SPECIAL ARTICLE

Clinical Implications of Blood Rheology Studies

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SUMMARY

Blood viscosity is dependent on the shear rate at which it is measured. Reversible red cell aggregation is largely a function of fibrinogen-red cell interaction at normal hematocrits. Red cell aggregation is the basis for the anomalous rheological behavior of blood, since a considerable fraction of the shear stress applied to blood flowing at low shear rates is required to break up the aggregates accounting for the greater shear stress required to produce a given shear rate of low magnitude. Erythrocyte sedimentation rate is also a measure of red cell aggregation and has been used as an indicator of the "suspension stability" of blood. The tendency for red cell aggregation is greatest during periods of low flow states and is maximum when the blood is standing still. At such times, a certain shear stress, the yield stress, must be applied to overcome the reversible red cell-fibrinogen bond, causing the blood to "yield" or begin to flow. Manipulation of blood viscosity and yield shear stress, by hemodilution or fibrinogen dilution are readily accomplished, and experimental studies indicate that these rheological alterations have circulatory and metabolic significance.

Additional Indexing Words:
Vascular resistance
Polycythemia
Viscosity
Hyperfibrinogenemia
Yield shear stress
Blood flow

The BEST MEASURE of circulatory adequacy, it is generally agreed, is the quantity of blood flow to the tissues. Major investigative emphasis has been placed on the development of supportive techniques during periods of inadequate tissue perfusion that have generally involved improving cardiac or vascular function. Considerable basic work has clearly defined the rheological behavior of blood; yet little has been done to apply this information in situations involving circulatory insufficiency in man. This paper is a general review of blood rheology, emphasizing the possible clinical applications of the subject.

Rheological Terms and Concepts

The interrelationships of viscosity, shear stress, and shear rate in a fluid can be considered as follows:

One supposes that the fluid is like a deck of playing cards on a table. If one pushes...
horizontally on the top card, the cards will progressively slip over each other horizontally, each card experiencing slipping friction with the card immediately above and below. The less the friction, the more the cards will slip horizontally within a given instant under a given horizontal push. Continuing the analogy of the deck of cards, we define shear stress as the horizontal pushing force divided by the area of the card (force/area); shear rate (also called the velocity gradient) is the horizontal distance of displacement per second of a given card beyond its immediate lower neighbor, divided by its thickness—hence the dimensions cm per sec per cm, or sec⁻¹; and viscosity (the analogy of friction) as the shear stress divided by shear rate.

Newtonian fluids (after Isaac Newton) are those for which the ratio \( \frac{\text{shear stress}}{\text{shear rate}} \) is not dependent on either shear stress or shear rate. The viscosity remains the same whatever the shear rate at which it is measured. These fluids also follow the equation derived by Poiseuille for flow through long thin tubes, namely,

\[
Q \text{ flow rate} = \frac{\pi dP r^4}{8\eta}
\]

where \( dP = \text{pressure drop along tube} \)

\( l = \text{length of tube} \)

\( r = \text{radius of tube} \)

\( \eta = \text{viscosity} = \frac{\text{shear stress}}{\text{shear rate}} \).

The so-called coaxial cylinder or couette viscometer fundamentally is a cylindrical approximation of the planar "flow" of the deck of playing cards, and it is particularly useful because shear rate and shear stress can be separately, and clearly, determined. Therefore, such a viscometer is appropriate for the study of non-Newtonian fluids, that is, those in which the ratio of shear stress to shear rate varies depending on how fast or forcefully the fluid is sheared.

Colloidal suspensions, like blood, do not obey either Poiseuille's or Newton's principles and have anomalous rheological behavior; blood viscosity varies with the shear rate at which it is measured. Both plasma and serum are Newtonian fluids; their viscosities do not change with alterations in shear rate. The importance of clearly understanding the significance of the relationship of shear rate to blood viscosity is illustrated by figure 1. At a shear rate of 0.01 sec⁻¹ the viscosity of normal blood is 800 centipoises, a value 40 times that of blood flowing at a shear rate of 1 sec⁻¹. The relative ranges of shear rate for various anatomic areas of the circulation are marked off on figure 1. These impressive changes in viscosity occur at shear rates approximating those of the microcirculation.

