SLUDGED BLOOD

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This paper constitutes a brief introduction to a series of observations made mostly with microscopes in living animals and men which leads to a more precise understanding of a variety of mechanisms whereby injuries and diseases damage the human body. It is felt that these observations clarify a group of fundamental ideas, explain many old experiments, and make the solution of several groups of currently perplexing problems quite simple. The observations also permit, and we think necessitate, a subdivision and reclassification, a much-simplified and, for guiding investigations, a more useful classification of many of the currently known pathologic mechanisms of the diseases of animals and men. Our purpose is to present and define certain properties of normal blood, blood flow, and vessel walls; to offer evidence that these properties are necessary to the normal functioning of the circulatory system; to describe certain visible responses of the vascular system and/or blood to specific stimuli; to describe certain visible pathologic structures and processes; and to define goals now necessary for therapeutics.

The material presented is an outline and summary of 16 years of observation and experimentation during which two major methods have been used. Living animals—frogs, salamanders, mice, rats, guinea pigs, cats, rabbits, dogs, and monkeys—have been carefully anesthetized and operated upon, and internal organs such as striated muscles, smooth muscles, gastrointestinal tract linings, surface areas of brain, peripheral nerves, uterus, spleens (22), livers (27), omentum, mesenteries, frog kidneys, etc. exposed. Parts of these organs have then been transilluminated with light-conducting fused quartz rods (23) and studied with microscopes at 16-600 × magnifications. This was necessary in order to learn about the structure, dimensions, and natural behavior of the blood and vessels of living internal organs.

Since 1941 binocular dissecting microscopes have been focused on the obliquely illuminated bulbar conjunctival vessels of living, unanesthetized, unoperated animals and men (23). When skilfully used, this method causes almost no discomfort to most subjects (16, 28, 29, 45) (see cover). Because the blood is thoroughly swirled and mixed in the chambers of the heart and the arch of the aorta, this method permits continuous, careful study of a statistically valid sample of all the subjects' circulating arterial blood (29). It also permits study of one set of small human vessels, including both their vasomotor conditions and responses (3, 11, 14, 30, 38, 49) and various aspects of the normal and/or pathologic reaction states of their walls (6). Magnifications of 32, 48, 64, and 96 × have been used.

The dimensions of many observed structures have been measured or estimated closely with transparent scales mounted in the microscope ocular or recorded in motion pictures.

Healthy, Normal Blood and Vessel Walls

In the internal organs of about 3,500 healthy frogs, 1,100 salamanders (Amblystoma), and 500 laboratory mammals anesthetized with pentobarbital sodium and in the bulbar conjunctiva of 50 healthy, unanesthetized medical students and student nurses the following observations have been made:

1. The circulating red cells not only were not agglutinated but tended to repel each other slightly. In carefully handled tissues red cell rouleaux were not present. The normal red blood cells were not coated with any microscopically visible protein precipitate. The fact that they show no tendency to adhere to each other is evidence that they are not coated with any very thin, transparent, or otherwise invisible sticky precipitate. These observations are in strict agreement with those of many

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previous investigators (1, 2, 36, 35, 36, 44). The observations of unagglutinated blood cells in young, healthy human beings are particularly valuable as a strict control for animal experiments since these human beings had not been subjected to fright, anesthetics, or operations.

(2) No white cells or erythrocytes stuck to the inner surfaces of the walls of small vessels. The inner surfaces of the linings of normal small vessels were smooth and clean (6, 35, 36).

(3) The flow of the unagglutinated blood was laminar or "streamlined." In small arteries and veins the blood cells were in an axial stream and around them was a peripheral concentric layer of plasma (30, 44, 49, 30). The cells of this stream were arranged in concentric laminae, the center one passing along most rapidly and each additional layer passing more slowly than the one inside it. The wall of each lamina of this system consisted of unagglutinated blood cells; each layer was exactly one red cell thick (cinema recorded). This arrangement of unagglutinated blood cells in fluid plasma is a necessary part of the highest degree of good health, as the next and succeeding paragraphs show.

The rates of flow of blood through each tissue of the body set the maximum rate at which the cells of that tissue can receive blood-borne materials. For this discussion the most important of these is oxygen: it is of that tissue can receive blood-borne materials. For this discussion the most important of these is oxygen: it is necessary for oxigenation of tissue and in the equilibrium between "constrictor and dilator" substances which can reach the vessel wall by three paths—from blood flowing through the vessel, from cells of the particular tissue or organ around the vessel, and from nerve endings in, upon, or near the vessel wall. The responses of the contractile elements are also continuously affected by temperature changes in the tissues around vessels and in the entering arterial blood. Many of these reaction patterns are exceedingly complex (22, 27); all are necessary parts of the internal adjustments of normal good health. The previously described arrangements of the semisolid blood cells suspended in the moving plasma cause the minimal internal friction in the columns of blood in arteries and veins, thus permitting the available pressure drop along each open vessel to cause the most rapid possible rate of blood flow through that vessel. As a direct, and most important, consequence of this, every homeostatic dilatation of any set of small vessels is immediately followed by the maximum hydrodynamically possible increase in the rate of flow of blood through that set of vessels and the maximum possible increase in the rate of supply of oxygen, rate of removal of wastes, etc.

