The Journal of the American Medical Association

VOL. XXIII.

CHICAGO, JULY 28, 1894.

No. 4.

ORIGINAL ARTICLES

THE STRUCTURE OF BLOOD AND ITS RELATION TO PRACTICAL MEDICINE.

Read in the Section on Practice of Medicine, at the Forty-fifth Annual Meeting of the American Medical Association, held at San Francisco, June 5-8, 1894.

BY J. H. WYTHE, M.D., LL.D.

PROFESSOR OF HISTOLOGY AND MICROSCOPY, COOPER MEDICAL COLLEGE, SAN FRANCISCO.

Physicians have always realized the importance of the study of blood. The ancient Hebrews regarded it as the life of the body, or the meeting point of body and soul. The humoral pathology, first elaborated by Hippocrates, and which was the prevailing doctrine of all medical theorists for hundreds of years, gave great importance to the evacuation of the blood by the lancet, the scarificator, and the cupping glasses. So universal was this practice that it attracted the censure and witticism of the literary world, culminating in the immortal "Doctor Sangrado" of Le Sage. Many who are still living can remember the careful directions given respecting blood-letting—how it should be drawn by a full stream into a warm deep basin, so that it may be set aside to coagulate gradually. Then the appearance of the clot, and of the buffy coat, had much to do with the judgment of the physician. A soft and uniform clot indicates deficiency of fibrin, as in typhoid fever, etc. A uniformly great contraction shows a predominance of fibrin over red corpuscles, as in chlorosis. Blood highly buffed and cupped occurs in acute rheumatism and other severe inflammations. These, and similar aphorisms, were based upon observation of the general structure of the blood as seen by the naked eye. May it not be that the modern practitioner has gone too far in the opposite extreme?

With the invention of the microscope, the study of the blood has been greatly promoted. No part of the animal organism has been more frequently examined, and yet its true structure is but partially known. It may be said of the blood more than of any other histologic structure that there is no end to investigation and research. It has been examined under a variety of physiologic and pathologic circumstances and exposed to different physical and chemic conditions. It has been boiled and roasted and fried, and cooked in all sorts of menstrea, in the hope of torturing nature to reveal her secrets, and it has also been treated kindly and delicately with the same hope. Under such circumstances, the opinions of observers have naturally been different, and sometimes contradictory. Many of these discrepancies were due to the imperfection of early microscopes, and the almost universal habit of using too low magnifying powers. The optical improvements of the past few years have doubled our ability to penetrate the arcana of nature. The numerical aperture, or

standard measure of excellence, of the best objectives of eight or ten years ago was but .75 or .80 per cent., compared with 1.33, or 1.50 of our present lenses, or as a circle of three-fourths of an inch diameter compares with one of an inch and a half. With such improved power of research, nothing but lack of industry or care can prevent more accurate knowledge of minute structures. The delicacy of adjustment in our best objectives has also rendered more perfect mechanical appliances and optical accessories a real necessity. In addition to the widest possible numerical aperture in the objectives, the microscope of the future will have a wide-angled achromatic condenser with coarse and fine adjustments equal to those required for the objective itself, and with an iris-diaphragm for regulating the illuminating cone of light. No really critical work can be done without such provision. The images given with high powers and such appliances are so different from those of low powers in inferior instruments as hardly to be recognized as the same structures. It is certainly quite reckless to give testimony affecting human life based on observations made with inferior means.

The brilliant discoveries in bacteriology during the last few years seem to have eclipsed all purely histologic investigation, yet within a recent period microscopic examination of blood is assuming the importance which it deserves, and although it remains to a large extent an unexplored territory enough is known to justify its careful study by the practical physician as a guide both to diagnosis and treatment. To the young graduate, desirous of distinction, no more inviting field is open in all the realm of medical science. To tabulate the microscopic analyses of blood in different ages and diseases, with a comparison of clinical symptoms, will require years of labor, but will be a priceless boon to the medical profession.