If whole blood is defibrinated, or, if washed red cells are suspended in saline or Ringer's solution (at a hematocrit below 30%), almost Newtonian behavior of the suspension is observed. When fibrinogen is added to these suspensions, they again demonstrate non-Newtonian characteristics. It is apparent then, that it is fibrinogen and its effect on red cells that is largely responsible for the anomalous rheological behavior of whole blood.

Fibrinogen may act as an intercellular bridge, bonding red cells together, causing groups of them to clump in multicellular aggregates. The propensity for red cells to clump is greater when they have little dynamic force, that is, aggregation is at its maximum when the cells are not moving, and the cells break apart following agitation. The photomicrographic studies of Fulton and Lutz clearly show complete cessation of blood flow for short periods in the smaller blood vessels and it is here that red cell aggregation most frequently occurs. Aggregation, or sludging, has been described in vivo in the smaller blood vessels of the bulbar conjunctiva and nail bed, and considerable speculation has arisen about the effect of this phenomenon on blood flow in the microcirculation. Red cell aggregation is reversible and, as the velocity of blood flow increases, the aggregates are stirred up and break apart. The extent of disaggregation is directly proportional to the velocity of blood flow.

During intervals of low flow, a considerable portion of the shear stress applied to the blood
Graph illustrates the great importance of shear rate to the viscosity of a non-Newtonian fluid such as blood. Blood with a normal hematocrit and fibrinogen concentration has a viscosity at a shear rate 0.01 sec\(^{-1}\) 40 times that when it is measured at a shear rate of 1 sec\(^{-1}\). The effect of increased red cell or fibrinogen concentration can be readily seen. A combination of elevated red cell and fibrinogen concentration is the worst possible situation rheologically. When fibrinogen is absent, the blood has Newtonian characteristics, that is, viscosity does not vary with shear rate.

must be expended to break up the red cell aggregates, which are constantly forming and breaking up. This means that only part of the applied shear stress is used to produce flow velocity. As the flow velocity increases, the red cell aggregates quickly break up, and it becomes necessary for proportionally less of the shear stress to be utilized to separate the clumps of cells. At high shear rates, the fraction of the total shear stress needed to disrupt the aggregates is very small, and blood viscosity measured at shear rates above 100 sec\(^{-1}\) has Newtonian characteristics,\(^1\) (fig. 1). Despite the abundant literature describing red cell aggregation in the microcirculation as a disease or a symptom of a disease, it seems clear that the extent of blood "sludging" is a function of red cell-fibrinogen interaction and the extent of this interaction is dependent upon the concentration of each. As the concentration of red cells increases, the contribution by direct red cell-red cell interaction becomes increasingly important. A combination of polycythemia and hyperfibrinogenemia is the worst possible rheological combination. Burton\(^8\) has calculated that
the maximum hematocrit that may exist in a closed vessel before all the red cells are in contact is 58%. Above this value, the red cells must be in contact, and it seems likely that the contribution of fibrinogen-red cell interaction to red cell aggregation above this hematocrit level must be relatively less important. There has been some evidence to support the thesis that the extent of the red cell negative charge may be an important factor in red cell aggregation, but recently Brody and Oneley have clearly demonstrated that aggregation and rouleaux formation depend on factors that are not influenced by the net charge on the red cell. We believe that red cell aggregation is almost entirely related to fibrinogen and red cell interaction.

**Yield Stress**

Merrill and associates have reported that the behavior of blood flowing at very low shear rates closely follows the Casson equation, which predicts a linear relationship of shear stress to shear rate. As an alternative to direct measurement, a value for shear stress at zero shear rate can be determined by plotting the square root of shear stress against the square root of shear rate (the Casson plot) and by extrapolating these data to zero shear rate. The point on the ordinate indicates the force that may be applied to static blood without causing it to flow; this value is the *yield shear stress*. Measurements of shear stress at shear rates approximating zero flow can be achieved by the use of the GDM viscometer, which is capable of precise shear stress measurements at shear rates as low as 0.01 sec\(^{-1}\). Figure 2 illustrates the Casson plot for red cells suspended in plasma or saline; the intercept of the plot for red cells in plasma is at a positive value on the ordinate indicating yield shear stress; the intercept of the plot for cells suspended in saline passes through the ordinate at zero.