(4) The small, normal vessels of most tissues and organs did not leak appreciable amounts of fluid for (a) there was no visible hemoconcentration occurring (30, p. 14); (b) in the mesenteries and ovaries of animals the fat cells outside vessels were tight together, not pushed and held apart by escaping fluid; and (c) in human beings the bulbar conjunctiva was not forced up and held away from the sclera, whereas this does occur and can easily be seen with stereo-microscopes in human beings at times when visible continuous hemoconcentration is occurring in leaking bulbar conjunctival vessels. The complicated permeability phases of spleen and liver vessel walls are described elsewhere (22, 27).

(5) The blood flowed so rapidly in most arterioles and venules which were from 60 to 120 μ in diameter that individual red cells could not be seen. This is a crude but accurate and useful criterion for adequate rates of blood flow through most open-tissue capillaries. If the rates of flow of oxygen-saturated arterial blood are fast enough so that individual unagglutinated blood cells cannot be seen in vessels of this size in normal animals and men, high magnifications show that no visible hemoconcentration is taking place in capillaries, i.e. almost no blood fluid is being lost through the walls of the tissue capillaries.

(6) The shapes and dimensions of the vessels of the peripheral vascular beds constitute a perpetual bottleneck in the circulatory system. All the vessels which carry blood toward tissues are long, narrow, slowly tapering, truncated cones. When arterioles branch, each branch has a narrower lumen than that of the parent stem. The capillaries or sinusoids which carry blood through tissues are approximately cylinders, and the veins are slowly widening cones again. Arteriovenous anastomoses have been
found in some tissues, but these have small total surface areas; if oxygen, glucose, and other blood-borne anabolics are to be distributed effectively to the cells of a tissue, the blood must flow through the capillaries or sinusoids of that tissue.

We have found that almost every whole arteriole-to-capillary or sinusoid-to-venule pathway can contract tightly shut throughout its length, making its internal diameter zero and thus forcibly resisting the entrance of blood, and that individual parts or all its parts can dilate maximally (27). As noted, the pathway is not capable of infinite physiological dilatation because of the elastic limit provided by the basketwork of connective tissue fibers surrounding each arteriole. Forcibly dilated capillaries begin to leak proteins and do not retain blood plasma.

In the internal organs of the mammals we have examined, the open arteriole tips were, for the most part, narrow enough so that every red and white cell passing through was forcibly distorted—usually pinched and elongated or folded. This is also clearly shown in frogs in a motion picture prepared by Fulton and Lutz (14). The capillaries through which blood is flowing normally vary from a little less than once to as much as two to two and a half times the diameters of the passing red cells. Most true capillaries can dilate without losing tonus, weakening and sacculating to a little more, but not much more, than two or two and a half times the diameters of the animal’s own red cells.

These statements are true of the arterioles and capillaries of the bulbar conjunctiva of human beings, whose red cells are usually a little less than 8 μ in diameter, and almost certainly true of all the arterioles and capillaries of most human organs during life. Thus, as is well known but not always remembered, under all conditions of health and disease the arterioles and capillaries are a perpetual bottleneck in the vascular system.

Normal, unagglutinated, circulating blood and normal vessel walls of monkeys have been recorded in colored motion pictures (see Reel 1 of the motion picture, “Knowlesi Malaria in Monkeys,” 29).

One other aspect of normal circulation, although important, has not been studied in living human beings. In living frog and rhesus monkey livers the normal naked red cells slide and bump along the surfaces of the highly phagocytic cells which line the hepatic sinusoïds, but no normal naked red cell has ever been observed to be ingested. These phagocytes continually “ignore” normal naked erythrocytes (27).

The factors of normal blood, blood flow, vessel walls, and vascular behavior listed above set the stage for recognition, understanding, and evaluation of, and planning new therapy for, a variety of factors of circulatory pathology. Once any anatomical, physiological, behavioristic, or chemical aspect of normal healthy animals or human beings can be sharply recognized and clearly defined, all detectable deviations from that aspect of the normal can also be recognized and defined. Once a kind of deviation can be defined, the detectable degrees of that kind of deviation can be arranged in scales whose extremes are the minimal perceptible deviation from normal and the maximal degree of that deviation which can exist and still have life continue. The return of each kind of pathologic deviation to the previously defined healthy normal then becomes an immediate and continuing goal of rational experimental and applied therapeutics.

