two or three variable model would be appropriate, but if a wider range of TPMA is to be investigated, then the best three variable model should be chosen.

D. Dependence on Plasma Lipids

On the basis of an intensive literature search, this author could find no work relating the plasma lipids to the viscosity of whole blood. The only references which dealt with lipids were those of Rohrer [51,52] and Naegeli [53] which were published in 1916 and 1923 respectively. These investigators reported that the non-protein constituents of serum play a minor role in determining the viscosity of the fluid. The results of the present study tend to confirm this finding, at least for the case of the plasma lipids.

The only reasonable model which includes total lipids has an R-square value of 0.8805. It has the form of equation (5.1) where

$$k = C_1 e^{C_2(\text{Hematocrit}) + C_5 \left(\frac{\text{total lipid}}{\text{albumin}^2} \right)}, \text{ and} \quad (5.7)$$

$$n = 1.0 - C_3 \text{ (Hematocrit)} \quad (5.8)$$

with the constants given as follows:

$$\begin{aligned} C_1 &= 0.0434, \\ C_2 &= 0.00059, \\ C_3 &= 0.0051, \text{ and} \\ C_5 &= 0.900. \end{aligned}$$

The T value for each of the above coefficients is 0.0001 and the mean square error is 0.00714, so statistically this model is significant. However the R-square increase over the BTVM is 0.00149, only a 0.17% increase, and is actually 0.0244 less than the best three variable model discussed previously in section C. Consequently, this study confirms that the plasma lipids probably play a minor role in affecting the viscosity of blood.

CHAPTER VI

Summary and Conclusions

A. Constitutive Equations Developed

Three rheologic equations, from a one variable model to a three variable model, were developed in this study. As the number of variables increased, so did the statistical fit to the experimental data. The equations for k and n were developed from a relation of the form

$$\mu_a = k\dot{\gamma}^{n-1} \text{ poise.} \quad (6.1)$$

By definition, a constitutive equation relates the stress to the rate of strain in a fluid. In this study a power-law functional form was assumed, i.e.,

$$\tau = k\dot{\gamma}^n \text{ dynes/cm}^2. \quad (6.2)$$

where

τ = the shear stress,

$\dot{\gamma}$ = the shear rate,

k = the consistency index, and

n = the non-Newtonian index.

The best one variable model led to the following results:

$$k = 0.134 = \text{constant}, \quad (6.3)$$

$$n = 0.785 = \text{constant}, \quad (6.4)$$

$$R\text{-square} = 0.6187,$$

mean square error = 0.0218, and

$T = 0.0001$.

The best two variable model yielded:

$$k = C_1 e^{C_2(\text{Hematocrit})}, \text{ and} \quad (6.5)$$

$$n = 1.0 - C_3(\text{Hematocrit}), \quad (6.6)$$

where

$$C_1 = 0.0148,$$

$$C_2 = 0.0512, \text{ and}$$

$$C_3 = 0.00499.$$

The R-square value for this model is 0.8789; the mean square error equals 0.0069; and the T values are 0.0001.

The best three variable model has the form

$$k = C_1 e^{C_2(\text{Hematocrit}) + C_4 \left(\frac{\text{TPMA}}{\text{Hematocrit}^2} \right)}, \text{ and} \quad (6.7)$$

$$n = 1.0 - C_3(\text{Hematocrit}), \quad (6.8)$$

where

$$C_1 = 0.00797,$$

$$C_2 = 0.0608,$$

$$C_3 = 0.00499, \text{ and}$$

$$C_4 = 145.85.$$

The R-square value is 0.9049, the mean square error is 0.00546, and the T values equal 0.0001.

In each of the rheologic models developed, the variables $\dot{\gamma}$, hematocrit, TPMA, albumin, and total lipid were considered to be independent variables. That is, it was assumed that a change in one variable would not produce a change in any of the others. In reality, blood in the cardiovascular system of man and animals is constantly changing in chemical composition and shear rate--the two having a non-linear interrelationship. Additionally, the various chemical constituents are dependent on each other. These complexities tend to invalidate the assumption of the independence of chemical variables. However, for a first order effect of chemical composition on viscosity, the assumption of independence of chemical variables is reasonable.

B. Results Summarized and Conclusions

An equation including only the shear rate was found to be lacking any real degree of significance. When hematocrit was added as a variable, the R-square increased from just 62% to almost 88%. Of the chemical variables studied, the least significant, as far as effects on viscosity is concerned, was the plasma lipids. Fibrinogen and globulin, in the form of TPMA, had a much greater effect on viscosity than did albumin. The best three variable model, which includes TPMA, increased the R-square from 88% to nearly 91%--a significant increase.

On a microstructural level, there is much to be done, but for a first order approximation of the effects of plasma chemistry on whole blood viscosity, this thesis offers a reasonable constitutive equation.

C. Direction of Future Studies

Information about the fibrinogen concentration would be desirable in order to determine which of the two variables comprising TPMA has the most effect on viscosity. Moreover, in a future study the chylomicron count might be examined. Chylomicrons are globules of emulsified fats and are large enough to be seen with a light microscope. In addition, the chylomicron count is expressed in volume percent, which, dimensionally, is more compatible with hematocrit than is gram percent (gm/100ml). Many other variables should also be investigated. These include the various subgroups of the globulins and albumin. Perhaps even the shape of the hematocytes could be related to the viscosity of blood.

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FIGURES

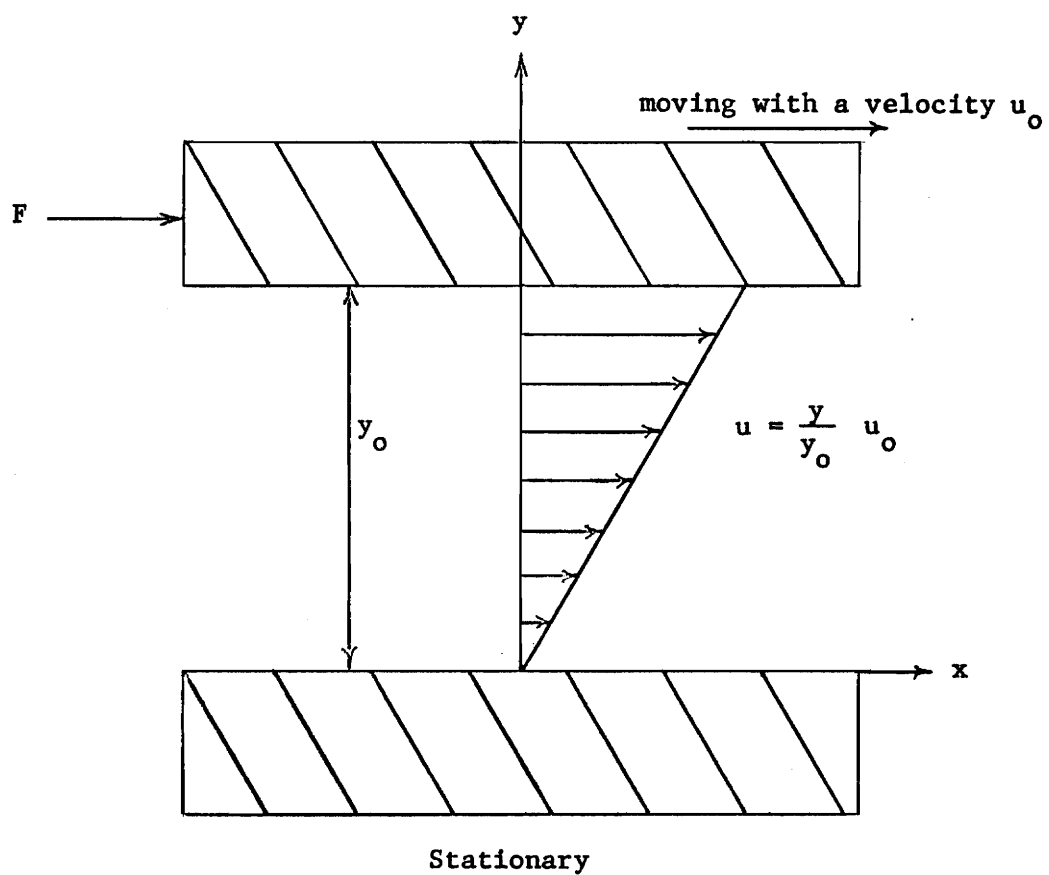


Figure 1. Newtonian Velocity Profile.

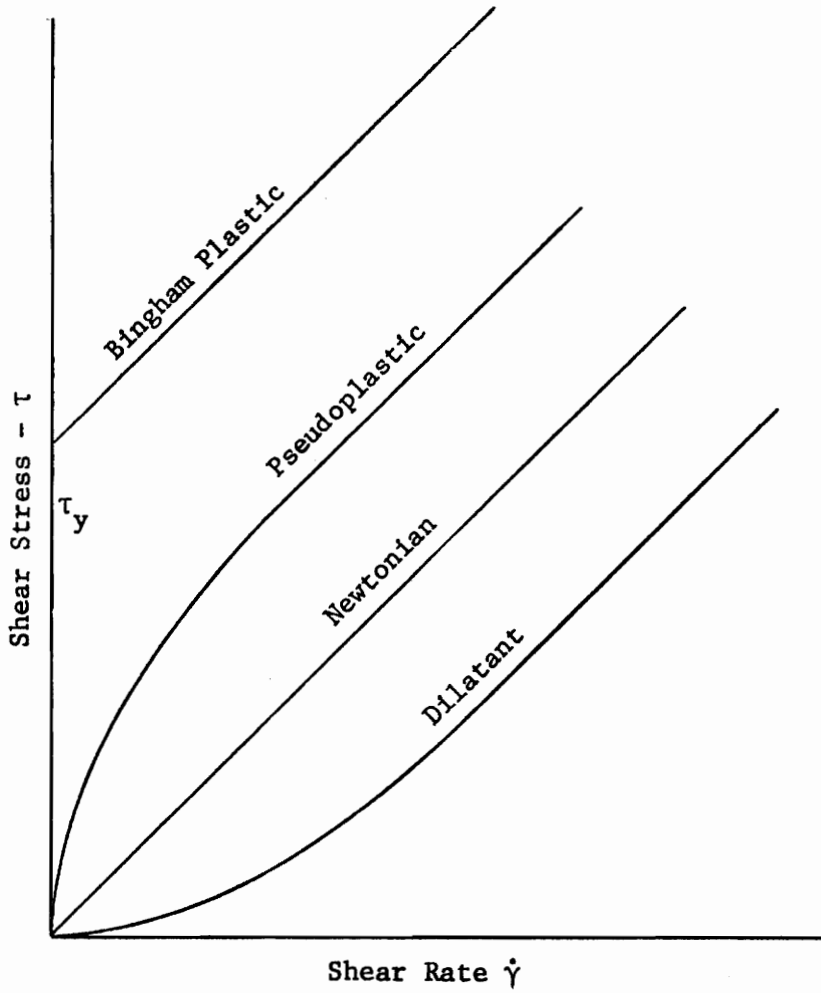


Figure 2. Types of non-Newtonian Fluids.

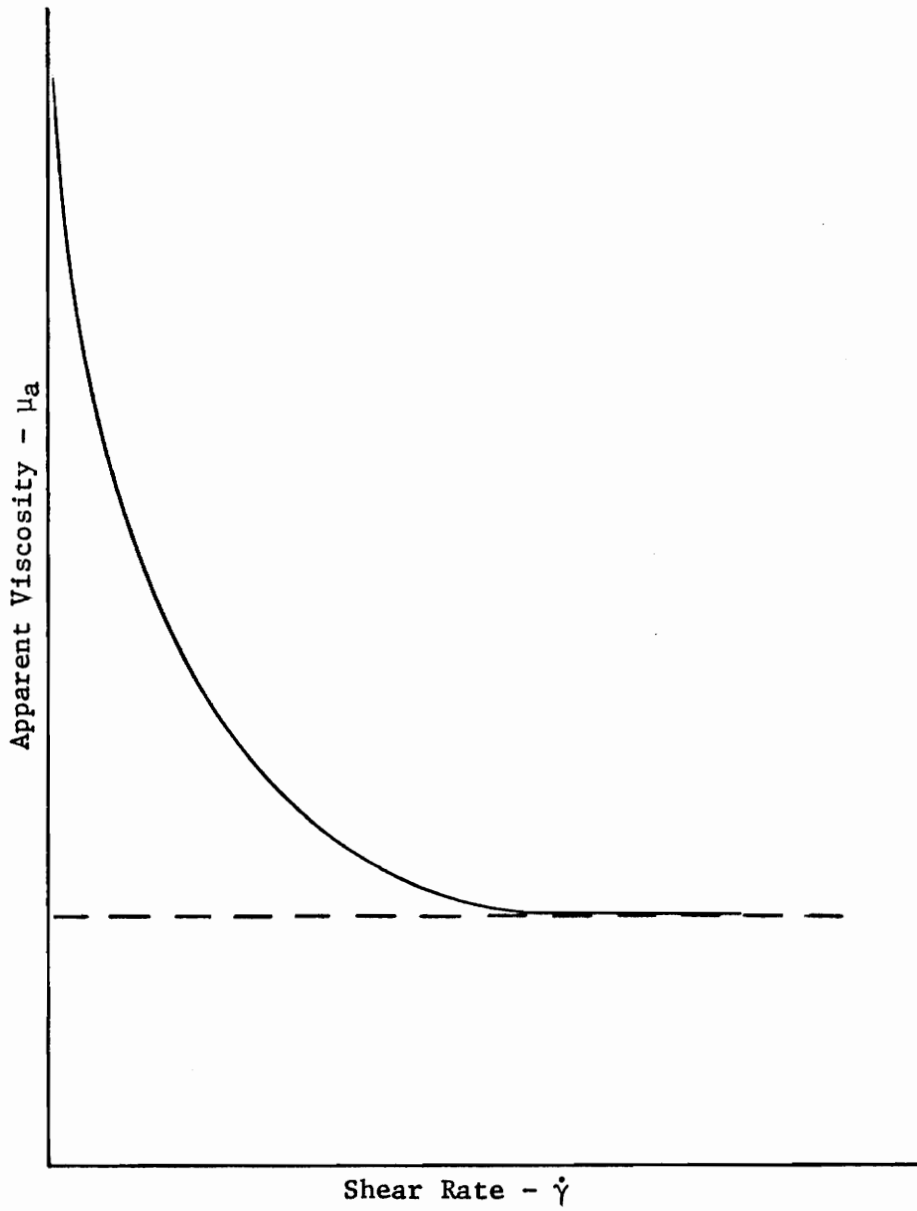


Figure 3. A Pseudoplastic Fluid.