Yield shear stress represents the force necessary to disrupt red cell clumps or aggregates formed in standing blood. It is increased by the same factors that promote the tendency for red cells to aggregate, that is, the fibrinogen and red cell concentration of the suspension (figs. 3 and 4). Yield stress appears to be the ultimate expression of the non-Newtonian characteristics of blood, since it represents

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*Figure 2*

By plotting the square root of shear stress against the square root of shear rate, the value for shear stress at zero shear rate can be obtained; this is the yield shear stress. Yield shear stress is a result of the reversible formation of red cell aggregates by fibrinogen-red cell interaction. In the absence of fibrinogen, that is, red cells suspended in saline, there is no yield stress. (From Meiselman)

*Figure 3*

The value for yield stress is a direct function of fibrinogen concentration in a suspension of red cells in saline. It is important to note, however, that a minimum of 90 mg% of added fibrinogen must be present in the suspension before the yield stress becomes apparent.
the shear stress that must be applied to overcome the greatest degree of red cell aggregation, that is, in static blood. As the shear rate increases, the fraction of the shear stress that is represented by the yield stress becomes less and less (as the red cell aggregates are broken up), until at very high shear rates the relative value of yield stress is small. However, at low shear rates (as in the microcirculation) it seems likely that the yield stress may represent a significant portion of the peripheral resistance to blood flow. Yield stress is not affected by various anticoagulants. This may be an important consideration clinically, since thrombotic tendencies are believed to be associated with an elevated hematocrit, high blood viscosity, and low flow states. Although the yield stress increases nonlinearly with the plasma fibrinogen concentration at normal hematocrit levels, in vitro studies have demonstrated that at least 140 mg% of added fibrinogen must be present in a red cell suspension before any significant yield shear stress is observed (fig. 3). Since apparently 60 mg% of plasma fibrinogen is sufficient for a satisfactory clotting mechanism, this fortunate differential makes the modification of yield stress theoretically feasible in a clinical situation.

Another measure of the propensity for red cells to form aggregates is provided by the red cell sedimentation rate. Based largely on Fahraeus and Hardwicke and Squire's work, red cell sedimentation rate has been used to indicate the "suspension stability" of the blood, that is, the tendency for red cells to settle out of suspension. The sedimentation rate of a blood sample is generally regarded to reflect or parallel the degree of intravascular red cell aggregation observed in vivo.

Clinical Implications

An elevated blood viscosity has been reported to be associated with polycythemia, hyperlipemia, and hyperfibrinogenemia, and implicated in such disorders as hypertensive vascular disease, myocardial infarction, Raynaud's disease, and Waldenström's macroglobulinemia.

The extensive studies of Gelin reportedly demonstrated that intravascular red cell aggregation and blood viscosity were increased following various types of trauma. These changes were found to be associated with a decrease in tissue blood flow and were implicated in the tissue damage which followed injury. Gelin observed that the adverse rheological effects of trauma could be reversed by the infusion of low molecular weight dextran (LMWD, average molecular weight = 40,000), a member of the family of polysaccharides produced by the conversion of sucrose into dextrans by certain bacteria. Gelin's observations on the beneficial effects of LMWD infusion were received enthusiastically, as judged by the volume of literature that appeared in subsequent years, culminating in 1963 in a conference sponsored by the National Research Council. Unfortunately, much of the data presented in support of the rheological benefits of LMWD were inadequately controlled with regard to red cell and fibrinogen dilution. In experimental animals during hemorrhagic hypotension, we did not find any beneficial effects of LMWD infusion, hemodynamically or rheologically, apart from the effects of hemodilution.
circulation following the infusion of LMWD during hemorrhagic hypotension (fig. 5), but it should be noted that this effect is associated with hemodilution (as well as fibrinogen dilution). If hemodilution is avoided by infusing the LMWD in a suspension of packed red blood cells, keeping the hematocrit constant, no effect on blood flow during hemorrhagic hypotension is observed (fig. 6). These in vivo studies are supported by the extensive viscometric observations of Meiselman, who found no lowered blood viscosity and yield stress when dextran was added to whole blood, provided the hematocrit was maintained at a constant value; on the contrary, except for dextran 20,000 mol wt, all the other types increased yield stress and viscosity. The increase in yield stress is proportional to the molecular weight of the dextran and to its concentration in the suspension (fig. 7). The greatly increased yield stress produced by the higher molecular weight dextrans parallels the tendency to promote red cell aggregation demonstrated by these substances.