The Circulating Blood of Human Patients

In about 600 unanesthetized human patients diagnosed by practicing physicians as having a wide variety of pathologic conditions and diseases, we have seen the blood cells agglutinated into masses (not rouleaux); this changed the blood from its normal, relatively fluid state, to a circulating sludge. The variety of the diagnoses is attested to by the following partial list, which includes the number of patients seen with each: 10 bronchietasis, 55 Buerger’s disease, 13 large acute burn, diphtheria, eczema, acute streptococcal endocarditis, gonorrheal salpingitis, granuloma inguinale, hystereis, chronic lymphatic leukemia, uncomplicated vivax malaria, multiple myeloma, normal uncomplicated pregnancy, thyrotoxicosis, typhus fever, whooping cough, traumatic shock without external hemorrhage (1 each); bronchitis, lung abscess (nontuberculous), malignant hypertension, measles, myelogenous leukemia, multiple sclerosis, subacute bacterial endocarditis, trichinosis, tularemia, Well’s disease (2 each); nephritis, portal cirrhosis, smallpox, thrombopemic purpura, typhoid fever, varicose leg ulcers (3 each); common cold (4); meningococcic meningitis, neoplasms of testis, colon, esophagus, pancreas, and one of unknown primary origin with multiple metastasis (1 each); traumatic shock complicated by hemorrhage and acute alcoholism (automobile accident cases) (5 each); scarlet fever, sickle cell anemia (6 each); acute arsenical reactions (7); gonorrheal arthritis, syphilis of the central nervous system (8 each); acute rheumatic fever (9); central nervous system syphilis under treatment with falciparum malaria (11), with vivax malaria (10), with quarten malaria (18); undulant fever (19); pneumococcic pneumonia (18); acute alcoholism

1 The patients in these lists were studied at the John Gaston Hospital, Memphis, Tennessee, where the investigation was initiated, the Iroquois County Hospital at Watseka, Illinois, where the undulant fever patients were available, and the Municipal Tuberculosis Sanitarium, Michael Reese Hospital, Billings Hospital, and the Chicago Lying-in Hospital in Chicago. The administrative officials and staffs of these hospitals have all been most generous and cooperative in creating opportunities for us to study their patients. Many physicians have taken considerable time to be certain that we studied very carefully diagnosed patients. Among these are L. W. Dugas of Memphis, who provided the sickle cell anemia patients; Earl Roberts of Watseka, the undulant fever patients; Gilbert Levi of Memphis and Archibald Hoyne of Chicago, patients with highly infectious diseases; Henry C. Sweeney, patients with tuberculosiis; and Charles Durham of the University of Chicago, the arthritis patients. To these and many others we are deeply grateful.

2 The agglutinated circulating blood of one Well’s disease patient was photographed on Eastman Super spectator 2X 16-mm. movie film.
plugged with masses of sludge, and, in some, short, tients: arterioles both temporarily and permanently visible in blood.

Found sludged blood in 12. Of 23 women with various out states of capillaries and small veins in terms of increasing
tic, 5; arteriosclerotic, 15; pericarditis, etiology unknown, degrees of response to increasing degrees of experimental (20); acute anterior poliomyelitis (21); heart disease (lue-
tic, 5; arteriosclerotic, 15; pericarditis, etiology unknown, 2; rheumatic, (6); pulmonary tuberculosis (58); and rheu-
matoid arthritis (125).

Odel, Aragon, and Pottinger, using a modification of our apparatus, have studied the circulating blood of 21 women with normal uncomplicated pregnancies and found sludged blood in 12. Of 23 women with various pathologic complications of pregnancy, 22 had sludged blood.

Vessel Walls of Human Patients

Almost all the known types of vessel wall pathology visible in vivo have been seen in this study of human patients: arterioles both temporarily and permanently plugged with masses of sludge, and, in some, short, spindle-shaped bulges (aneurysms) of arterioles (47).

The Clarks (6) arranged a series of pathologic reaction states of capillaries and small veins in terms of increasing degrees of response to increasing degrees of experimental injury, which permits classification of many of our observ-
ations in terms of the damage already done the vascular system rather than in terms of the patient's diagnosis. Following their classification, we have observed (a) white cells rolling along vessel linings; (b) white cells sticking, sometimes for hours; (c) white cells in layers (particularly prominent in the 3 leukemic patients, who also had circul-
ating masses of agglutinated white cells); (d) weakened, dilated, bulged, sacculated, rapidly leaking capillaries and postcapillary venules; (According to the Clarks, and our experience is in agreement, the above stages of individual capillary and small vein wall injury are reversible to normal.) (e) true stasis, i.e. vessels which had been leak-
ing rapidly, packed with red cells and/or masses of agglu-
tinated red cells; (f) scattered red cells; and (g) small hemorrhages outside vessels which are evidences of high previous porosity or rupture of vessel walls.