When we speak or read of blood, it is natural to think of it as the red stream which courses through the arteries and veins, yet in strict propriety the fluid plasma, continuous with the lymph which bathes every tissue and organ of the body, is the real blood, conveying life to every cell and fiber, while the white and red corpuscles are incidental accompaniments, conveyed by the fluid blood for special purposes. Much has yet to be learned respecting the chemical and vital properties of the plasma, yet there can be little doubt that much of the immunity against zymotic diseases is due to these properties. Dr. Prudden has shown that serum and non-inflammatory exudations in the living human being possess a marked germicidal power, and this has been confirmed by several European observers.

This serum is not only a solvent for bacteria, but for other structures. In August, 1891, I published in the *Pacific Medical Journal* some observations of

the blood in a case of lymphadenoma, in which the red corpuscles were seen to dissolve in their own plasma, but after a month's treatment with iodid of iron and manganese, the corpuscles resisted dissolution. Sterling tells us in his "Histology" that the red corpuscles of a rabbit or guinea-pig are completely dissolved in a few minutes in the blood serum of a dog. The corpuscles of a frog or pigeon dissolve more slowly and their nuclei remain. The dog's serum loses this power after being heated to 50 or 60 degrees for half an hour.

In pathologic conditions, as relapsing fever, anthrax, tuberculosis, etc., the serum loses its germicide power, and bacilli may be found with the microscope, with or without staining.

Changes in the specific gravity may be found by using a single drop of blood in a mixture of chloroform and benzole. When it is just suspended in the fluid, the specific gravity of the latter is taken in the usual way and is the same as that of the blood. The specific gravity of blood varies with the proportion of hemoglobin in the red blood discs, so that this simple mode may be used in anemia, and so forth, instead of resorting to costly apparatus.

Changes in the acidity or alkalescence of the blood occur in various diseases, and the time of coagulation also varies. The solution of ptomaines resulting from decomposing bacteria is doubtless irritant or poisonous to the tissues, but the leucomaines which are formed by decomposing detritus, of the blood corpuscles or other albuminoid substances, unless eliminated by excretion, will lead to auto-infection, or an alteration of structure or function by a blood poison originating in the body itself.

Dr. Prudden well expresses the significance of the germicide power of serum in the living human being by saying that it consists chiefly in recalling "the attention of therapeutic adventurers from germicidal warfare to what appears to be a natural defense of the organism against bacterial invaders, namely, a healthy condition of the blood."

"Proud of our already long list of well-defined bacterial species; consciously masters of the morphology of many forms of bacterial disease; well on the way to an intelligent and efficient prophylaxis, and glorying in the possession of ptomaines so definite as to enter at our will into the composition of tangible and even formulatable metallic salts, it is a little humiliating, though doubtless salutary, to find ourselves face to face with a series of phenomena, which seem to lie at the very basis of the knowledge of the acute infectious diseases, and yet be able to say only that they are the result of the vital forces, vitality, life. It is fortunate that we have these words and phrases, however, which conceal so much and express so little, since, under their cover, we may take breath for the assault on another of Nature's tantalizing and well-fortified secrets."—*Microscopical Bulletin*, February, 1890.

The white corpuscles are found in lymph as well as in red blood. They are merely embryonic or detached particles of living matter of different sizes. With the best homogeneous immersion objectives, they appear as spherical or ovoid, but are often quite irregular in shape, and made up of a convoluted or sponge-like reticulum. They may have one or more nuclei which consists of a denser or finer network than the rest of the corpuscle. They have amœboid motions, by which they change their shape

and place from time to time. The conventional pictures repeated from one text-book to another give no adequate conception of them.

The white corpuscles are normally increased during digestion, and are in excess of a normal proportion to the red cells in a number of pathologic conditions, as typhoid fever, erysipelas, anemia, etc. In leukemia, the abnormal proportion is long continued and very marked, in some cases showing one white to ten or twenty red cells, or even greater proportion. Ehrlich has shown that the leucocytes or white cells are variously affected by certain aniline stains. In leukemia only he finds some which are distinctly stained with eosin, and calls them eosinophile cells. It was thought at one time that Ehrlich's method of staining would indicate whether the leukemia depended on disease of the lymph-glands, the spleen, or the medulla of the bones, but recent investigations have thrown doubt upon such discrimination, and Jaksch has found eosinophile cells in tuberculosis, in pneumonia and in anemia.