While enthusiasm for low molecular weight dextran as a primary rheological agent has
WHOLE BLOOD LOW MOLECULAR WEIGHT DEXTRAN EXCHANGE WITHOUT HEMODILUTION

Figure 6
Similar experimental method as that for figure 5. However, in these experiments a suspension of packed cells and LMWD (Hct. 40%) was exchanged for the blood of the animal after the period of hemorrhagic hypotension. The same quantity of LMWD was infused as in figure 5, but there was no hemodilution. As can be seen, the hemodynamics of these animals did not change. (Reprinted from Replogle and associates.)

diminished, the data obtained from the investigation of its use suggest that the hemodynamic effects of hemodilution in hemorrhagic hypotension are of such a magnitude that they may be of considerable physiological importance. The use of hemodilution as a therapeutic technique has been suggested from time to time, particularly in polycythemia, and is not without considerable theoretical and some experimental justification. Some of this evidence will be reviewed.

Neurological manifestations of polycythemia vera were reported shortly after the condition was first described, the most serious being thrombosis of a cerebral artery with cerebral infarction which occurred in 10% of the 263 patients studied by Lawrence and associates. Millikan and co-workers reported a syndrome of intermittent carotid and vertebralbasilar insufficiency associated with polycythemia and responding favorably to phlebotomy with reduction in hematocrit. These observations reflect the observations of Kety that a marked decrease in cerebral blood flow is associated with the high blood viscosity of polycythemia. In experimental polycythemia in dogs, changes in cerebral blood flow following the induction of polycythemia appear to be secondary to reduced cardiac output and increased peripheral vascular resistance associated with the greatly increased blood viscosity (fig. 8). While there are few data regarding plasma fibrinogen concentrations in patients with primary polycythemia, the relationship of plasma fibrinogen, yield stress, and red cell aggregation to the circulatory and thrombotic complications known to develop in these patients is probably important.

Association of neonatal respiratory distress and a high hematocrit is not unusual although the studies of Inall and associates suggest that this is not always the case.
Dramatic clinical improvement was reported to follow hemodilution in an infant with severe respiratory distress and a hematocrit of 78%. In this case, 5% dextrose and water was exchanged for whole blood until the hematocrit was lowered to 45%. Recently, an infant in severe respiratory distress and evidence of congestive heart failure has been seen at the Children’s Hospital of Boston. This child had a hematocrit of 82% and a plasma fibrinogen concentration of 985 mg% (normal 200 to 300 mg%). Plasma was exchanged for whole blood until the hematocrit reached 50%, and at this time striking clinical improvement was apparent. The child was discharged from the hospital 10 days later without any evidence of heart disease.*

Some of the most striking examples of polycythemia exist in children with cyanotic congenital heart disease, and it has been generally assumed that the increased red cell production results from a hypoxic stimulus to some target area responsible for erythropoietin production. However, Erslev has recently demonstrated that despite deficient tissue oxygenation in both anemic (hematocrit, 15%) and polycythemic (hematocrit, 65%) rabbits only the anemic animals showed increased erythropoietin levels.

A greatly increased red cell concentration in hypoxemic patients may represent a “homeostatic” mechanism that has overcompensated and has become a liability. Circulatory and coagulatory improvement have been demonstrated after hemodilution in severely polycythemic patients. While there is a widely held conviction among clinicians that children with cyanotic congenital heart disease appear better compensated when their hematocrit is above 65%, this misconception