Further, in many patients large areas of the conjunctiv-al vascular system, arterioles, capillaries, and veins had been so tightly constricted that no red cells were vis-
ible or passed through, sometimes for hours. This can fre-
quent be seen in white patients who have marked general pallor and was conspicuous in every one of 10 consecutive patients who had far-advanced pulmonary tuberculosis.

The arterial blood pressure of many of these patients was taken. In all those listed it was within normal range or above. Further, these did not show evidences of in-
creased venous pressure. Hence, the slow passage of this sludged blood through open vessels was directly due to the sizes and rigidities of the masses, not to increased venous pressure, falling venous return, or cardiac failure.

These patients have been studied as a part of a general survey designed to find the extent of the phenomenon of intravascular agglutination of the blood. This list includes all patients in similar lists published previously (25).

The patients in the lists are unselected—that is, no attempts have been made to keep from studying patients with any particular disease, and every patient seen who had any particular diagnosis is listed. Sludged blood has been observed in men and women, white and colored people, and persons of all ages.

Thus far, completely unagglutinated blood has been found only in strictly healthy animals and men. Mild de-
grees of intravascular agglutination have been seen in many laboratory workers, students, and colleagues in the Chicago area, where sinusitis of various degrees of severity and other afflictions of the upper respiratory system are endemic. The more severe degrees of intravascular agglutination have been exhibited only in animals during controlled experiments and in persons who were suf-
ciently ill to have placed themselves under the care of physicians. No severely ill person has yet been seen who did not have intravascular agglutination of the blood and visibly pathologic vessel walls. The survey is, of course, still in progress and should be extended as rapidly as skilled observers can be trained and opportunities made available. The ultimate survey obviously should include all the diseases and pathologic conditions of other verte-
brates, including those of food fish, birds and poultry, household pets, laboratory animals, and all the mammals on which people depend for food, clothing, transportation, and the commercial production of the vaccines and therapeu-
tic sera, as well as all the other diseases of humans.

Since 1852, when Coccius (8) published microscopic ob-
servations of agglutinated blood in living human patients, sludged blood has been seen or demonstrated in living animals and in human patients and some of its results observed in vitro or in histological sections by many in-
vestigators (9,12,13,19,21,23-27,33,35,36,39,45,46,52).

Since Landsteiner's (32) demonstration of the human blood groups, microscopic study of phenomena associated with, or resulting in, agglutination of blood cells on slides and macroscopic studies in test tubes have been in con-
tinuous use in research laboratories and are now a standard part of the blood-matching techniques in all the hospitals of the world. As a result of such studies, there is an im-
ense immunological literature describing and analyzing in vitro agglutinations (68).

Further, as a part of the classical investigations by which Robin Fahraeus (9) initiated the well-known erythro-
cyte sedimentation-rate test, he and his student, Pic-
man, clearly demonstrated by three separate methods that there is increased aggregation of circulating red cells within living human patients. Fahraeus' work is sharply
relevant to subsequent discussions in this paper, for it forms a major connecting link between (a) the humoral pathology of the ancients, which dominated all of med-
icine from Hippocrates to the beginning of the cellular pa-
thology of Virchow, (b) a large and continually growing body of knowledge about the composition and physical behavior of blood drawn from different classes of patients,
and (c) the whole subject of intravascular agglutination of the circulating blood.

By means of \textit{in vitro} studies Fahraeus showed that the increased sedimentation rates of the red cells of blood drawn from human patients were due to alterations in the chemistry of the plasma rather than to detectable changes in the blood cells themselves, and he made the first direct contributions to the understanding of the chemical changes in plasma which are associated with, and can initiate, increased \textit{in vitro} sedimentation rates.

After a great many \textit{in vivo} observations, Fahraeus deduced and carefully pointed out that (a) "the gas exchange between the corpuscles on the one hand, and the tissues and the alveolar air on the other, takes place via the plasma. As the aggregation of the corpuscles reduces the surface between the corpuscles and the plasma we must a priori conclude that it affects the gas exchange of the corpuscles in an unfavorable manner"; (b) agglutinated red cell masses could be expected to act as minute embolae, i.e. be carried into and plug small arterioles and capillaries, and multiple minute embolae are found at autopsy following many diseases; (c) reduced suspension stability of the blood must "play an important part in the genesis of thrombi—as well as concerning the red parts of the mixed great thrombi in the larger vessels as with regard to certain kinds of hystil thrombi of the capillaries, which according to the statements of the literature are composed of fused red corpuscles and which especially characterize the changes of the bodily organs in eclampsia."