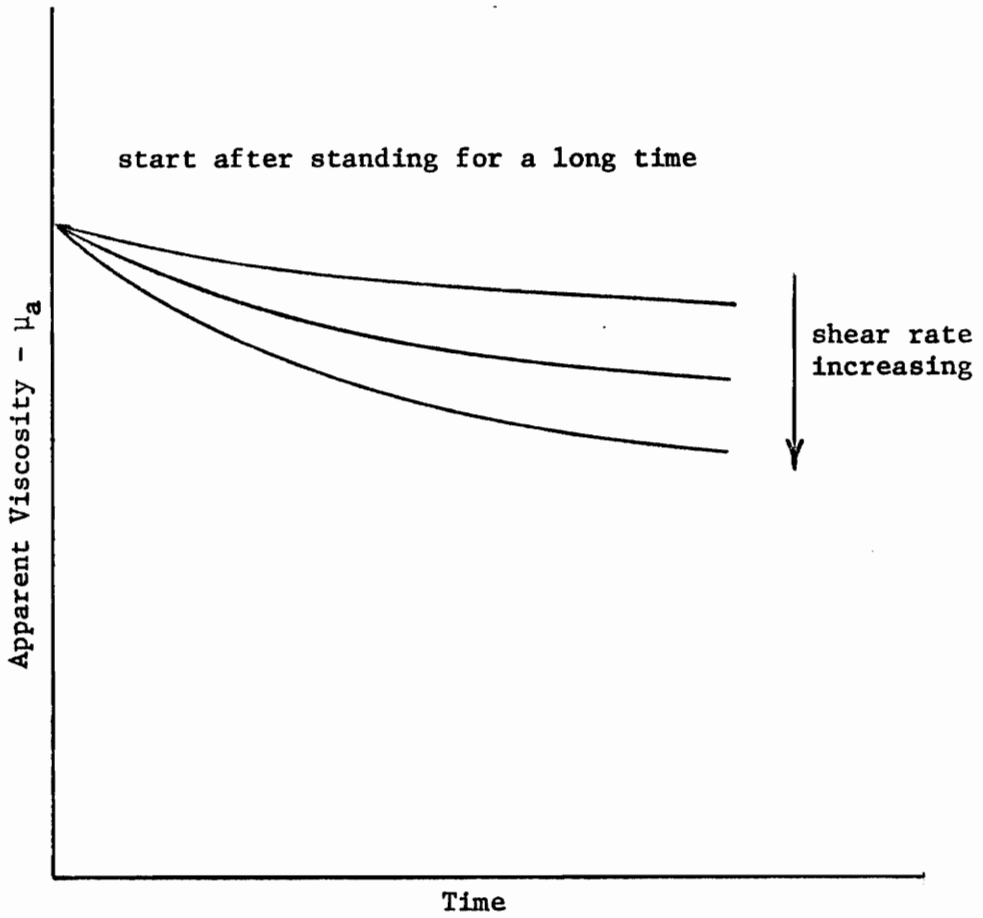


Figure 4. Behavior of a Time Dependent Fluid.

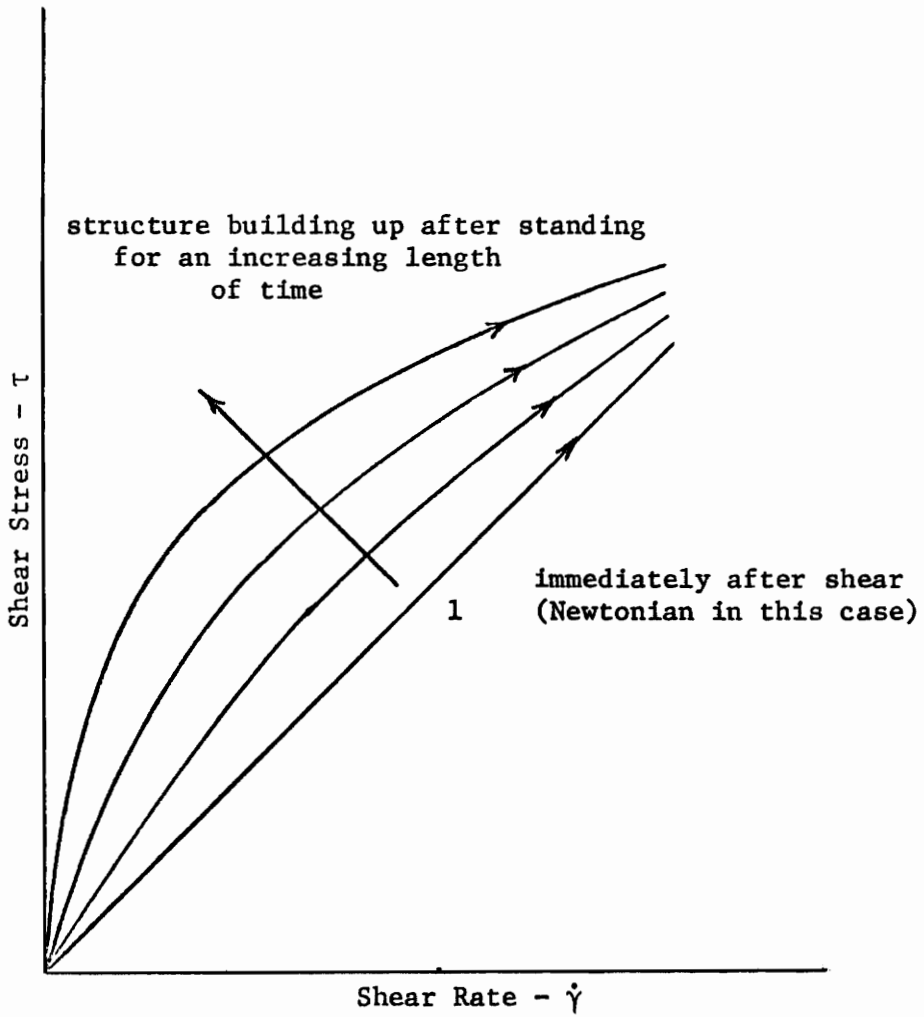


Figure 5. Behavior of a Time Dependent Fluid.

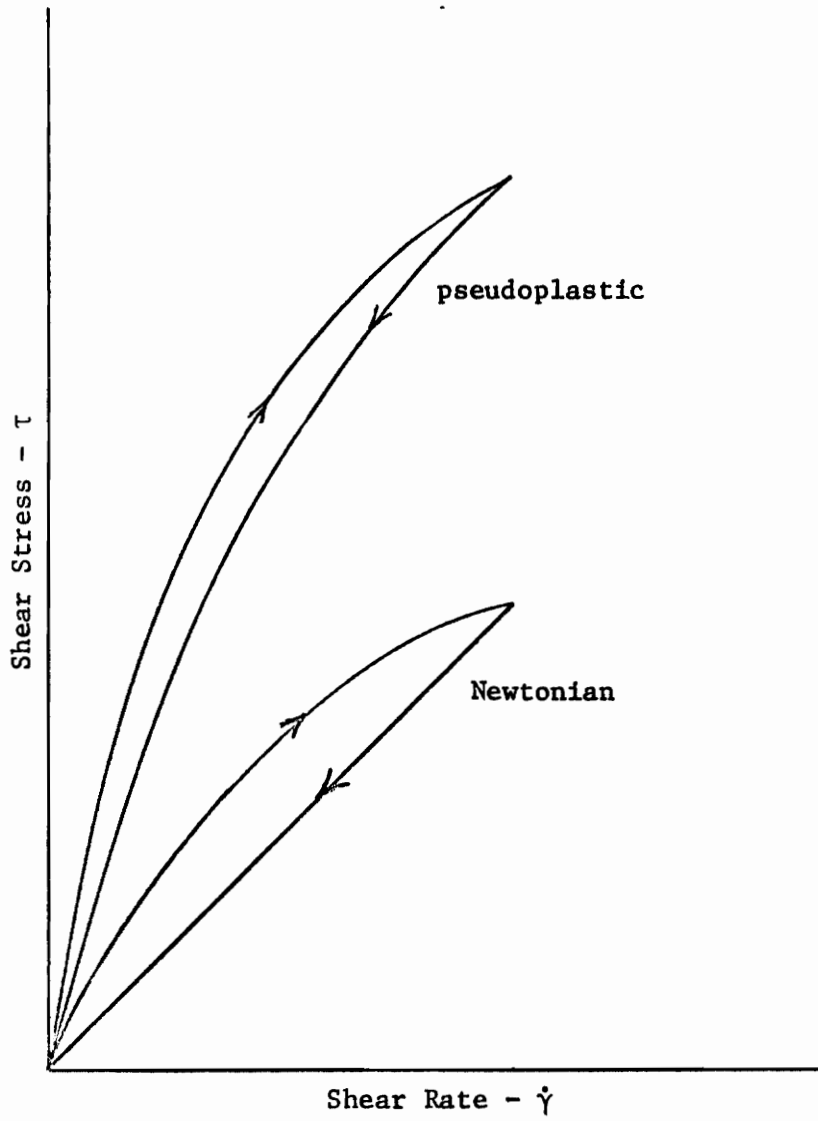


Figure 6. Hysteresis Loops.

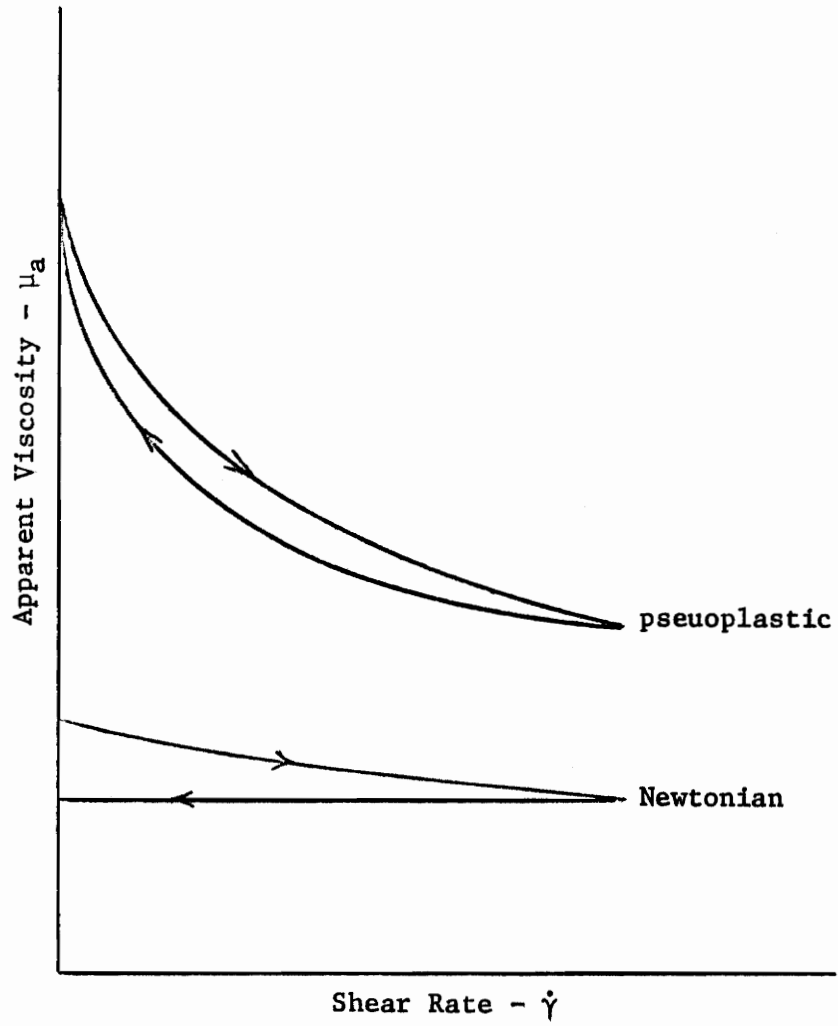
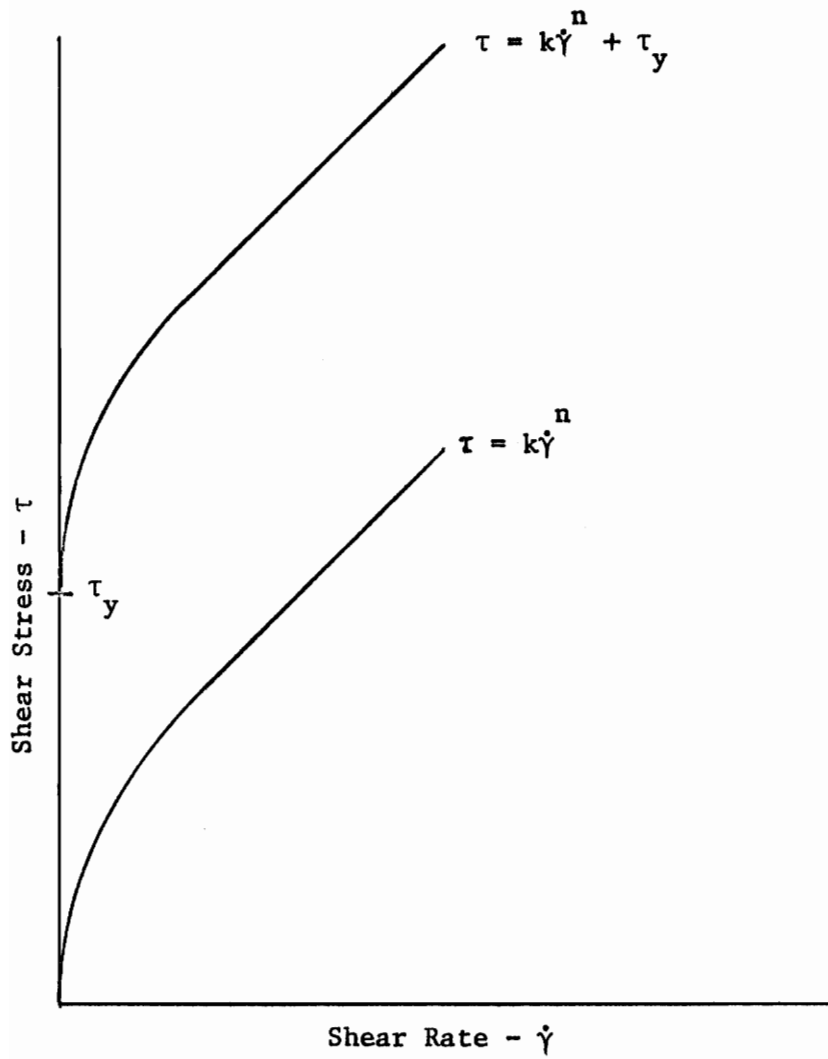
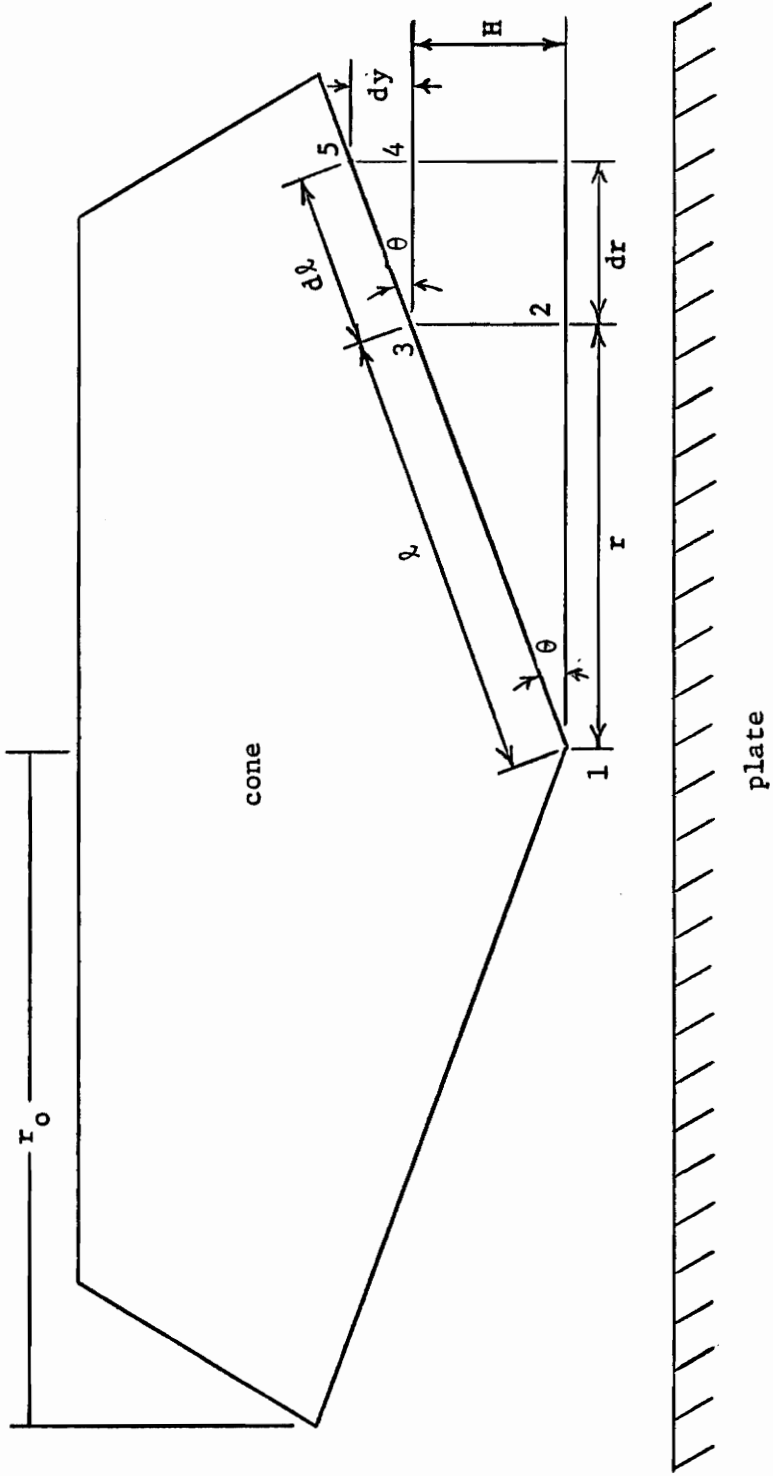