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*Circulation, Volume XXXVI, July 1967
is based on interpretation of hematocrit-viscosity relationships that were obtained by the use of an Ostwald capillary viscometer. Studies of blood viscosity carried out with the use of capillary viscometers are of little physiological relevance, since these instruments preclude consideration of the influence of shear rate on blood viscosity (fig. 1). It has been estimated that the shear rate in the aorta of man is of the order of 100 sec⁻¹ and is about 10 sec⁻¹ in the arteriolar bed. The Ostwald capillary viscometer measures blood viscosity at shear rates of 1,200 sec⁻¹, and at this shear rate, the measurement of blood viscosity has little physiological significance. Changes in viscosity with increasing red cell concentrations are paralleled by substantial increases in yield stress brought about by increased red cell concentration (fig. 3). Therefore, the liability produced by polycythemia is twofold: viscosity is increased and yield stress is increased. A self-perpetuating cycle is initiated in polycythemia since, with the reduction in peripheral flow that is associated with the increased viscosity and yield stress, shear rate is reduced. The lower shear rate is associated with a higher blood viscosity because of the anomalous rheological behavior of blood, giving rise to a vicious cycle.

There is little support for the view that a hematocrit above the normal level is useful, and there is considerable evidence to suggest that a red cell concentration somewhat less than the usually accepted normal range may be sometimes beneficial. Crowell and associates⁴³ have reported that oxygen consumption in dogs increased as the hematocrit was increased from 10 to 42%. Further increases in red cell concentration resulted in a progressive fall in peripheral oxygen utilization. Crowell and his associates⁴⁴ also reported that the time required for the development of irreversible shock (using the Lamson-Fine technique) in the dog was maximal at a hematocrit of 35%, and thus suggested that the circulatory homeostasis of this animal operates best at this red cell concentration. Our studies indicate that cardiac output is greatly reduced and blood viscosity and yield stress are increased by the acute induction of polycythemia in normal dogs, and these hemodynamic effects seem to be metabolically important as evidenced by the elevation of the ratio of lactate to pyruvate at the height of polycythemia. Hemodilution in the same animal restores the hemodynamic and metabolic alterations to the normal levels (table 1).

Blalock⁴⁵ demonstrated that adequate vascular volume replacement was more important than red blood cell replacement in the treatment of hemorrhagic shock. More recently, it has been reported that the tissue shift to anaerobic metabolism following hemorrhagic shock may be reversed as rapidly by volume replacement with red cell-free colloidal solution as with whole blood infusion, even though the hematocrit may fall as low as 15 to 20%.⁴⁶ Murray⁴⁷ has demonstrated that the increased cardiac output following hemodilution results from reduced blood viscosity and not from the vasodilatation of peripheral hypoxia. Severely anemic animals were given 100% oxygen to breathe, elevating the mixed venous oxygen tension well above the control levels and increasing the systemic oxygen transport almost to normal levels (despite a hematocrit which ranged from 9 to 16%): suggesting that little, if any, tissue hypoxia was present. The same increase in cardiac output followed severe hemodilution in those animals breathing oxygen as in those breathing only room air.

The studies of Sanders and his associates⁴⁸ demonstrated that the normothermic dog ventilated with 100% oxygen can meet its oxygen requirements for satisfactory cardiac performance even with a hematocrit as low as 6%. Only one of 11 animals in this study showed evidence of "excess" myocardial production of lactate at this low hematocrit, suggesting that little anaerobic metabolic activity was taking place.

Burrows and Nider⁴⁹ reported that the apparent diffusing capacity of the alveolar-capillary membrane might be dependent
upon the hematocrit level, but Laver and associates\textsuperscript{50} did not observe any limitation to adequate pulmonary oxygenation in animals with hematocrits as low as 6%. That metabolic acidosis is not necessarily a consequence of extreme hemodilution\textsuperscript{46, 50, 51} has been confirmed repeatedly, indicating that the oxygen requirements and acid buffering of the tissues may be met by the increased perfusion that is associated with a low hematocrit.

A survey of the comparative physiology of various animal species does not demonstrate any correlation between the hematocrit of the blood and the oxygen requirements of animals, based on the intensity of their cellular metabolism.\textsuperscript{52} As a function of body weight, the mouse has a metabolic rate tenfold that of man: yet they have identical hematocrit levels.\textsuperscript{53} However, the mean cellular hemoglobin concentration in the white mouse ranges from 45 to 48\%, as opposed to 33\% in man. This permits the mouse to maintain a higher oxygen-carrying capacity at a lower hematocrit, avoiding the disadvantages of a higher blood viscosity.