As a result of Fahraeus' \textit{in vitro} investigations, the red cell sedimentation-rate test has become a standard part of clinical medicine and is in use in all hospitals and by nearly all practicing physicians throughout the world; in consequence, significant alterations of the rates of settling of erythrocytes have been found in blood from patients having many different diagnoses.

There has, however, been no rigorous, systematic search for all the biological, physical, and chemical etiologic agents capable of initiating intravascular agglutination of the blood or for all the chains of specific chemical and/or immunological reactions which can and do initiate \textit{in vivo} agglutination; nor have there been systematic attempts to correlate observed and measured effects of intravascular agglutination with the signs and symptoms presented by sick people or animals, to determine the role of intravascular agglutination in the development of the lesions observed at autopsy, or to determine the kinds, degrees, and rates of damage this set of mechanisms can do to living animals and men.

\textbf{How Sludged Blood Damages the Body}

The concepts presented below were developed over a 7-year period, partly by comparing many observations of the agglutinated blood and damaged leaking vessel walls of diagnosed sick persons with those of the unagglutinated blood and intact vessel walls of healthy animals and men, partly by almost painless experiments upon anesthetized, unoperated, healthy adult human volunteers, but most of all by completely indispensable, sometimes almost daily, laboratory experiments upon carefully anesthetized amphibians and mammals, including cats, dogs, and rhesus monkeys.

\textbf{I. The resistance of sludged blood to its own passage through the bottlenecks of the circulatory system forcibly reduces the rates of blood flow through all the open vessels of the body.}

\textbf{II. Agglutinated red cells are ingested and destroyed in the phagocytic cells of liver and spleen.}

\textbf{III. There is settling and sedimenting of masses of agglutinated blood cells out of the moving blood plasma during life.}

\textbf{IV. Various degrees of reduction in circulating blood volume caused by I and II, above, initiate intermittent, prolonged, controlled shutting off of the arterioles of a selected series of tissues and organs.}

Each of these categories has its own set of associated phenomena and known and probable consequences.

There are many different kinds of blood sludges, and the known and probable kinds of injury, degree of these, and the rates at which any particular sludge damages an animal or man, depend to a great extent upon two sets of factors: (a) the as yet largely unknown chemical composition of the material or materials which hold blood cells together in clumps; and (b) the easily observable physical characteristics of the masses of which that particular circulating sludge is composed.

A very simple sludge is one in which all the red cells are in masses, all masses are approximately the same size when they are in vessels which do not compress them, every mass is sufficiently cohesive internally so that it does not break up as it passes through the peripheral arteriole-capillary-venule bottlenecks, and all masses passing through any one bottleneck are compressed and elongated to an equal degree. By definition we are calling these masses which do not break up as they pass through the bottlenecks the "basic masses" of a sludge, usually abbreviated to "the basics." If we call the resistance of a mass to distorting the "rigidity" of the mass, then the sludge designated above would be described as homogenous—one with no free red cells, all basics having the same size and rigidity.

In addition, there are mixed sludges of many kinds: those in which free, unagglutinated red cells are also present; those in which several sizes of basic masses are simultaneously present; those in which the largest basic masses continually act as temporary embolae, i.e. temporarily plug each and every arteriole they enter. The concentration of such large masses per cubic centimeter of blood determines, of course, the frequency with which every terminal arteriole of the body is temporarily plugged. The time during which any arteriole is temporar-
ily plugged, and the tissue it supplies receives no blood, 
often depends upon the rate at which the mass distorts to 
a spindle narrow enough to pass through the bottleneck, 
_i.e._ probably on the thixotropic properties of the mass 
(40). In addition, the plugged arteriole sometimes goes 
through slow, rhythmical contractions which may or may 
not compress the mass to a spindle.