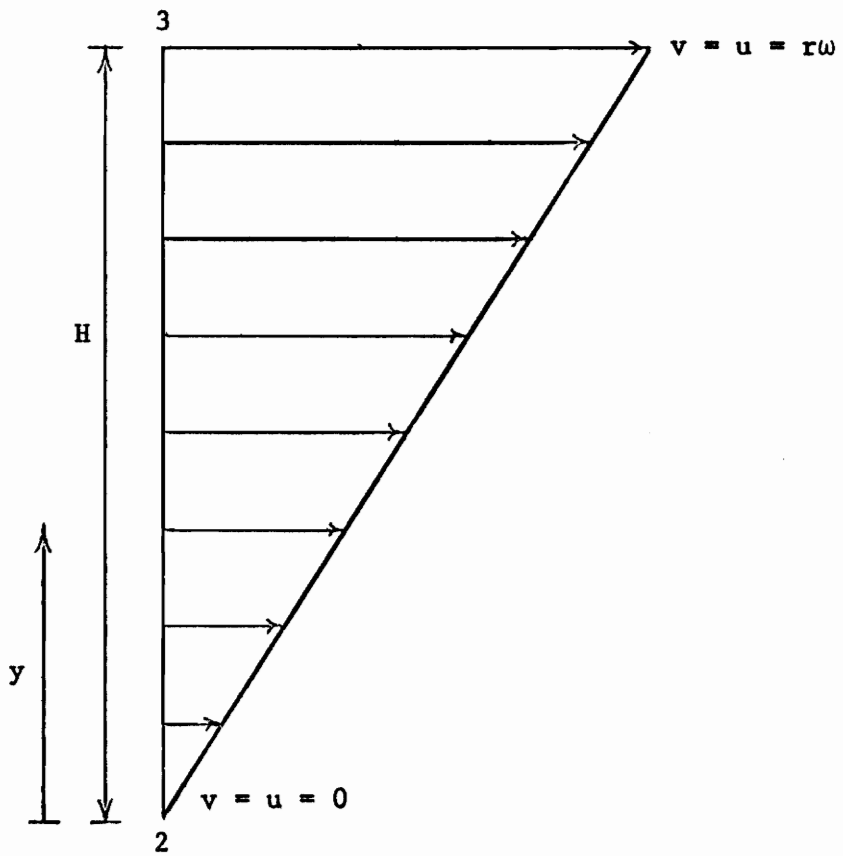
Figure 7. Hysteresis Loops.



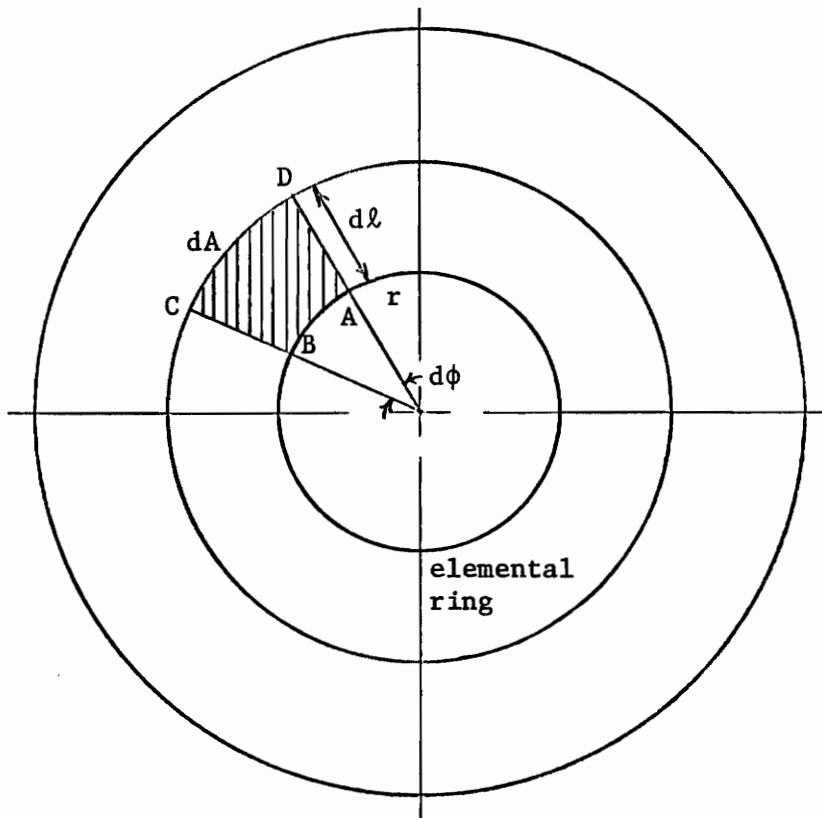
Power Law Equation with a Yield Stress.



Cone Configuration.



Velocity Distribution Between the Cone and Plate.



Bottom View of the Cone.

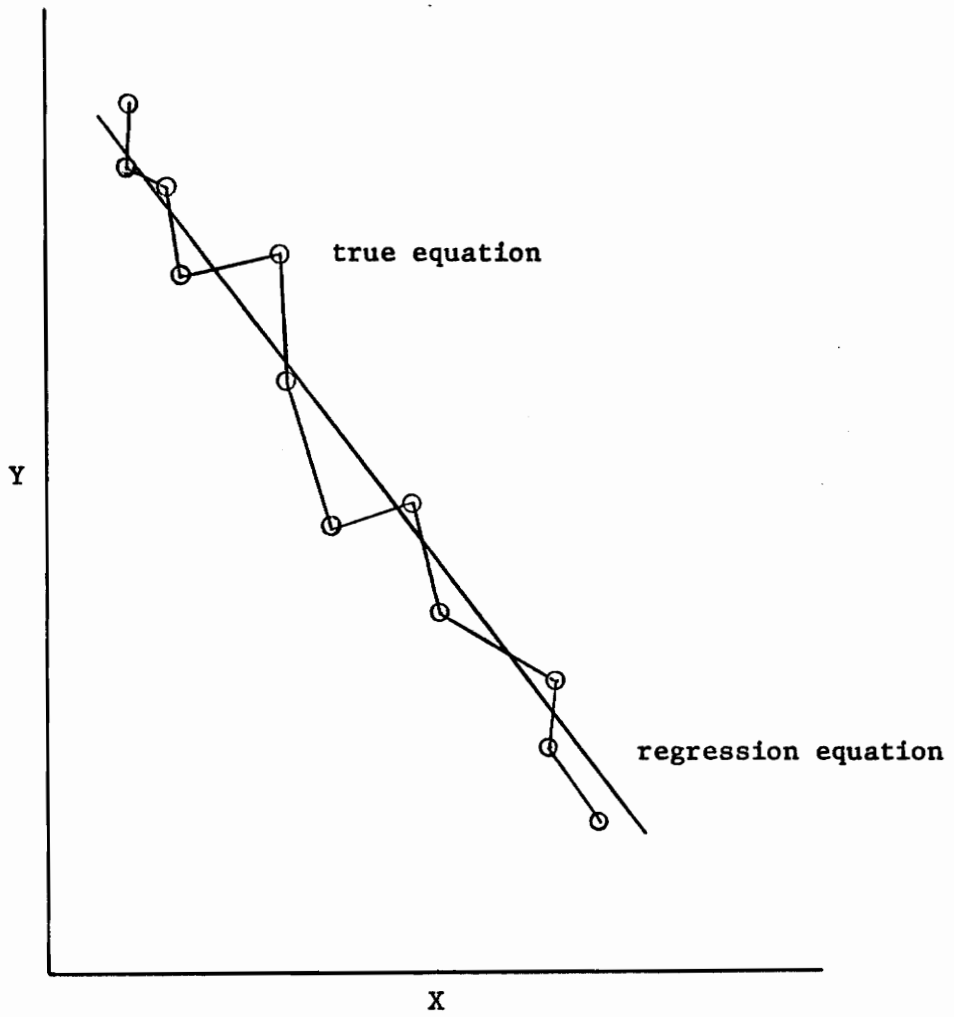


Figure 12. A True Equation and a Regression Equation

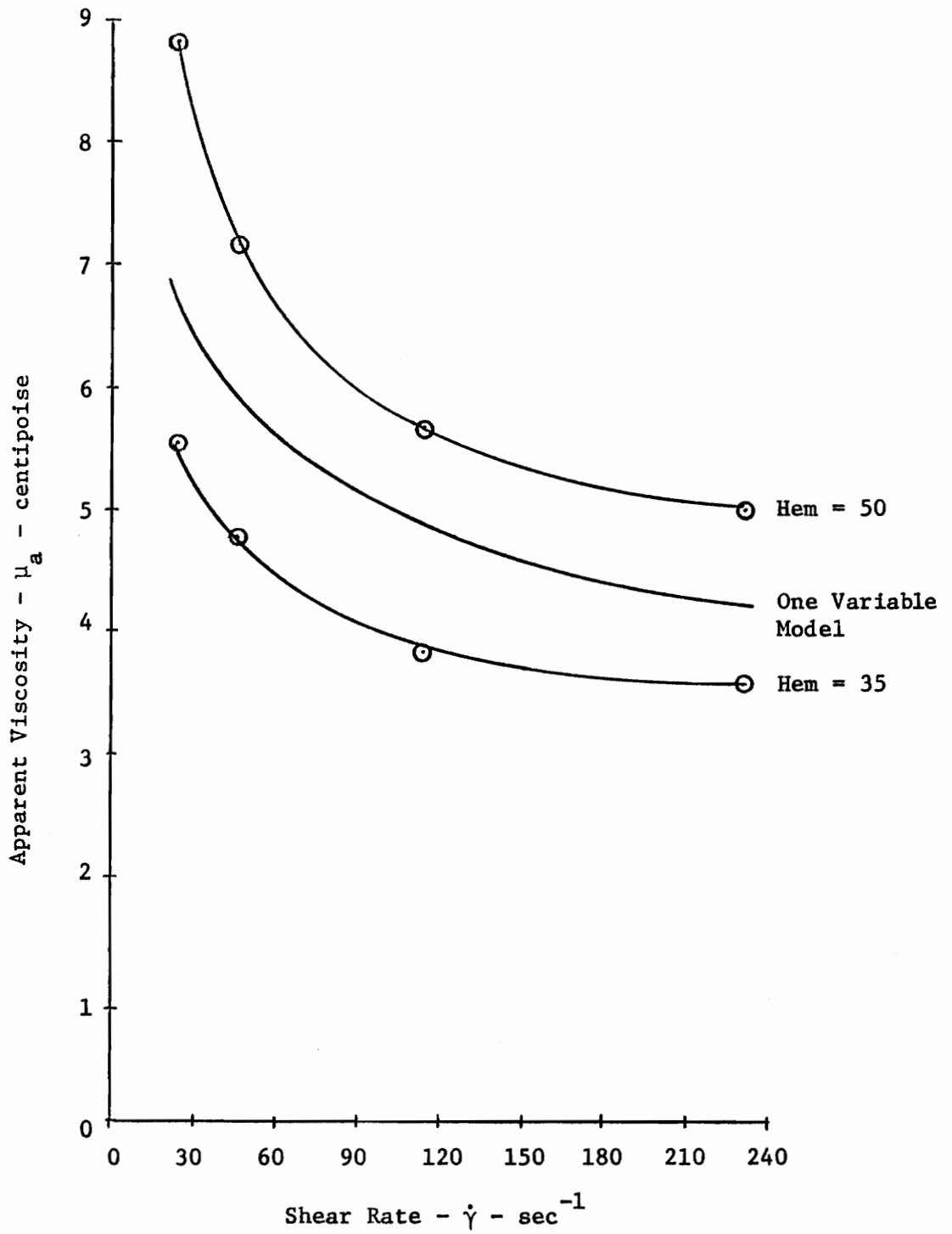


Figure 13. The One Variable Model and Two Experimental Curves.