The red corpuscles normally are flat roundish discs with thick edges, so soft and flexible that they readily adapt themselves to the curves and angles of the blood vessels. They are of different sizes, not only in different animals but in the same animal. A few microscopists believe that by careful measurement of a large number of discs and comparing the average sizes, a discrimination may be made between the blood of one kind of animal and another. Some have made themselves ridiculous by testifying that they could distinguish the blood of a man from that of a woman. The consensus of opinion among prominent writers is that the size of the red corpuscles is insufficient for the purposes of medical jurisprudence. A view of the red corpuscles in the field of a modern microscope, with a power of 1000 diameters or more will show such a variety of size, above and below the average, as to render an accurate judgment doubtful.

As to the presence of a nucleus, or of an investing membrane in human red blood corpuscles, writers differ greatly, doubtless because of the imperfection of the instruments or reagents employed.

The protrusion or retraction of knobs, projections, or bead-like processes from the corpuscle has been often described, and termed "angular," "rosette" "stellate," etc. Brucke, Stricker and others consider the red corpuscle as really double, consisting of a stroma or matrix which is permeated by a softer or more fluid substance containing the hemoglobin, or coloring matter. Treatment with astringent solutions, as tannin, boracic acid, etc., causes these constituents to separate.

Klein, Heitzman and Flemming describe a fibrillar network in the nuclei of reptile blood, and others speak of fine radial filaments proceeding from the nucleus to the surface.

Elsberg, in Heitzman's "Microscopical Morphology," describes the examination of fresh human blood in a 40 or 50 per cent. solution of bichromate of potash, with a one-twelfth of an inch immersion objective, and a magnifying power of 1,000 diameters. He states that in a short time, indentations occur in the red corpuscle, producing irregular and stellate forms, which may persist or lead to separation by constriction of minute portions, or the corpuscle may become rounded again. After about half an hour protrusions of knobs take place, which may be again retracted or a pedunculated knob may be de-

tached. Sometimes several corpuscles unite, forming chains or compound bodies. Others appear with one or more vacuoles in their substance. In many corpuscles, a distinct reticulation is seen, with thickened points at the intersection of the filaments which, without careful focusing, might be mistaken for granules. Some of the corpuscles become pale, and mere rings or "ghosts," detached portions of which accumulate as detritus.

The reading of Elsberg's descriptions several years ago impressed me with the thought that such a variety of forms and activities indicated a corresponding variety in the structure and functions of the red corpuscles, and I instituted a series of experiments with analogous but even more complex results than those of Elsberg. The very best instruments were employed, as Zeiss's largest microscope stand, and the modern Van Heurck stand made by Watson. For objectives, I had Powell & Lealand's one-tenth apochromatic of 1.50 N A, the Bausch & Lomb H I one-eighth of 1.40 N A, a Gundlach's 1.20 H I, and several others. I used also an Abbe condenser or a Powell & Lealand's apochromatic condenser of 1.40 N A, together with the compensating eye-pieces of the latter firm. The magnifying powers varied from 900 to 3,000 diameters.

Various solutions were used in the examinations, as 1 per cent. solution of osmic acid, Flemming's solution, and 20 to 50 per cent. solution of bichromate of potash. The latter fluid gave most satisfaction. According to Rollett and Elsberg, bichromate of potash does not alter or seriously impair the living matter, but acts as a preserving medium, and enables us to trace normal development or natural degeneration. I found, however, that the alterations of the red corpuscles occurred sooner in strong than in weak solutions, so that some astringent action seemed due to the menstruum.

A small drop of blood was placed upon the cover-glass and quickly put on a drop of bichromate solution upon the slide. Blood from different persons and of different ages was examined, and although differences in amount and in time of alteration were perceptible, nearly all showed great irregularity in the shape of the red corpuscles.