There are sludges in which most basics are small, but 
larger masses come along at short or longer intervals, each 
permanently plugging whichever arteriole it enters. The 
damage done by these permanent plugs depends, of 
course, upon their numbers, their concentrations in blood 
at any one time, the particular tissues they happen to 
enter, and the summations of the lengths of time such 
masses enter small, isolated parts of organs. Such masses 
can, in relatively low concentrations, be utterly devas-
tating over a period of a few weeks, months, or years. 
One young woman referred to us from a psychiatric divi-
sion because she had a slightly elevated red cell sedi-
mentation rate in addition to her "functional" psycho-
logical disturbances had 8 small permanent plugs in the 
terminal arterioles of the bulbar conjunctiva of one side 
of one eye. They were in different stages of the familiar 
hemoglobin chemical disintegration color series. Every 
once in a while a slightly smaller mass came along, tem-
porarily plugged a vessel, and passed on again. Two weeks 
later the patient had three more similar permanent emb-
olae of terminal conjunctival arterioles. From the 
branching pattern of the aorta and the great arteries to 
the head, and the fact that the blood going to the eye 
comes directly from these, one cannot doubt that this 
woman's whole central nervous system was slowly 
showered with permanent plugs, each of which destroyed 
a small volume of irreplaceable nerve cells. When one con-
siders the parallelism between the known effects on nor-
mal persons of breathing slowly decreasing concentrations 
of oxygen (cerebral effects of anoxia), the slightly to 
greatly increased irritability, the euphoric tendency to 
laugh uproariously at meaningless trivia, the dull-witted 
phases, the compulsive behavior at times, and the coma-
tose condition as the anoxia approaches the lethal stage, 
and similar phases of some of the symptom complexes 
studied in mental hospitals, it is obvious that several 
groups of psychiatric patients now need to be studied to 
determine the role which sludge is playing or has played 
in their pathologic physiology. Oster himself pointed out 
that psychic disturbances can and do follow infectious 
diseases (43).

There are sludges composed of masses which repel each 
other slightly when they are in venules and sludges in 
which the basic masses come together slowly or rapidly, 
sometimes from relatively long distances, whenever the 
vein blood slows down or temporarily stops. These ag-
gglomerates we have been calling "charge aggregates," 
because the basics obviously exert force on each other 
from a distance.

There are sludges in which the masses, both basics and 
aggregates, are very sticky and hold together with various 
degrees of tenacity, as can be seen where streams of blood 
come together in small veins, setting up "couples" of force 
which produce torques tending to pull such masses apart. 
There are also sludges in which the masses seem coated 
with glassy, hard materials and display no tendency to 
adsorb to each other.

There are sludges in which the masses are bright red, 
in which case it must be presumed that little, if any, ma-
terial is between and around the red cells holding them 
together; and there are still other sludges in which the 
masses are pale pink and, when they bump each other, 
have as though a transparent invisible layer was around 
the red cells in each mass extending beyond the red cells.

I. All the sludges in which the masses are large and 
rigid enough to resist passage through the bottlenecks of 
the circulating system forcibly cause reduced rates of 
flow through all open vessels and thereby continually act 
toward reducing the rates of supply of oxygen to endo-
thelium, initiating and maintaining endothelial anoxia 
and its consequent inevitable, well-known permeability 
of the endothelium to blood plasma proteins (28-31). This 
initiates continuous loss of fluid from, and continuous 
heomoconcentration of, the passing blood and, if the lost 
fluid is not rapidly removed by lymphatics, edema of the 
surrounding tissues. Monkeys with the stiff Stage III 
'Knowlesi' malaria sludge often die mainly from this series 
of effects. This has been carefully recorded in motion pic-
tures (29). When these effects of forcibly reduced flow 
rates are of sufficient magnitude in the vessels of the con-
junctiva of ambulatory patients, the patients almost al-
ways have grossly visible edema of the feet and ankles 
when they stand or walk for a time. This is particularly 
noticeable in patients with rheumatoid arthritis.

In each patient in which these sludge factors are pres-
ent, they may, as far as we now know, be expected to 
operate in addition to any other known factors which 
may be increasing the rates of fluid loss through endo-
thelium. No human patient whom we have studied who 
had grossly visible edema during bed rest has failed to 
have large semirigid masses, visibly slowed rates of blood 
flow through the conjunctival vessels, different degrees of 
plasma loss through the walls of these vessels and of 
microscopically visible hemoconcentration, conjunctival 
edema, etc. As is well known, many human patients have 
various degrees of unexplainable edema, particularly of 
the ankles when ambulant, continually or for shorter or 
longer periods, for years. These can now be examined for 
sludges and their detectable effects.

In view of the recent excellent studies of O'Neil (42) on 
the anatomy and physiology of the small vessels in the 
walls of large vessels (the vasa vasorum) which are neces-
sary to nourish the tissues of the larger ones, and the role 
which stopping the blood flow through these small vessels 
plays in the damage of the lining of the large vessel, it is

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necessary to examine the possible roles of the sludges, which must forcibly decrease the rates of flow of blood through these small vasa vasorum, in initiating those pathologic histological changes found in human beings with arteriosclerotic disease, etc.