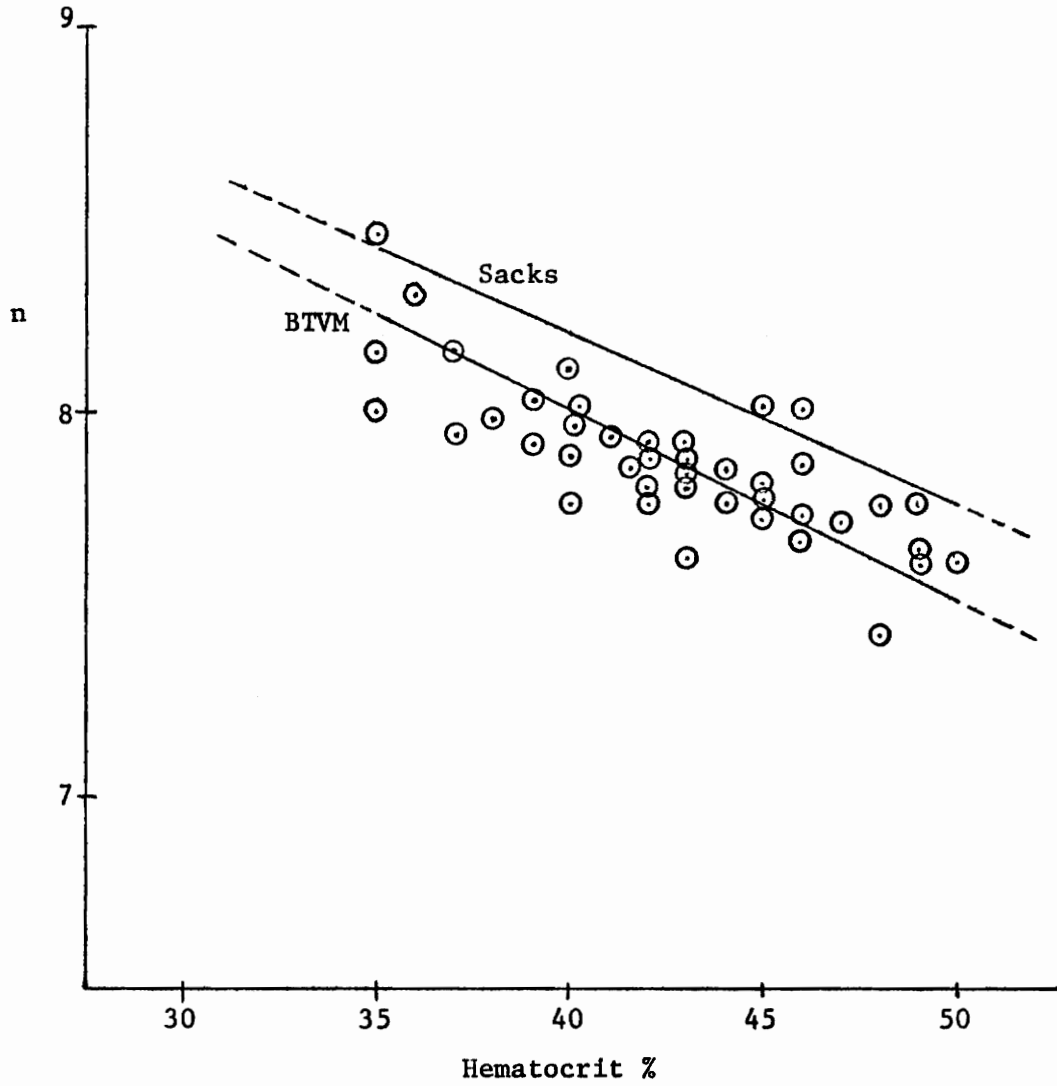


Figure 14. n vs. Hematocrit for the BTVM and Sacks.

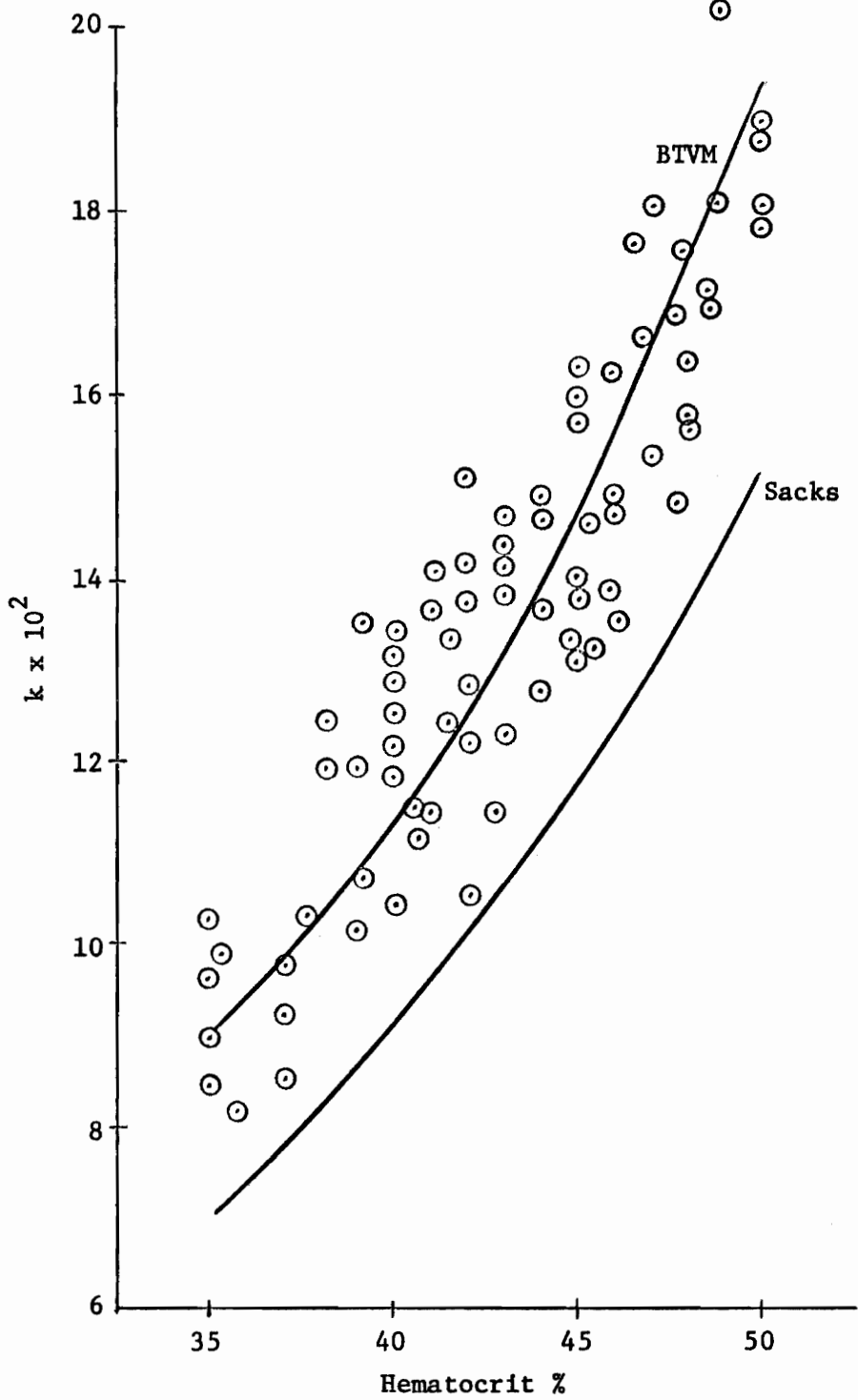


Figure 15. Comparison of k vs. Hematocrit for the BTVM and Sacks.

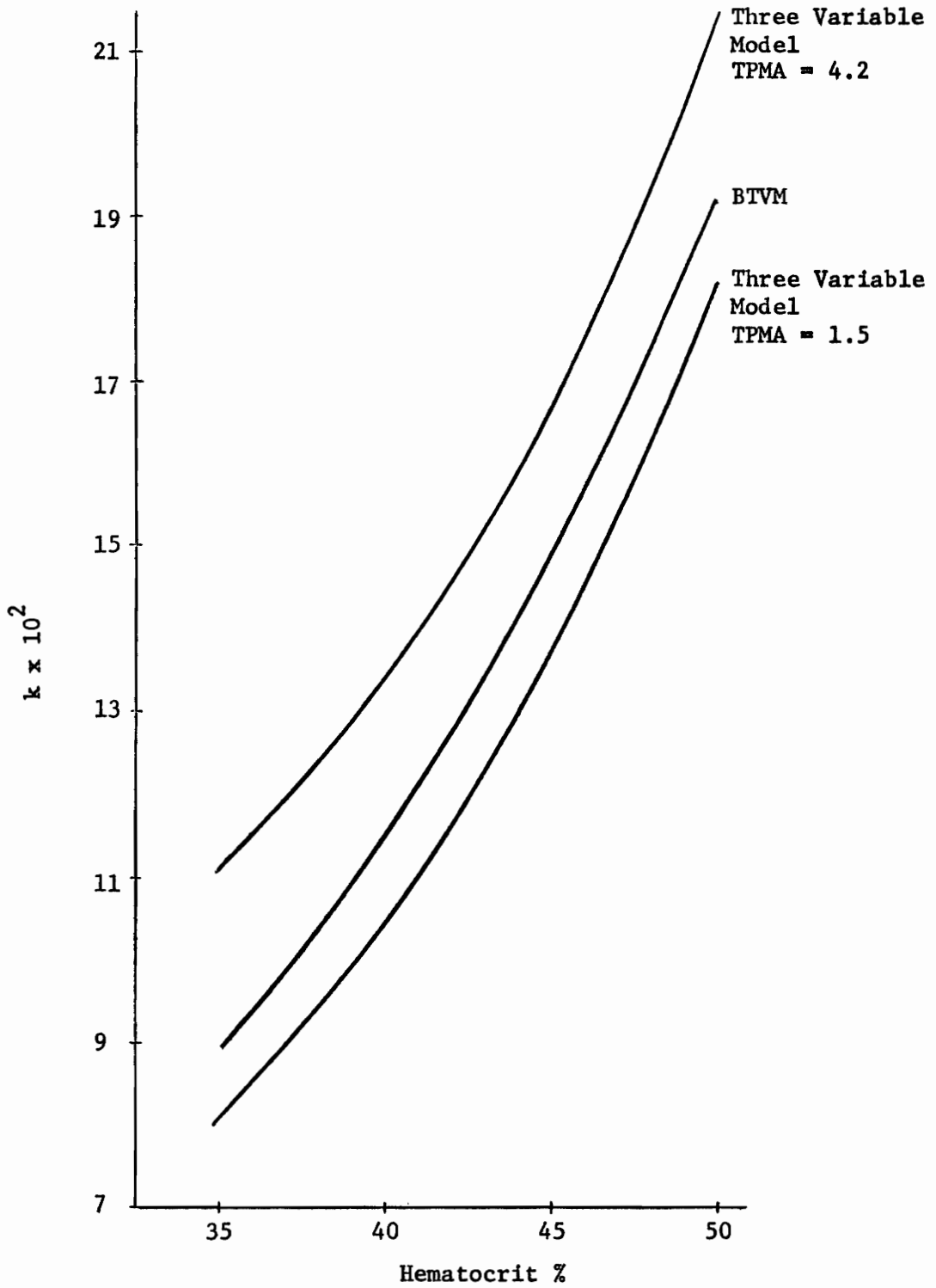


Figure 16. Comparison of k vs. Hematocrit for the BTVM and the Best Three Variable Model.

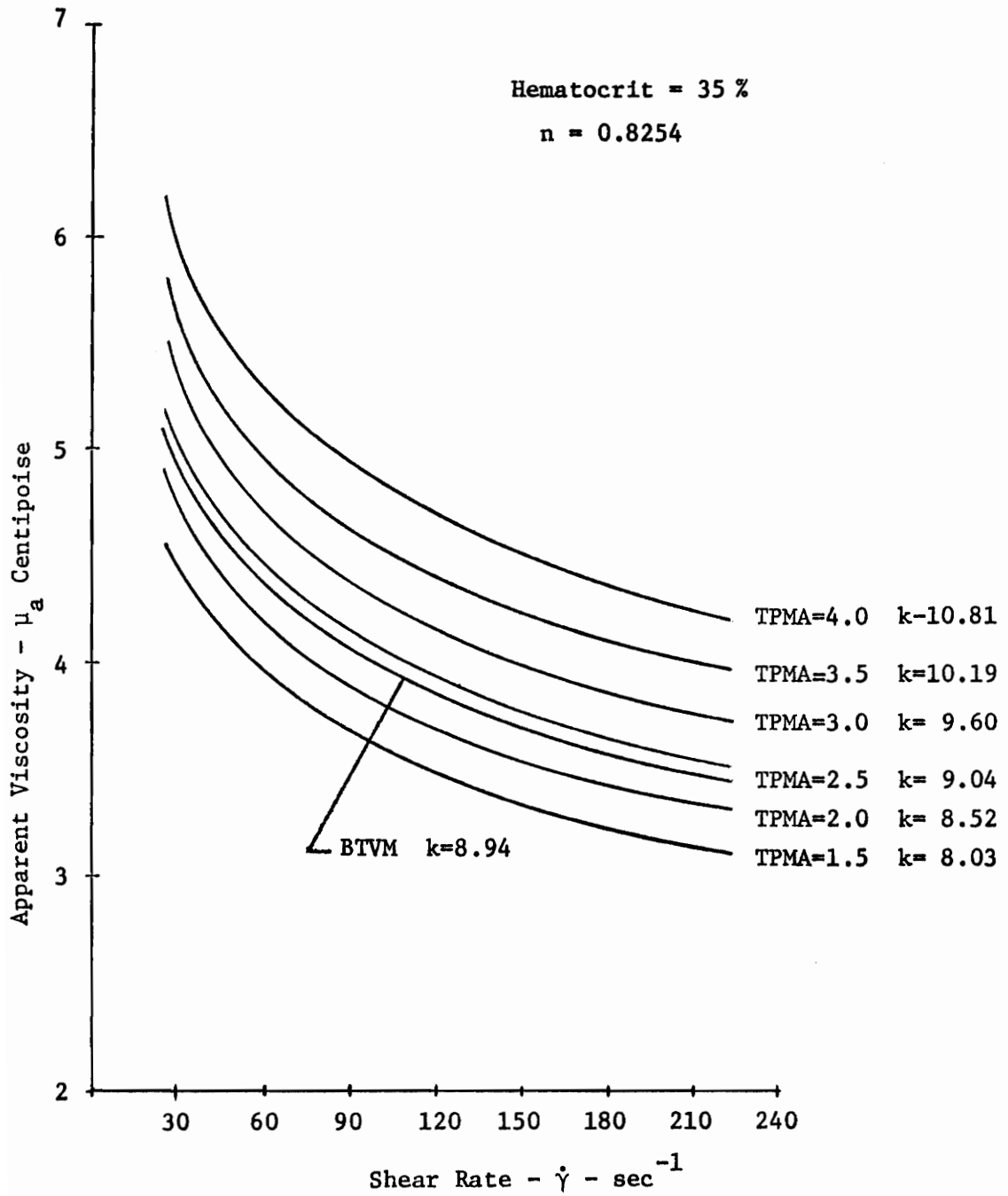


Figure 17. The Best Two and Three Variable Models at a Hematocrit Level of 35% (TPMA Expressed in gm/100 ml.)