Some controversy exists about whether a higher blood viscosity is associated with coronary artery disease. Burch and DePasquale,\textsuperscript{27} Mayer\textsuperscript{28} and Dintenfass and associates\textsuperscript{54} observed elevated blood viscosity in patients with coronary artery disease which was associated with an increased hematocrit. Burch and DePasquale\textsuperscript{55} reported distinct improvement in patients with severe angina when the hematocrit was reduced from 50 to 55\% to 40 to 45\%. Conley and associates\textsuperscript{56} did not confirm the observation of Burch and DePasquale\textsuperscript{27} that moderate erythrocytosis was often associated with coronary artery disease. However, the average age in the control group in the Conley series was 27 years, as opposed to a control group averaging 52 years in the Burch study, and the hematocrit in the Conley control group was significantly higher than that in the Burch group. Rosenblatt and associates\textsuperscript{57} did not find any differences in blood viscosity between normal and coronary patients, although these observations are not pertinent since the viscosity measurements were made at a high shear rate (230 sec\textsuperscript{-1}).

Improving peripheral circulation by reducing the blood viscosity and yield stress by hemodilution and reduction of plasma fibrinogen would seem to provide an approach for treatment in patients with circulatory inadequacy that can supplement the

### Table 1

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<tr>
<th>Hemodynamic and Metabolic Changes after Acute Induction of Polycythemia in a Dog, Followed by Exchange Dilution with Dextran (80,000 mol wt)</th>
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<td>Control</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Yield stress (dynes/cm\textsuperscript{2})</td>
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<tr>
<td>Cardiac output (ml/min)</td>
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<td>Oxygen consumption (ml/min)</td>
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<td>Hematocrit (%)</td>
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<tr>
<td>Plasma fibrinogen (mg%)</td>
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<td>Lactate pyruvate ratio</td>
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<td>Arteriovenous oxygen difference (vol %)</td>
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measures currently used to treat circulatory failure. Since the metabolic requirements of the heart (assessed by myocardial oxygen consumption) are chiefly a product of the pressure load imposed upon it, rather than the flow load, 58, 59 the reduction in peripheral resistance that follows hemodilution may reduce the metabolic demand of the myocardium while improving tissue perfusion during circulatory failure. Case and co-workers 60 have shown that, when the left ventricular work is kept constant, increasing the hematocrit from 32 to 55% decreases left coronary blood flow from 193 to 83 ml per minute, a reduction in flow greater than the relative increase in oxygen-carrying capacity of the blood.

References

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Try Missing Them in Front

Writing is, for most, laborious and slow. The mind travels faster than the pen; consequently, writing becomes a question of learning to make occasional wing shots, bringing down the bird of thought as it flashes by. A writer is a gunner, sometimes waiting in his blind for something to come in, sometimes roaming the countryside hoping to scare something up. Like other gunners, he must cultivate patience; he may have to work many covers to bring down one partridge.—E. B. White: An Approach to Style. In William Strunk, Jr. and E. B. White: The Elements of Style. New York, The Macmillan Company, 1962, p. 55.

The above quotation has stimulated the following musings.

There is a story about a veteran of the shooting sport who, having observed an obvious incompetent banging away at geese flying overhead but never causing even one to falter in its flight, lost his patience and manners and sarcastically yelled, “Try missing them in front” (so that the poor gunner might “lead” the birds more). How often may not this theme pertain to other efforts; if one could only anticipate the course (or flight) of a disease or of a discussion, how much greater would be the number of facts that could be accurately recorded (brought down to be counted in one’s “bag” at the end of the day)?

However, in conversation, not infrequently there may be some one who is so anxious to express his own thoughts, that he interrupts to disagree without waiting to learn (let alone ponder) what another has said. Continuing the analogy, the person shoots at anything appearing on the horizon.

In writing, to what degree should an author be responsible for misinterpretations of his writing? Numerous qualifying clauses, “expertise” and jargon are invitations to a critic inclined to misinterpret to do so, whether motivated consciously or unconsciously. Authors may be stubborn to change statements, concerning which misinterpretation might be readily anticipated. Even as a good thought, or a duck, may be brought down by the proper lead, so may a bad one, the beginning of a misinterpretation, as a scout varmint crow, be destroyed by the anticipation of his flight.

H. B.
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