When all the masses of a relatively homogeneous sludge are sufficiently large and rigid, they resist passage through the peripheral vascular beds enough to cause death in a relatively short time, sometimes in experimental animals within 3 to 6 or, at most, 12 hours. Many of the details of this kind of death in monkeys have been carefully described and recorded in motion pictures taken through microscopes (29). Untreated, unanesthetized, unoperated monkeys with stiffly agglutinated Stage III Knowlesi malaria blood go into a slowly deepening coma state, ending in death in many instances within 24 hours. The heavily sludged blood of these animals could be studied by the phagocytes of the spleen, liver, or bone marrow. Depending upon the number of new red cells one assumes that this monkey might have made during that three-hour period, this experiment may be interpreted as demonstrating that the phagocytes of this monkey ingested and destroyed from one-fourth to one-third of all the animal's circulating red cells in three hours—the maximum rate of phagocytosis of coated blood cells thus far observed. Present experimental evidence does not permit quantitative estimates of the rates at which the phagocytes of these three organs can selectively remove clumps of, or perhaps even uncoated, agglutinated red cells from the bloodstream. There is the further problem of attempting to find which kinds of masses are ingestible, which not, and what factors limit the rates of ingestion of any particular set of pathologic processes (27).

Whenever these phagocytes ingest protein-coated red cell masses, each ingestion must remove a finite amount of protein from the circulating blood. The rapid ingestion of large numbers of red cell masses, each jacketed with a finite amount of protein, may be a major factor in the protein depletions which occur in many human hospital patients (27). If such jacketed masses contained specific immune proteins when phagocytized, this conceivably could waste large amounts of these exceedingly precious substances (4). If viruses attach to red cells in vivo, as Ernst (17) has found them to do in vitro, the ingestion of coated "red cell plus virus complexes" could be an important part of the defense against these organisms.

One limiting factor which would seem to prevent the phagocytosis of agglutinated blood cells from running an animal or man into hemorrhagic shock is the fact that the phagocytes which remove these masses from the blood are in the blood reservoirs, spleen, liver, and that with progressively decreasing blood volume the vasomotor system empties these organs and then sharply reduces the blood flow into them (27).

In rhesus monkeys with malaria and in traumatized frogs the masses of agglutinated red cells tend to settle out of the columns of moving blood mostly in those vessels which are vertical or nearly so and particularly in those nearly horizontal vessels in which the blood is running slightly uphill. This is the sedimentation of blood cell masses is now being actively investigated because the sedimentation and subsequent cementing together of large numbers of stationary agglutinated masses probably is a major factor in the formation of venous thrombi (cf. 5, 10, 18, 20, 34, 37, 41, 47, 52, 53).
Frequently in human beings after operations or during infectious diseases (5) large venous thrombi form in the big veins of the legs. These may be of the diameter of a person’s thumb and several inches long or more. Later, parts or all of such big masses break loose, pass up into the right heart, and enter the big arteries going to the lungs. Small masses plug small pulmonary arteries, causing pulmonary infarcts of various sizes. Large masses may fill the right heart or completely plug the pulmonary artery, causing instant death. This is an even more common cause of human death than had been suspected until recently (5).

By suspending a fan-shaped loop of intestinal mesentery of a frog in the vertical plane and sending a beam of light through the membrane into the objective of a horizontal microscope, it is possible to view the side of all the vessels in the mesentery and watch the effects of gravity on the masses of agglutinated cells in the moving blood of all these vessels. The operation must be done without losing any blood from the frog (27). The trauma caused by the laparotomy initiates formation of adequate amounts of sludge for study in this preparation. The masses of sludge passing through the vessels begin to settle in every vessel which is horizontal or nearly horizontal when certain very definite physiological and physical conditions are provided. The masses must be heavier than the fluid, and the rate of flow in the nearly horizontal vessels must become slow enough so that masses cannot be carried in suspension. The resistance of the sludge to passage through the bottlenecks frequently provides sufficient reduction in flow rates. There is probably a critical speed for each size of vessel above which the red cell masses are rolled over and over and up into the axial stream; below this critical rate of flow the masses settle, the largest first. Once this process begins, the bottom layer of masses stays relatively still, and the upper layers may roll along rather slowly. Thus, the effective cross-sectional area of the vessel changes from something which approximates a circle to something which approximates the upper two-thirds or one-half of a circle. In some preparations in frogs, the masses of settled agglutinated red cells remained free from each other even when packed tightly together for an hour or two. In other preparations those masses packed together in the bottom of a vessel slowly became cemented together into long, gelatinous masses (Fig. 1). The masses settle more rapidly if the animal has a low rather than a high red cell count. This is in strict agreement with the fact that blood cell masses sediment very rapidly in vitro in blood with low red cell counts. The rates of flow of blood through the frog mesentery vessels can be decreased by giving drugs which decrease the animal’s rate of heart beat. After a hemorrhage a frog shuts off the arterioles in many tissues (27). The rates of flow in small veins are thereby sharply decreased, in addition to the slowed flow already forcibly produced by the resistance of the sludge to its own passage through the bottlenecks. In animals in this condition the rates of settling of agglutinated masses in horizontal vessels are the fastest we have seen.