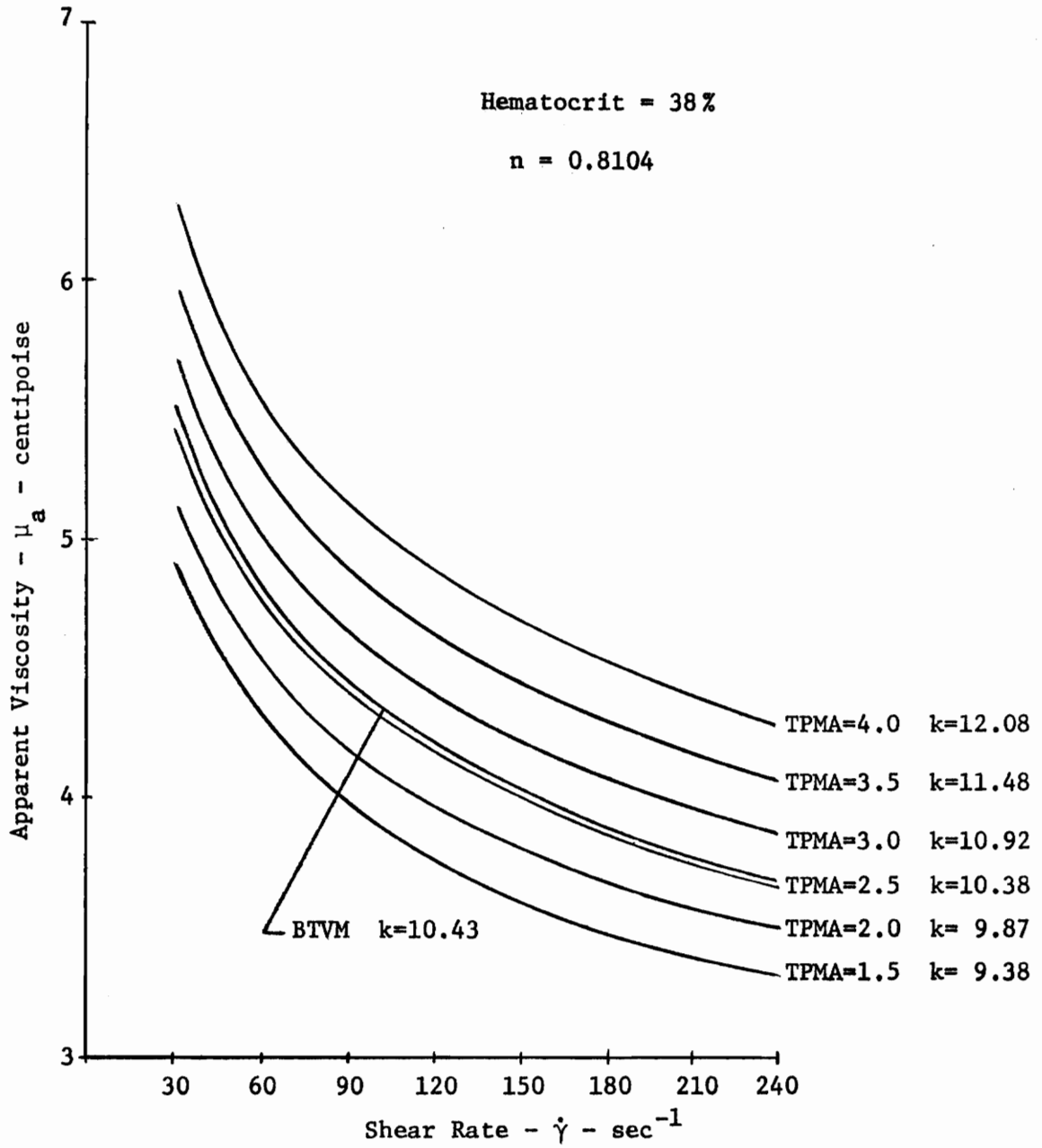


Figure 18. The Best Two and Three Variable Models at a Hematocrit Level of 38% (TPMA Expressed in gm./100 ml.)

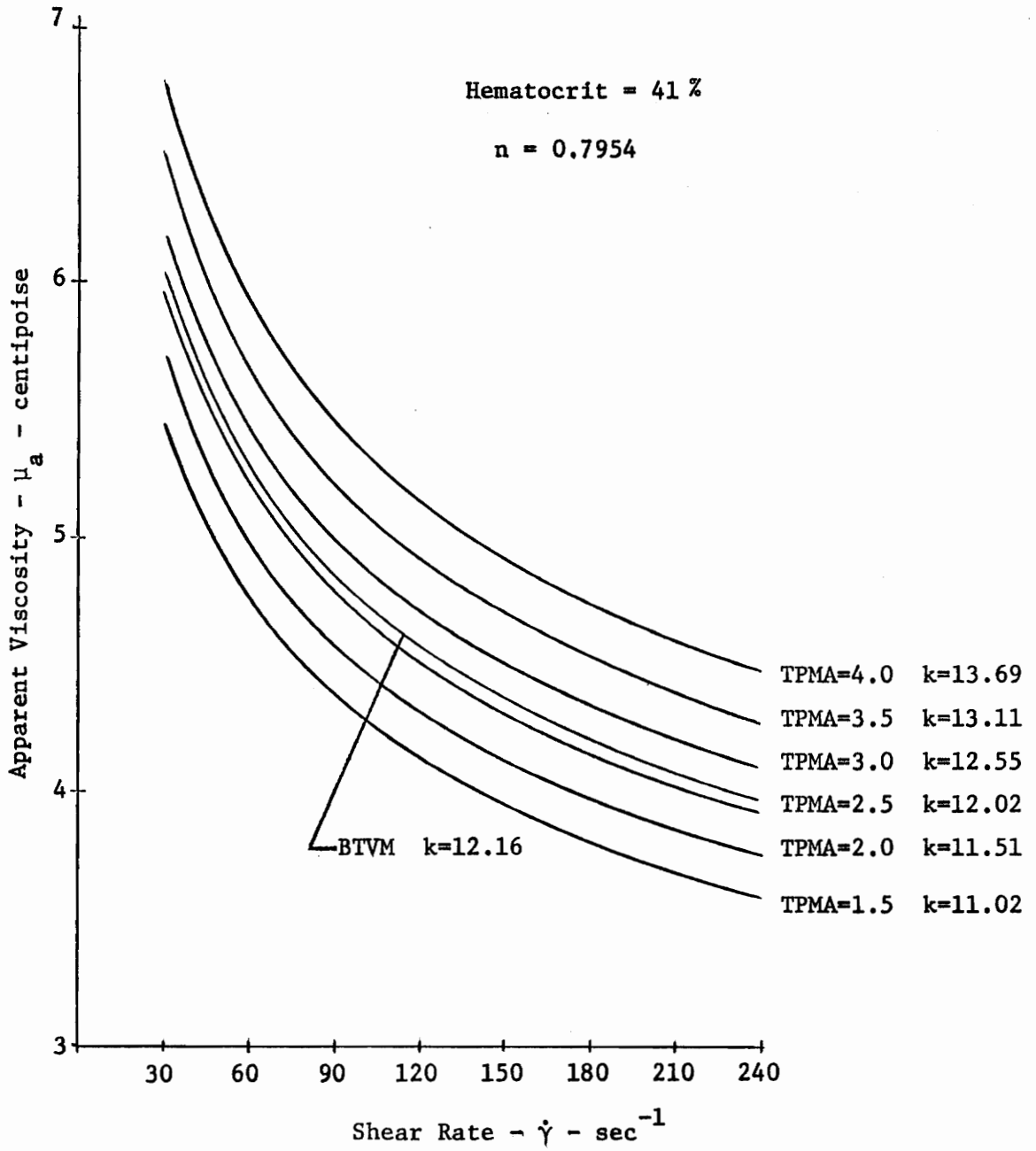


Figure 19. The Best Two and Three Variable Models at a Hematocrit Level of 41% (TPMA Expressed in gm.100 ml.).

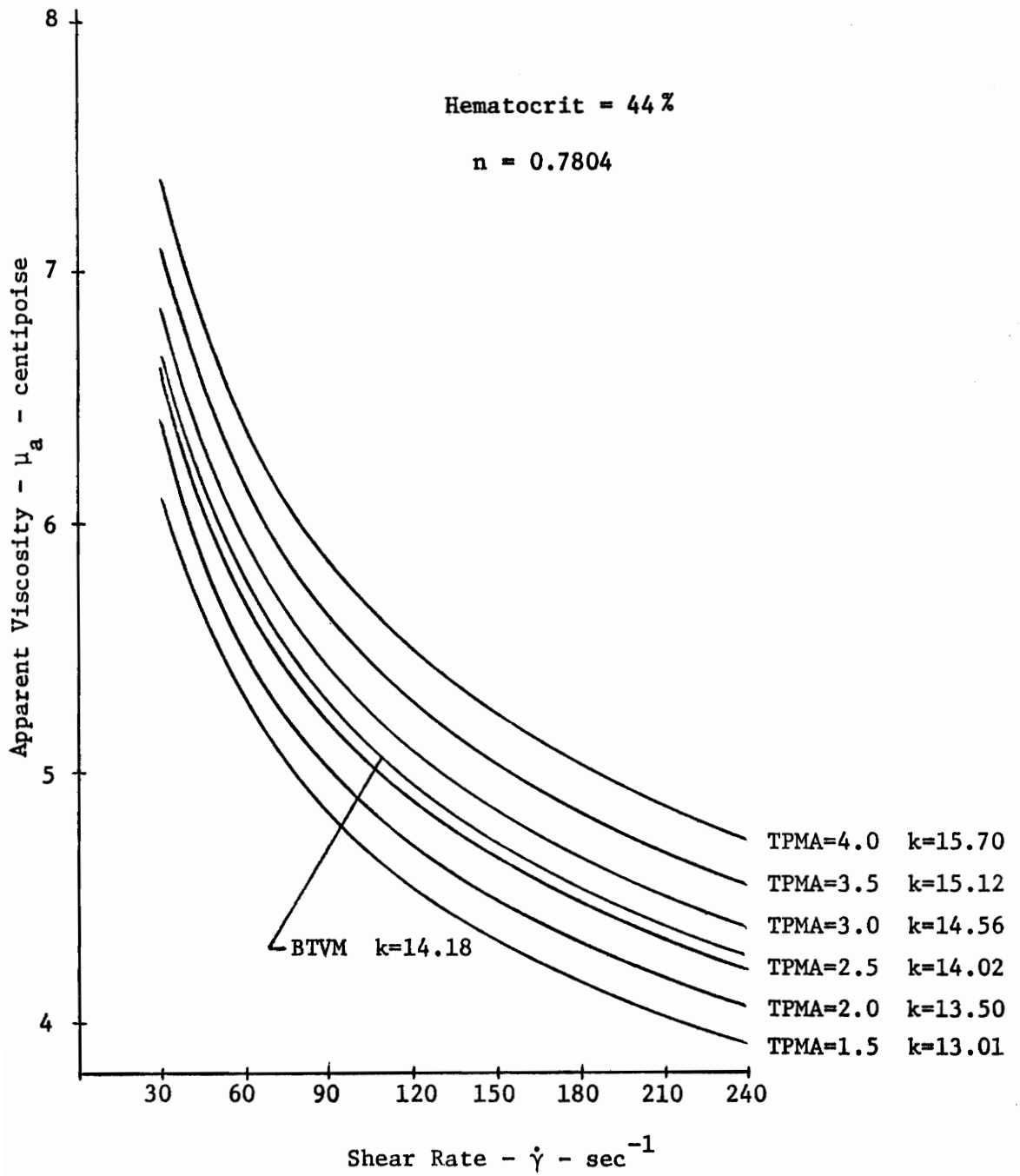


Figure 20. The Best Two and Three Variable Models at a Hematocrit Level of 44%. (TPMA Expressed in gm./100 ml.).

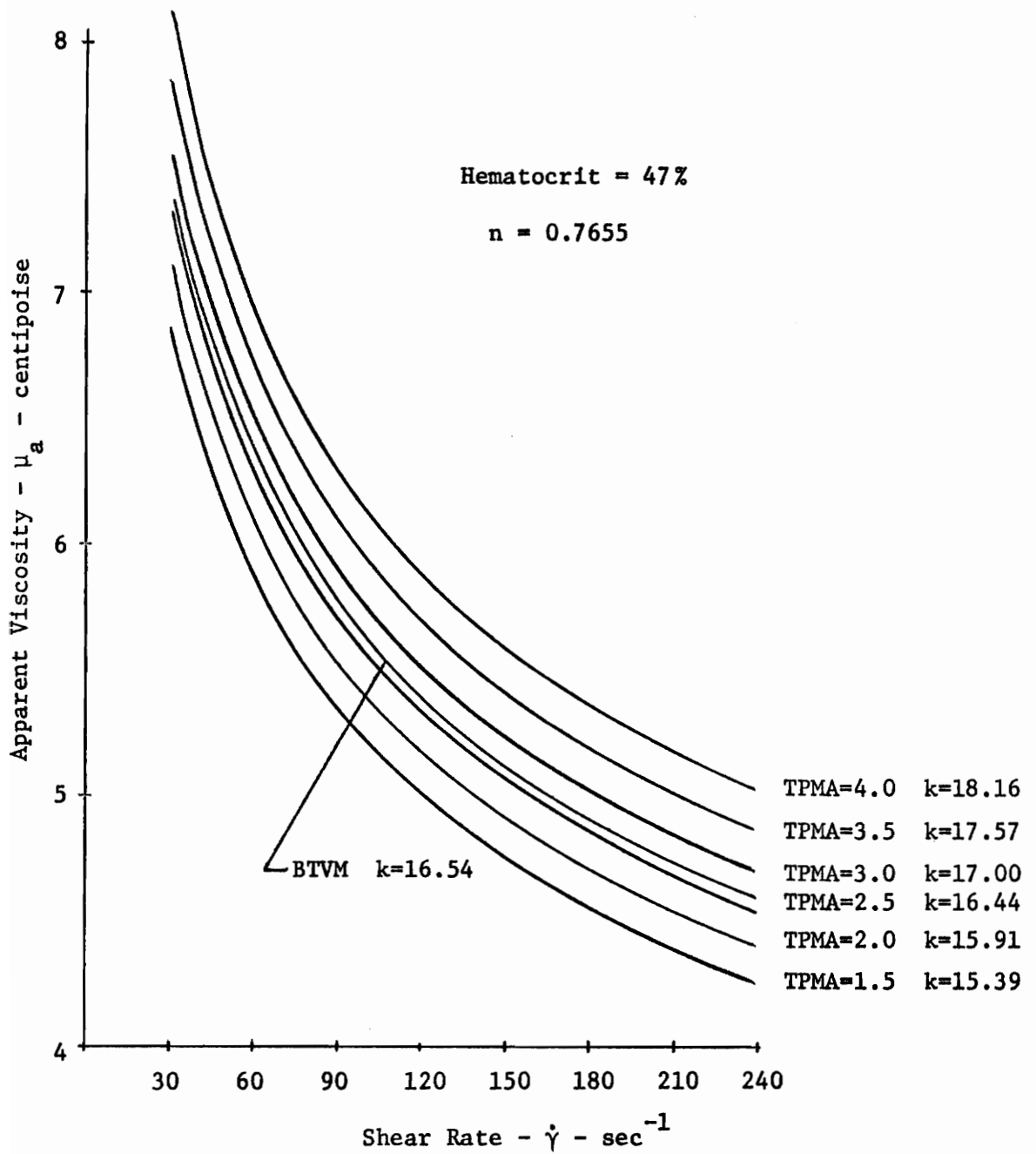


Figure 21. The Best Two and Three Variable Models at a Hematocrit Level of 47% (TPMA Expressed in gm./100 ml.).