From the simple experiments described above and simple physical principles, it seems necessary to suspect that in many, and perhaps all, pathologic conditions in which blood cells are agglutinated, the masses tend to settle out of the moving blood stream and be deposited upon the bottom of almost every horizontal vessel of the body. Whether these masses stick to each other should depend upon their charge, degrees of stickiness, etc. Whether the whole long mass sticks to the vessel wall, or a layer of white cells on the vessel wall, must very much depend upon their current surface characteristics (6, 42).

Such simple experiments with thin vertical tissue and horizontal microscope, and variations of them, which can be easily made using mammals with defined pathologic conditions, should make it an easy matter to determine (a) all the circumstances under which the masses will settle in the circulating blood; (b) the conditions under which they will become cemented together into a thrombus; and (c) the effects of blood transfusions and drugs toward preventing such settlings and thrombus formations in the horizontal vessels.

IV. Many hospital patients have had large areas of conjunctival vessels tightly closed for long periods. Some have shown other evidences of prolonged vessel spasms, e.g. cold lower legs and feet of far-advanced tuberculosis patients. One would expect that the leakage of vessels and phagocytosis of blood cell masses should reduce the blood volume. This, of course, could not be determined by red cell counts or the use of dye methods. Dye methods cannot be expected to have meaning in patients whose vessels are leaking the proteins on which the dyes attach, for the
dye dilutes into tissue fluid and lymph as well as into blood. In order to see if controlled hemorrhage does initiate visible spasms of the conjunctival vessels, the blood and vessels of 34 blood donors, unanesthetized, unoperated relatives and friends of hospital patients, were studied before, during, and for 30 to 60 minutes immediately after each donated blood at the hospital blood bank. The experiment was made originally to identify and separate the mechanisms of traumatic shock, trauma without hemorrhage, in which thick sludge has always been present (25, 28) from detectable effects of hemorrhage without trauma (38). This method permits study of the vascular responses of healthy persons following almost no trauma (one stick with a large needle) but with large, controlled hemorrhage.

When a donor had lost not less than 300 and not more than 500 cc. of blood, first one set and then another of the blood pathways made up of arteries, arterioles, capillaries, postcapillary venules, and venules of the bulbar conjunctiva began to contract tightly shut, ejecting all their contents into the venous system. By the time most persons had lost 500 cc. of blood, large areas of the conjunctiva were completely white, only a few small, open pathways remaining. One muscular man was bled 800 cc., whereupon he began to sweat profusely—a common sign of an approaching “shock” condition. He had almost no visible vessels or blood left in the conjunctiva. At no time within the first hour did any intravascular agglutination appear in response to this degree of hemorrhage. 

In most persons large areas of the vascular system, including the capillaries, remained tightly shut for at least 30 minutes. This series indicates that decreased blood volume is alone a sufficient stimulus, when inhibitions and counterstimuli are not present, to initiate prolonged contractions of a variety of small human vessels and that the tissues they nourish may, in consequence, go without oxygen, glucose, etc. for considerable periods (3, 11, 15, 27, 30, 38, 49, 51).

When one considers the numbers of already observed pathologic conditions during which a sludge was present, the fact that many sludges could be expected to do at least small amounts of permanent damage to the body, the fact that these damages must be cumulative over a long period, and the pitiful mental incompetence of the prematurely senile and of many aged persons, it becomes obvious that we now need to begin to determine carefully how all the damages done to the body by sludges can summate to parts of the aging processes. In which different and overlapping combinations can the anatomical and physiological decrements caused by sludges, and readjustments to these, summate over periods of years? How rapidly can they add up over short periods? How do these factors cumulate along with other nonsludge factors in the various aging processes?

The observations, experiments, and deductions outlined above are evidence that the sludges provide a common, easily understandable set of factors whereby many diseases can damage the bodies of animals and man. Once great hope provided by these studies is that, as we learn how to keep blood normally unagglutinated and fluid, vessel walls intact, normal red cells from being destroyed, and adequate blood volume present, many effects of other pathologic mechanisms will stand out clearly, unobscured by the sludge mechanisms. Each will, of course, then receive the undivided attention it merits.

The sludges are now ready for study by all the intensive investigative methods our age affords.

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