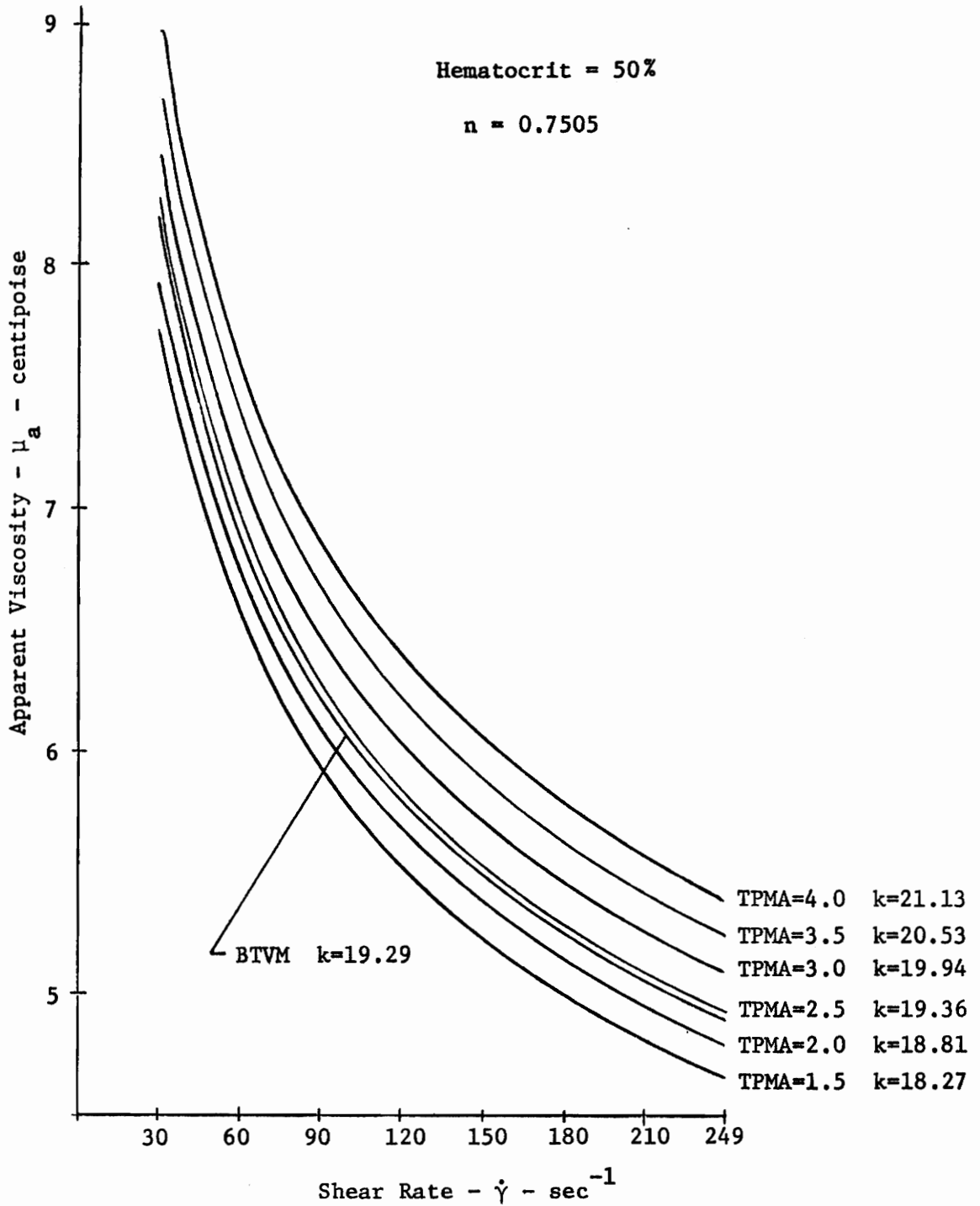


Figure 22. The Best Two and Three Variable Models at a Hematocrit Level of 50% (TPMA Expressed in gm./100 ml.).

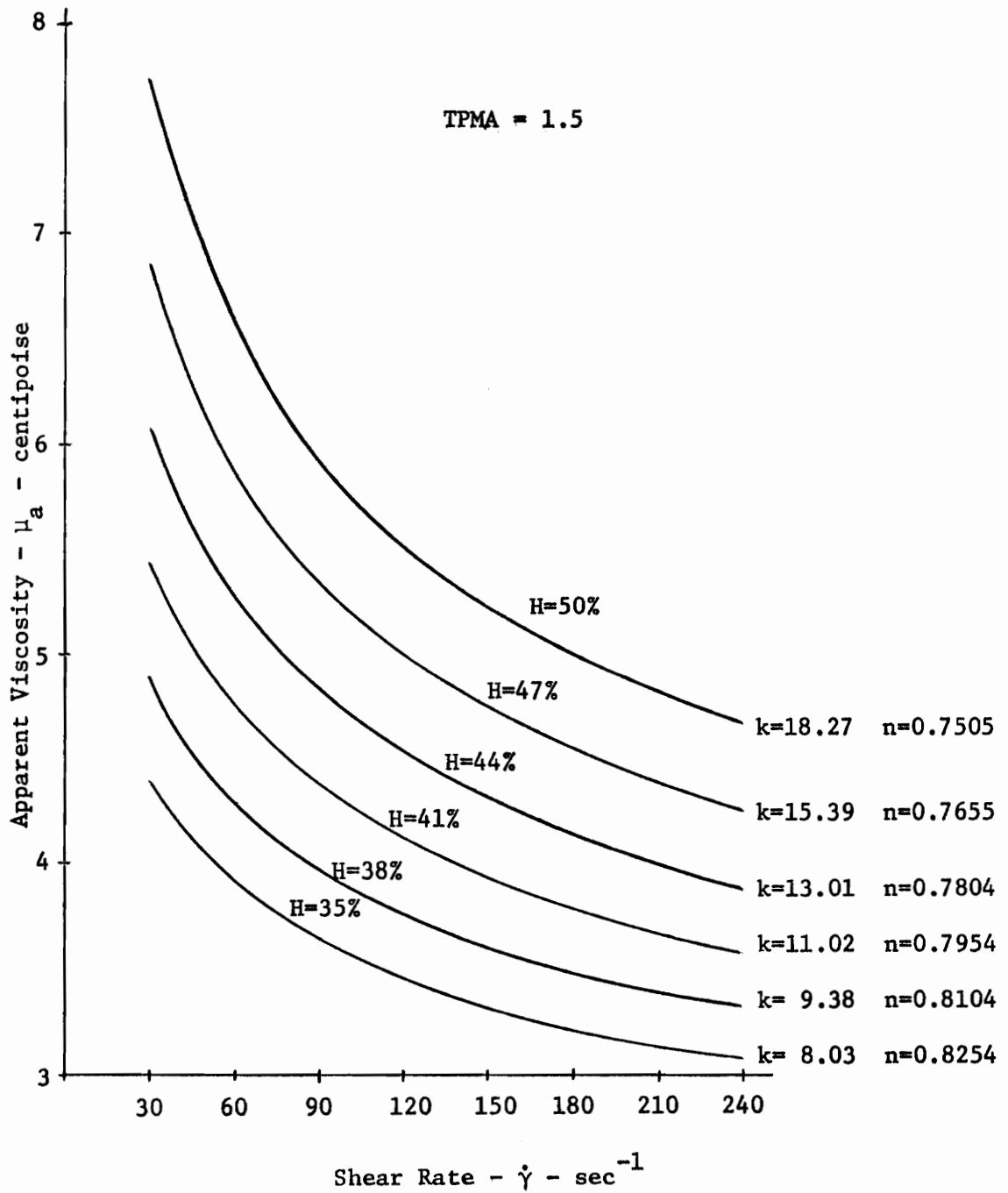


Figure 23. The Best Three Variable Model at a TPMA Level of 1.5 gm/100 ml.

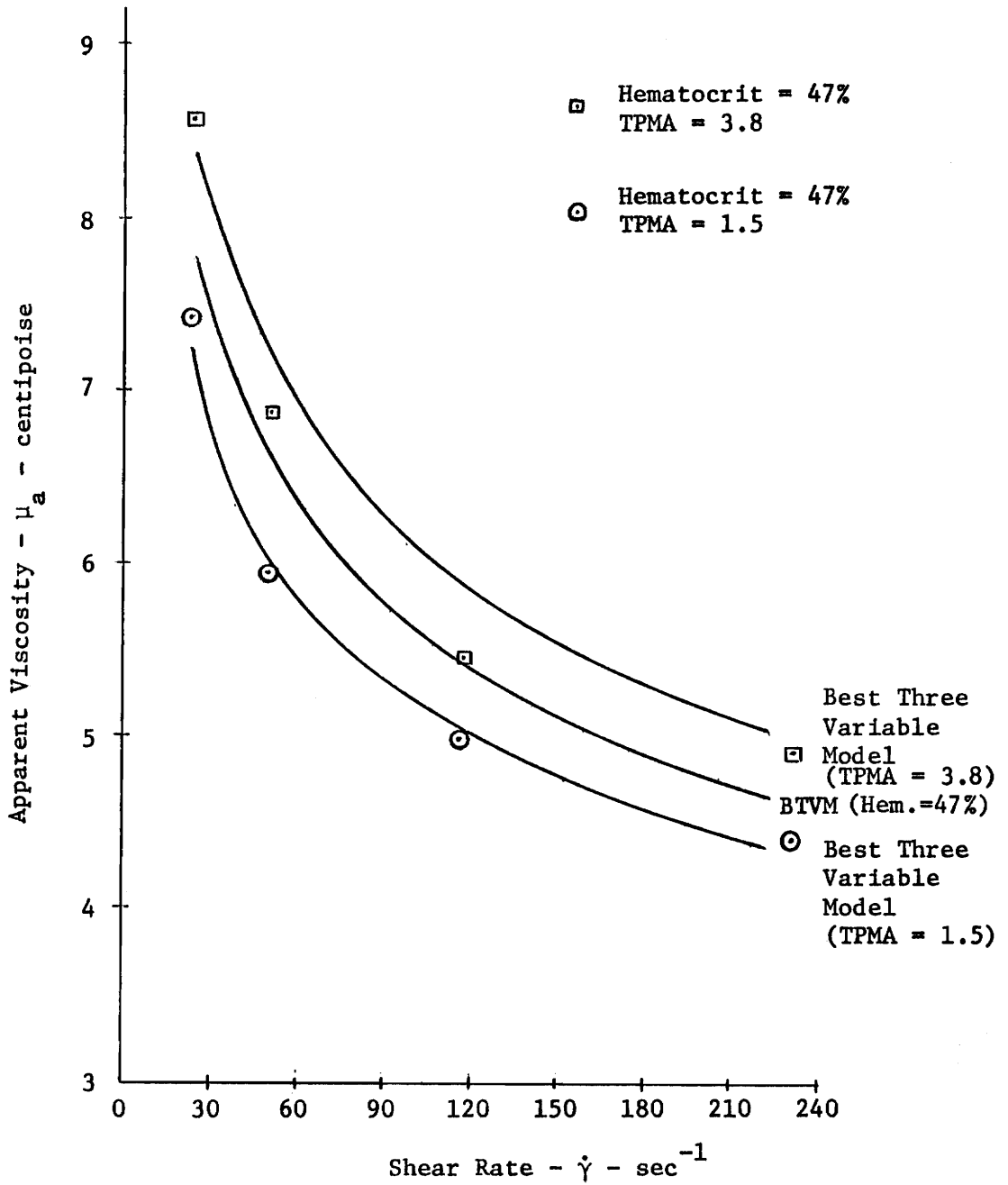


Figure 24. The BTVM and Two Curves of the Best Three Variable along with some experimental data points (TPMA Expressed in gm/100 ml.).

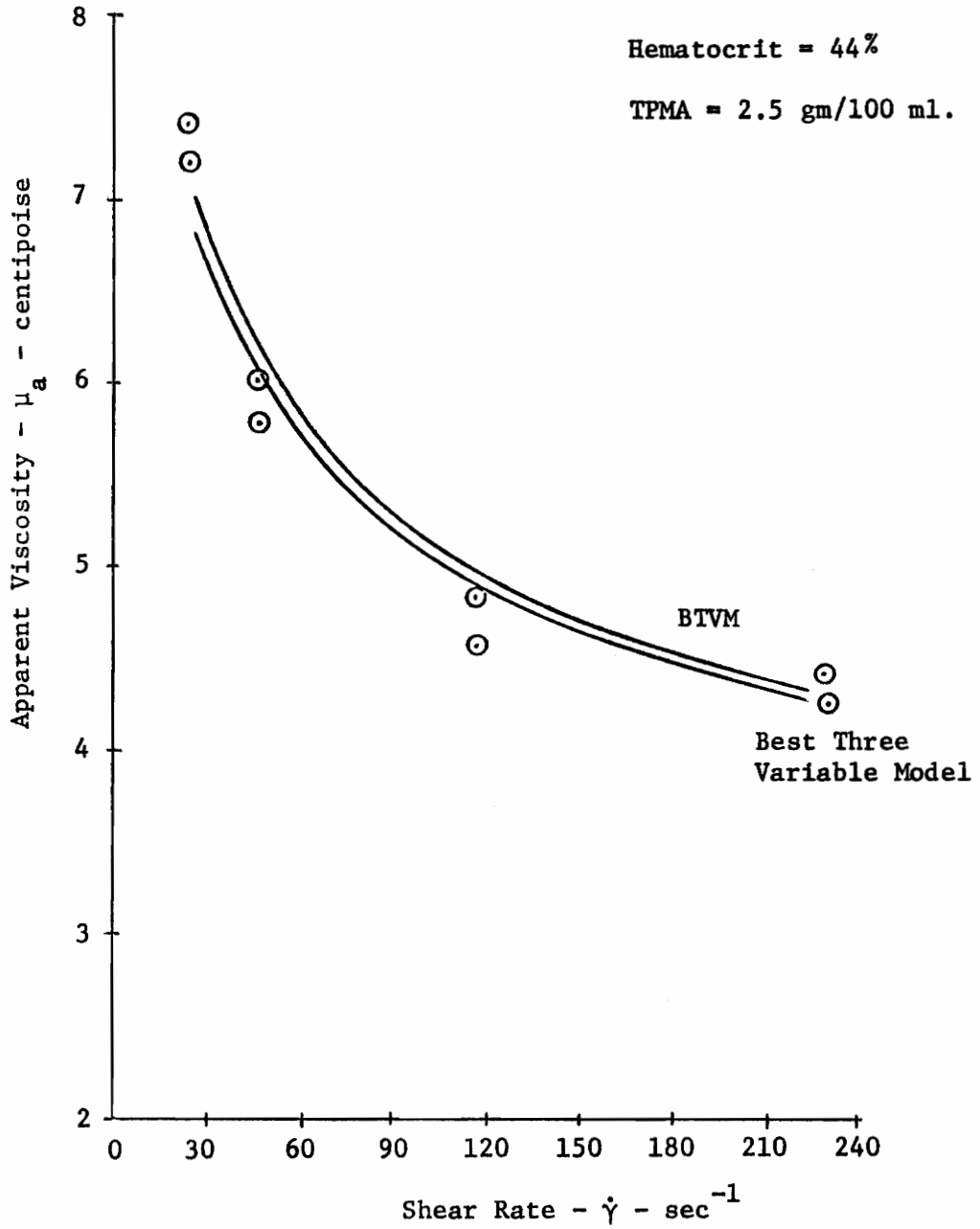


Figure 25. The BTVM and the Best Three Variable Model at an intermediate value of TPMA.

TABLES

	Sacks	Best Two Variable Model
C_1	0.0105	0.0148
C_2	0.0054	0.0512
C_3	0.0045	0.00499

Table I. Values of C_1 , C_2 , and C_3 for Sacks' Model and the Best Two Variable Model.

Best Two Variable Model

$$k = C_1 e^{[C_2][\text{Hematocrit}]}$$

$$C_1 = 0.0148$$

$$C_2 = 0.0512$$

$$n = 1.0 - [C_3][\text{Hematocrit}]$$

$$C_3 = 0.00499$$

Best Three Variable Model

$$k = C_1 e^{[C_2][\text{Hematocrit}] \left[C_4 \left[\frac{\text{TPMA}}{\text{Hematocrit}^2} \right] \right]}$$

$$C_1 = 0.00797$$

$$C_2 = 0.0608$$

$$C_4 = 145.85$$

$$n = 1.0 - [C_3][\text{Hematocrit}]$$

$$C_3 = 0.00499$$

Table II. Comparison of the Best Two and Three Variable Models

$$X = e^{C_4 \left[\frac{TPMA}{\text{Hematocrit}^2} \right]}$$

$$C_4 = 145,85$$

TPMA = 1.5 gm/100 ml

Hematocrit	X
30%	1.27
35%	1.19
40%	1.14
45%	1.11
50%	1.09

TPMA = 4.2 gm/100 ml

Hematocrit	X
30%	1.97
35%	1.64
40%	1.46
45%	1.35
50%	1.27

Table III. Some Values of the Additional Term in the Best Three Variable Model.

APPENDIX A

On Blood

Whole blood consists of red blood cells (erythrocytes), white blood cells (leukocytes), and platelets, collectively referred to as hematocytes, suspended in a fluid medium called plasma.

Red blood cells comprise over 99% of the hematocytes. The percentage by volume of the erythrocytes in the bloodstream is called the hematocrit of the fluid. For males this figure is around 40 to 50%, while females exhibit an average of 35 to 45%. The primary function of the red blood cells is to transport oxygen to living cells.

The other hematocytes aid in the prevention and control of disease (leukocytes) and in the clotting process (platelets).

Plasma, the supporting medium for the hematocytes, is a saline solution composed of proteins, electrolytes, dissolved nutrients, emulsified fats, dissolved gases, and various hormones and enzymes.

The addition of an anticoagulant to whole blood enables one to separate out the hematocytes by centrifugation, leaving behind the plasma. Centrifugation of coagulated blood allows one to separate out the fibrinogen-hematocyte complex, formed by the clotting process, leaving behind what is known as serum, i.e., serum is plasma with the protein fibrinogen removed.

For more details on blood, see appendix B in Schneck [27] or reference [72].

APPENDIX B

Non-Newtonian Fluids and Constitutive Equations

A. Introduction

Figure 1 shows a thin layer of fluid between two plates, one stationary and the other moving at a constant velocity, u_0 . If the fluid is viscous, a velocity profile will develop as indicated on the diagram, and a force, F , will be required to maintain u_0 constant. This force, F , will be balanced by internal shear stresses in the fluid. When the flow is laminar, the shear stress, τ , of a Newtonian fluid is linearly proportional to the velocity gradient. That is, the constitutive equation for such a fluid may be written as:

$$\tau = \mu \dot{\gamma} \text{ dynes/cm}^2 \quad (\text{B.1})$$

where

τ = the shear stress,

$\dot{\gamma} = \frac{du}{dy}$ = the shear rate, and

μ = the constant of proportionality which is defined as the Newtonian viscosity.

The Newtonian viscosity is independent of both time and shear rate, but it does vary with temperature and pressure. The plot of equation (B.1) is shown in figure 2. There are a large number of fluids for which equation (B.1) does not hold. These are termed collectively as being "non-Newtonian." Basically, there are three types of non-Newtonian fluids: time-independent, time-dependent, and

viscoelastic. The information that follows was primarily obtained from references [68] and [70].

B. Time-independent Fluids

The time-independent non-Newtonian fluids fall into three distinct groups as shown in figure 2.

Bingham plastic fluids exhibit a yield stress. That is, a minimum amount of force is necessary to initiate flow. At stresses above τ_y the fluid becomes Newtonian, i.e., its viscosity is independent of the shear rate. For a Bingham plastic, the constitutive equation may be expressed by:

$$\left. \begin{aligned} \tau - \tau_y &= \mu_p \dot{\gamma}, \quad \tau > \tau_y \\ \tau &= 0, \quad \tau < \tau_y \end{aligned} \right\} \text{ dynes/cm}^2 \quad (\text{B.2})$$

where

$\mu_p \equiv$ the Bingham plastic viscosity.

Generally, the equation used to describe a pseudoplastic fluid is a power law of the form

$$\tau = k \dot{\gamma}^n \quad \text{dynes/cm}^2 \quad (\text{B.3})$$

where

k = the consistency index, and

n = the non-Newtonian index having a value less than unity.

The parameters k and n are constant for a fluid of constant chemical composition.

For a pseudoplastic fluid, it is convenient to define an apparent viscosity, μ_a , as the viscosity the fluid appears to exhibit when the shear rate is kept constant. Thus, we write:

$$\mu_a = \tau / \dot{\gamma} \quad \text{poise.} \quad (\text{B.4})$$

Substitution of equation (B.4) into (B.3) yields:

$$\mu_a = k \dot{\gamma}^{n-1}, \quad n < 1, \quad \text{poise.} \quad (\text{B.5})$$

Equation (B.5) predicts that the apparent viscosity will decrease as the rate of shear increases. Real pseudoplastic fluids show exactly this behavior except that at high shear rates the apparent viscosity approaches an asymptotic value (see figure 3), which is not zero as equation (B.5) suggests. This fact does not completely invalidate the equation, however, because over the range of shear rates that are encountered in the physiologic system, the deviations from figure 3 are negligible. At high shear rates a power law type fluid exhibits nearly Newtonian behavior.

Pseudoplastic behavior is typical of suspensions of asymmetric particles. These particles have random orientations and interact a great deal at low shear rates, causing high values of apparent viscosity. As the shear rate increases, however, the particles have a tendency to line-up and become more uniformly oriented, decreasing interactions and therefore decreasing the apparent viscosity. When

all the particles have lined up, no further decrease in the apparent viscosity is possible and μ_a would then remain constant.

A time-independent fluid which shows an increasing apparent viscosity with increasing shear rate is called dilatant. Equation (B.5) also describes the behavior of dilatant fluids, except in this case the non-Newtonian index, n , is greater than unity. This behavior is typical of suspensions of solids where the solid content is so high that it forms large masses throughout the suspension. When a shearing stress is applied, these solid chunks begin to break up, resulting in more interactions which increase the apparent viscosity. Eventually, as the shear rate increases, all of the solid masses are broken up and the fluid becomes essentially homogeneous.

C. Time-dependent Fluids

There are many real fluids for which the apparent viscosity is a function of time as well as of shear rate. These fluids are divided into two categories: thixotropic and rheopectic.

A thixotropic fluid has a consistency which depends on the time over which the shear rate is applied as well as the magnitude of the shear rate itself. This behavior is due to the existence of an internal structure which breaks down as the fluid is sheared and builds up as the fluid rests. The longer the shearing force is applied, the more the internal structure breaks down. Conversely, the longer the fluid is at rest, the more its internal structure rebuilds. It is interesting to note, however, that the internal

structure breaks down more rapidly at higher rates of shear (see figure 4), whereas the buildup occurs at a constant rate. Thus, when a thixotropic fluid is sheared without allowing the internal structure to completely rebuild itself, the fluid exhibits the behavior shown in figure 5. Notice that as the fluid is left to rest for increasing periods of time, the internal structure builds up and the fluid exhibits higher and higher shear stresses. However, at high shear rates the structure breaks down completely and all curves approach curve 1 (figure 5).

When a thixotropic fluid is sheared at a constant increasing rate and then at a constant decreasing rate for a certain period of time, a hysteresis loop on the shear stress-shear rate plot results (figure 6). The fluid always has a smaller viscosity during the decreasing phase, since some of the internal structure is broken down during the increasing phase (see figure 7).

The other type of time-dependent non-Newtonian fluid is called rheopectic. This fluid exhibits a gradual increase in apparent viscosity as the shear rate increases. Such behavior exists only at small shear rates and disappears as the shear rate increases. It is thought (reference [68]) that the small shear rates aid in the formation of an internal structure, but then higher shear rates break down this structure.

D. Viscoelastic Fluids

A viscoelastic fluid exhibits both elastic and viscous properties. The most common viscoelastic fluids, such as tar or asphalt,

are very viscous. The essential difference between viscoelastic and other non-Newtonian fluids is that the rheological equation for the former contains time derivatives of the shear stress and shear rate:

$$\sum_{n=0}^N a_n D^n \tau = \sum_{m=0}^M \beta_m D^m \dot{\gamma}, \quad (\text{B.6})$$

where D is the differential operator, d/dt . See references [68] and [69] for more details.

E. Properties of a Constitutive Equation

A constitutive equation is an equation which describes the behavior of a material in terms of its properties. Since a stress-strain rate relationship describes the mechanical properties of a fluid, it is a constitutive equation. Other constitutive equations may describe heat transfer properties, electrical resistance, mass transfer, etc. Equations (B.1), (B.2), (B.3), and (B.6) describe the mechanical properties of various non-Newtonian fluids and thus are constitutive equations.

The first requirement for the objectivity of a constitutive equation is that it must be invariant under a coordinate transformation. That is, the mechanical behavior must be the same irrespective of the coordinate system chosen. The second requirement is that the constitutive equation should not violate the second law of thermodynamics. The details of these requirements may be found in chapter four of reference [70].

All of the equations that have been mentioned in this appendix include the variables τ and γ , each of which may be written as a tensor. Let

τ_{ij} = the stress tensor, and

$\dot{\gamma}_{ij}$ = the strain rate tensor.

Equations (B.1), (B.2), and (B.3) now become:

$$\tau_{ij} = \mu \dot{\gamma}_{ij}, \quad (\text{B.7})$$

$$\tau_{ij} - \tau_y = \mu_p \dot{\gamma}_{ij}, \text{ and} \quad (\text{B.8})$$

$$\tau_{ij} = k \dot{\gamma}_{ij}^n, \quad (\text{B.9})$$

where μ , τ_y , μ_p , k , and n are constant for a fluid of constant chemical composition.

Now, one property of a tensor is that it is always invariant under a coordinate transformation [71]. Therefore, if a constitutive equation can be written in tensor notation, it will also be invariant under the aforementioned transformation. It thus follows that since equations (B.7), (B.8), and (B.9) are tensor equations, they are invariant under a coordinate transformation. These equations also do not violate the second law of thermodynamics (see reference [70], chapter 4) and, from the mathematical point of view, are valid forms for constitutive equations.

Appendix C

Wells-Brookfield Theory

The Wells-Brookfield Micro Cone and Plate Viscometer is well suited for analyzing non-Newtonian fluids which exhibit different values of viscosity for different shear rates. When measuring the viscosity of a fluid which behaves in this manner, it is of the utmost importance to apply a constant shear rate to the fluid in order to be able to interpret the value of viscosity that is recorded. The Wells-Brookfield cone-and-plate viscometer produces an essentially constant shear rate in the fluid by utilizing a very obtuse (θ less than 4°) cone and plate (see figure 9), separated a precise distance from one another. The sample fluid is placed within this spacing.

The theory of the constant shear rate involves two assumptions which are valid for the geometry shown in figure 9. Observing triangle 1-2-3, it is seen that:

$$\tan \theta = H/r. \quad (C.1)$$

From trigonometry, the tangent of an angle is equal to the sine of the angle divided by the cosine of the angle. Therefore,

$$\sin\theta/\cos\theta = H/r. \quad (C.2)$$

Assumption number one is that if θ is very small, $\cos\theta \approx 1.0$.

Thus, equation (C.2) may be written:

$$\sin \theta = H/r,$$

or

$$H = r \sin \theta, \quad (C.3)$$

Now,

$$v = r\omega \quad (C.4)$$

where

v = the velocity of a point on the surface of the cone located a distance r from the axis, and
 ω = the angular velocity of the cone.

The angular velocity is defined as:

$$\omega = 2\pi N/60 \quad \text{rad/sec} \quad (C.5)$$

where

N = the revolutions per minute of the cone.

Equations (C.4) and (C.5) yield

$$v = 2\pi r N/60. \quad (C.6)$$

Assumption number two is that a fluid particle at point 2 (see figures 9 and 10) is at rest on the plate and the particle at point 3 is at rest relative to the cone, i.e., it is moving at the same velocity as the cone at that point. Therefore, a gradient of velocity exists, and, since H is small, it is assumed that there is a linear velocity profile from 2 to 3. The shear rate, $\dot{\gamma}$, is defined as:

$$\dot{\gamma} = \frac{du}{dy} \text{ sec}^{-1} \quad (\text{C.7})$$

where

u = the velocity of the fluid.

At the cone, u equals v so that from equation (C.4):

$$u = r\omega . \quad (\text{C.8})$$

Transforming equation (C.8) into a differential yields
(assuming ω is constant):

$$du = \omega dr . \quad (\text{C.9})$$

Substituting equation (C.5) into equation (C.9) yields:

$$du = \frac{2\pi N}{60} dr \quad (\text{C.10})$$

and transforming equation (C.3) into a differential produces (with θ constant):

$$dr = dH/\sin \theta . \quad (\text{C.11})$$

In accordance with the relation (C.11), equation (C.10) becomes:

$$du = \frac{2\pi NdH}{60 \sin \theta} . \quad (\text{C.12})$$

It can be seen from figures 9 and 10 that a differential y equals a differential H or $dy = dH$. Thus, equation (C.7) becomes, using the above relations:

$$\dot{\gamma} = \frac{du}{dy} = \frac{2\pi N}{60 \sin \theta}$$

or

$$\dot{\gamma} = \frac{2\pi N}{60 \sin \theta} \text{ sec}^{-1} . \quad (\text{C.13})$$

Notice that in equation (C.13) the shear rate is a function only of N. Since N is the revolutions per minute of the cone, by keeping N constant, a constant shear rate will be developed in the fluid.

The derivation of the shear stress begins by observing in triangle 3-4-5 (figure 9) that:

$$d\ell = dr / \cos \theta . \quad (\text{C.14})$$

Now, from figure 11,

$$\overline{AB} = r d\phi . \quad (\text{C.15})$$

Similarly,

$$\begin{aligned} \overline{CD} &= (r + d\ell) d\phi \\ &= r d\phi + d\ell d\phi , \end{aligned} \quad (\text{C.16})$$

where $d\ell d\phi$ may be neglected because it is of a smaller order of magnitude compared to $r d\phi$. From equations (C.15) and (C.16) we arrive at the conclusion that $\overline{AB} \approx \overline{CD}$ and it therefore follows that

$$dA = r d\phi d\ell . \quad (\text{C.17})$$

Substituting $d\ell$ from equation (C.14) into equation (C.17) yields,

$$dA = \frac{r d\phi dr}{\cos \theta} . \quad (\text{C.18})$$

Integration of equation (C.18) gives the area of the elemental ring:

$$A = \int_0^{2\pi} \frac{r dr}{\cos \theta} d\phi = \frac{2\pi r dr}{\cos \theta} , \quad (\text{C.19})$$

where r , dr , and $\cos \theta$ are constants in terms of integration with respect to ϕ . But θ is small, which means that the cosine of θ is approximately equal to one, so equation (C.19) becomes:

$$A = 2\pi r dr . \quad (\text{C.20})$$

Let τ (τ) be the shear stress in the fluid. Then the force on the elemental ring is:

$$\begin{aligned} F &= \tau A \\ &= \tau(2\pi r dr) . \end{aligned} \quad (\text{C.21})$$

The differential torque produced by the force on the elemental ring is defined by

$$\begin{aligned} dT &= r \times F \\ &= 2\pi r^2 \tau dr . \end{aligned} \quad (\text{C.22})$$

Integration of equation (C.22) yields the total torque on the conical surface:

$$\begin{aligned} T &= \int_0^{r_0} 2\pi r^2 \tau dr \\ &= \frac{2}{3} \tau \pi r_0^3 \end{aligned} \quad (\text{C.23})$$

where τ is assumed not to vary with r if the shear rate does not.

Solving equation (C.23) for τ gives:

$$\tau = \frac{3T}{2\pi r_o^3} . \quad (C.24)$$

Observe that equation (C.24) for τ is a function of T , the torque applied to the cone. Thus, by applying a constant torque to the cone, the shear stress in the fluid will also be constant.

Equations (C.13) and (C.24) include several known quantities:

$$\theta \text{ (cone angle)} = 1.565^\circ,$$

$$r_o = 2.409 \text{ cm.}, \text{ and}$$

$$\pi = 3.14159.$$

The torque (T) in equation (C.24) may be expressed as follows:

$$T = B'T^* \quad (C.25)$$

where

B' = a fraction of T^* , and

T^* = the total torque that can be developed
by the viscometer (673.7 dynes-cm.).

Let

$$B = B' \times 10^2 , \quad (C.26)$$

so that B is the direct numerical reading in percent of total torque from the viscometer dial. Then, substituting the values of θ , r_o , π ,

and T^* given above into equations (C.13) and (C.24), we obtain:

$$\dot{\gamma} = 3.88 \text{ N sec}^{-1}, \text{ and} \quad (\text{C.27})$$

$$\tau = 0.2327 \text{ B dynes/cm}^2. \quad (\text{C.28})$$

Finally, the apparent viscosity is defined as:

$$\mu_a = \tau / \dot{\gamma}. \quad (\text{C.29})$$

Substituting equations (C.27) and (C.28) into (C.29) yields:

$$\mu_a = 0.06\text{B/N poise} \quad (\text{C.30})$$

or

$$\mu_a = 6\text{B/N centipoise}. \quad (\text{C.31})$$

APPENDIX D

The R-square Statistic

A. Introduction

The information in this appendix was primarily obtained from reference [66]. Suppose an experiment results in n pairs of observations, X and Y , as shown in figure 12. From this data we wish to develop an equation, $Y(x)$, using the linear least squares method. The actual equation that describes how the data behaves is also plotted in figure 12 and is of the form:

$$Y = \beta_0 + \beta_1 X + \epsilon \quad (\text{D.1})$$

where

Y = the dependent variable,

X = the independent variable,

β_0, β_1 = parameters of the equation, and

ϵ = the increment by which any individual Y
may fall off the regression line.

$\epsilon, \beta_0,$ and β_1 are all unknown, but β_0 and β_1 remain fixed while ϵ changes for each observation. This makes it a difficult parameter to determine. The least squares method uses the data to determine estimates of β_0 and β_1 which results in an equation of the form:

$$\hat{Y} = b_0 + b_1 X \quad (\text{D.2})$$

where

- \hat{Y} = the predicted value of Y ,
 b_0 = the estimate of β_0 , and
 b_1 = the estimate of β_1 .

B. Linear Least Squares Analysis

Given n sets of observations, (X_1, Y_1) , (X_2, Y_2) , ..., (X_n, Y_n) , it is assumed that each data point can be described by:

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i, \quad i = 1, 2, 3, \dots, n. \quad (D.3)$$

In order to have the data fall near the regression line, it is desirable to have ε_i as close to zero as possible. Thus, we first define S as the sum of the squares of the deviations from the regression line:

$$S = \sum_{i=1}^n \varepsilon_i^2, \quad \text{or from (D.3),}$$

$$S = \sum_{i=1}^n (Y_i - \beta_0 - \beta_1 X_i)^2. \quad (D.4)$$

The next step is to choose the estimates b_0 and b_1 such that S will be as small as possible. Since S depends on β_0 and β_1 , a necessary condition for S to be minimum is:

$$\frac{\partial S}{\partial \beta_0} = 0 \quad \text{and} \quad \frac{\partial S}{\partial \beta_1} = 0. \quad (D.5)$$

Differentiation of equation (D.4) with respect to β_0 and β_1 yields, respectively,

$$\frac{\partial S}{\partial \beta_0} = -2 \sum_{i=1}^n (Y_i - \beta_0 - \beta_1 X_i), \text{ and} \quad (\text{D.6})$$

$$\frac{\partial S}{\partial \beta_1} = -2 \sum_{i=1}^n X_i (Y_i - \beta_0 - \beta_1 X_i). \quad (\text{D.7})$$

When equations (D.6) and (D.7) are set equal to zero, S will be minimum and β_0 and β_1 can be replaced by their estimates b_0 and b_1 :

$$\sum_{i=1}^n (Y_i - b_0 - b_1 X_i) = 0, \text{ and} \quad (\text{D.8})$$

$$\sum_{i=1}^n X_i (Y_i - b_0 - b_1 X_i) = 0. \quad (\text{D.9})$$

Recall that the summation of a sum of terms is equal to the sum of the summations providing the summations are convergent. Thus, rearranging terms, equations (D.8) and (D.9) become:

$$b_0 n + b_1 \sum_{i=1}^n X_i = \sum_{i=1}^n Y_i, \text{ and} \quad (\text{D.10})$$

$$b_0 \sum_{i=1}^n X_i + b_1 \sum_{i=1}^n X_i^2 = \sum_{i=1}^n X_i Y_i. \quad (\text{D.11})$$

These two equations are called the normal equations.

Equations (D.10) and (D.11) may be solved simultaneously for b_1 and b_0 . Thus,

$$b_1 = \frac{\sum X_i Y_i - (\sum X_i)(\sum Y_i)/n}{\sum X_i^2 - (\sum X_i)^2/n}, \text{ or} \quad (\text{D.12})$$

$$b_1 = \frac{\sum(X_i - \bar{X})(Y_i - \bar{Y})}{\sum(X_i - \bar{X})^2} \quad (\text{D.13})$$

where

$$\bar{X} = \sum X_i / n, \quad (\text{D.14})$$

$$\bar{Y} = \sum Y_i / n, \quad (\text{D.15})$$

and all summation signs mean the sum from $i = 1$ to $i = n$.

The various terms in equation (D.12) have been given names:

$\sum X_i^2$ = the uncorrected sum of squares of the X's,

$(\sum X_i)^2 / n$ = the correction for the mean of the X's,

$\sum X_i^2 - (\sum X_i)^2 / n$ = the corrected sum of squares of the X's,

$\sum X_i Y_i$ = the uncorrected sum of products,

$(\sum X_i)(\sum Y_i) / n$ = the correction for the means, and

$\sum X_i Y_i - (\sum X_i)(\sum Y_i) / n$ = the corrected sum of products
of X and Y.

Equation (D.12) is the form that is normally used when the value of b_1 is actually computed.

Similarly, solving equations (D.10) and (D.11) for b_0 , one obtains

$$b_0 = \bar{Y} - b_1 \bar{X}. \quad (\text{D.16})$$

Substituting equation (D.16) into (D.2) results in:

$$\hat{Y} = \bar{Y} + b_1(X - \bar{X}) \quad (D.17)$$

where b_1 is defined by either equation (D.12) or (D.13).

Equation (D.17) is the linear least squares equation for a set of n observations. But this equation is not an exact equation since the plot (figure 12) shows that not all of the data points lie on the regression line. There is thus an error inherent in the least squares method. This error may be presented in several forms. The form to be used in this analysis will be the R-square statistic.

C. The Precision of the Estimated Regression--the R-square Statistic

First we define the residual to be the actual data point value minus the value predicted by the regression line:

$$\text{Residual} \equiv Y_i - \hat{Y}_i \quad (D.18)$$

When there is a β_0 term, the sum of the residuals is always equal to zero, i.e., the distribution of data points on one side of the regression line is exactly balanced and cancelled by that on the other side. The omission of the β_0 term implies that the response is zero when all independent variables are zero.

Now consider the following identity:

$$Y_i - \hat{Y}_i = Y_i - \bar{Y} - (\hat{Y}_i - \bar{Y}) \quad (D.19)$$

Squaring both sides and summing from one to n yields:

$$\Sigma(Y_i - \hat{Y}_i)^2 = \Sigma\{(Y_i - \bar{Y}) - (\hat{Y}_i - \bar{Y})\}^2 . \quad (D.20)$$

When the right side is expanded, equation (D.20) becomes:

$$\begin{aligned} \Sigma(Y_i - \hat{Y}_i)^2 &= \Sigma(Y_i - \bar{Y})^2 + \Sigma(\hat{Y}_i - \bar{Y})^2 \\ &\quad - 2 \Sigma(Y_i - \bar{Y})(\hat{Y}_i - \bar{Y}) . \end{aligned} \quad (D.21)$$

Examine the last term on the right of equation (D.21),

$$- 2 \Sigma(Y_i - \bar{Y})(\hat{Y}_i - \bar{Y}) . \quad (D.22)$$

First, we have from equation (D.17),

$$\hat{Y}_i - \bar{Y} = b_1(X_i - \bar{X}), \text{ which,}$$

when inserted into equation (D.22) results in:

$$- 2 b_1 \Sigma(Y_i - \bar{Y})(X_i - \bar{X}) . \quad (D.23)$$

Second, from equation (D.13),

$$\Sigma(X_i - \bar{X})(Y_i - \bar{Y}) = b_1 \Sigma(X_i - \bar{X})^2 .$$

Substituting the latter into equation (D.23) yields:

$$- 2 b_1^2 \Sigma(X_i - \bar{X})^2 . \quad (D.24)$$

Next, from equation (D.17), introducing

$$(X_i - \bar{X}) = (\hat{Y}_i - \bar{Y})/b_1$$

into equation (D.24) will produce

$$- 2 \Sigma(\hat{Y}_i - \bar{Y})^2 . \quad (D.25)$$

Thus, replacing the third term on the right of equation (D.21) with (D.25) and rearranging terms results in:

$$\Sigma(Y_i - \bar{Y})^2 = \Sigma(Y_i - \hat{Y}_i)^2 + \Sigma(\hat{Y}_i - \bar{Y})^2 . \quad (D.26)$$

The terms in equation (D.26) are defined as:

$\Sigma(Y_i - \bar{Y})^2$ = the sum of squares of deviations
about the mean (S.S.M.),

$\Sigma(Y_i - \hat{Y}_i)^2$ = the sum of squares of deviations about the
regression line (S.S.A.R.) or the sum of
the squares of the residuals, and

$\Sigma(\hat{Y}_i - \bar{Y})^2$ = the sum of squares of deviations of the
predicted values from the mean due to
regression (S.S.D.R.).

Thus equation (D.26) reads:

$$S.S.M. = S.S.A.R. + S.S.D.R. . \quad (D.27)$$

Ideally we would like each predicted value of Y to be equal to the actual value:

$$\hat{Y}_i = Y_i , \quad (D.28)$$

which is the same as saying that the residuals should be as small as possible. In terms of equation (D.27), it is desirable to have:

$$\text{S.S.A.R.} \approx 0 . \quad (\text{D.29})$$

When S.S.A.R. is approximately zero:

$$\text{S.S.M.} \approx \text{S.S.D.R.} . \quad (\text{D.30})$$

Dividing both sides of equation (D.30) by S.S.M. yields:

$$\frac{\text{S.S.D.R.}}{\text{S.S.M.}} \approx 1 . \quad (\text{D.31})$$

Thus, we define the R-square statistic as:

$$\text{R-square} = \frac{\text{S.S.D.R.}}{\text{S.S.M.}} = \frac{\sum (\hat{Y}_i - \bar{Y})^2}{\sum (Y_i - \bar{Y})^2} . \quad (\text{D.32})$$

Expressing equation (D.32) in words, we would say that the R-square statistic is the ratio of the sum of squares of deviations of the predicted values from the mean to the sum of squares of deviations about the mean.


When the fit is perfect (i.e., $\hat{Y}_i = Y_i$ and therefore no residuals), the R-square statistic is equal to one. As the predicted values deviate from the actual values, the R-square statistic becomes less and less, until finally, if there is no relation between the predicted values and the actual values, the R-square statistic is equal to zero.

The R-square statistic is a convenient measure of the significance of the estimated regression equation because it includes only one assumption, that is, a linear least squares method is used to

compute the regression equation.

VITA

The author was born in Cumberland, Maryland on February 7, 1951. He attended Parkside Elementary School and graduated from Allegany High School in 1969. From 1969 until 1973 he attended Virginia Polytechnic Institute and State University where he obtained a B.S. in Engineering Science and Mechanics in September. After graduation he began graduate studies at the same university and department. He has worked as a graduate teaching assistant and is currently working as a graduate research assistant and plans to continue his studies with a Ph.D. degree as his goal.


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AN EMPIRICAL CONSTITUTIVE EQUATION FOR
ANTICOAGULATED HUMAN BLOOD

by

Frederick James Walburn

(ABSTRACT)

A constitutive equation for whole human blood was developed using a power law functional form. This power law equation contains two parameters, the consistency index and the non-Newtonian index for the fluid. Viscometric data, utilizing a cone and plate viscometer, were obtained from anticoagulated blood samples of known hematocrit levels and chemical compositions. A multiple regression technique with apparent viscosity as the dependent variable was used to determine the consistency index and the non-Newtonian index.

A model including only the shear rate as the independent variable was found to be lacking any substantial degree of significance. When hematocrit was added as an independent variable, the degree of fit increased considerably.

Of the chemical variables examined, the least significant, as far as effects on viscosity is concerned, were the plasma lipids. The proteins, fibrinogen and globulin were found to have a much greater effect on viscosity than the protein, albumin. The best constitutive equation involving the chemical composition of blood was found to include the shear rate, the hematocrit level, and a

variable which is the sum of fibrinogen and globulin. This model produced a statistically significant increase in the correlation between experimental and theoretical data compared with the best two variable model.