Many of the corpuscles appeared as concentric rings in a flat disc around a central nucleus. Some showed protuberances around the edge, as if a semi-fluid substance had exuded, or had been squeezed out of the corpuscle. These protrusions differed both in size and number. By the use of the sub-stage condenser and oblique illumination, occasional glimpses of fibers radiating between the rings were obtained. The shape and size of the discs greatly varied. Many were round, but others were oval, square, triangular, finger-like, and sometimes branched, but nearly all exhibited traces of ring structure. Some were merely flat plaques or discs, notched at the edge; others were more globular. Many had irregular knobbed protrusions both on the edge and on the flat surface, as described by Elsberg. Many of these protrusions became detached, and some of them would remain at rest while others showed amoeboid changes of shape, and would rotate or move across the field of view in different directions. Portions of protruded semi-fluid substance would remain for some time attached to the edge of a disc, then with a vibratory or oscillatory motion would detach themselves and form independent masses, some stationary and other motile. Some were attached to the disc by a fiber or

thread, and often such a thread would bind several masses together. In one instance two masses pulled apart so as to form quite a lengthy fiber. In others the fiber formed a tail with serpentine motion or would entirely separate from the mass. Careful focusing showed some of these fibers to be really chains of small granules, many of which appeared as scattered detritus. So similar were these granules, isolated or in chains, to micrococci, that they would have been deemed such if they had not been seen in the act of stripping themselves from the edges of the viscid red corpuscles.

The result of my observations convinced me that the phenomena described were the result of a natural degeneration of the red corpuscles, hastened perhaps by the action of the bichromate solution. The variety in the appearances may be due to essential differences in the corpuscles themselves; differences which are both morphological and physiological. Considering the various offices which the blood performs in the animal economy, embryonic, nutritive, metabolic and excretive, we may reasonably expect the structure of the corpuscles to differ, and the effects of chemical and physical agencies upon them to be far from uniform. The more embryonic forms may not exhibit the fully formed structure, while those engaged in carrying away effete matter may be ready to disintegrate. Thus we may account for the variety in the appearance of the corpuscles and for the ready decomposition of some, while the structural integrity of others persists longer.

Under the name of poikilocytosis, some have described the irregular forms of blood discs occurring in debilitating diseases, especially in pernicious anemia. A large number of minute cells has given rise to the term microcythemia, and abnormally large cells to macrocythemia. Such terms are really unnecessary, and are but additions to a list of technicalities already too large. The varying appearances of decomposing cells, especially when the normal process is exaggerated by morbidly depressing influences can not be described by such terms.

One of the effects of the bichromate solution on the red blood corpuscle is to harden and contract the outer surface so as to wrinkle it in such a manner as to simulate the plasmodium malarie. This has occurred so many times as to throw doubt upon some preparations and observations. I have not been able to examine many specimens of malarial blood, but some European slides, stained after Ehrlich's method, and marked plasmodia can scarcely be distinguished from the wrinkling of the cell in the bichromate solution. The amoeboid and flagellate forms of the organism will afford proof of its presence, but an irregular vacuity in the cell is no proof.

As an example of the relation which such examinations of blood as have been described bear to practical medicine, reference may be made to an examination made by the writer some years ago, of the blood corpuscles in eighteen cases of beri-beri, which had been transferred from a Brazilian corvette to the Marine Hospital in San Francisco. A full account, with microscopic illustrations, may be found in the Annual Reports of the Supervising Surgeon-General at Washington. Specimens of the blood from each patient were sent to me, and examination showed that the red corpuscles were in various stages of disintegration. The ring structure of the broken cells and the resemblance of the detritus to micro-

cocci was evident. The clinical history of each case fully confirmed the microscopic examination, although the patients had not been seen and the slides of blood drops were merely numbered from one to eighteen. Acting upon the suggestions of the microscope, iron and quinin were given in large doses, with a generous diet. Under this treatment, the blood corpuscles of the patients speedily recovered their normal appearance, and in a short time all the seamen returned to duty. The surgeon in charge of the hospital (Heber Smith, M.D.), in his report to Washington, says: "It is possible that a microscopic examination of the blood of all the men on board the corvette before she sailed from Brazil, would have revealed just those members of her crew who were to suffer from the disease."

FEVER, AND THE RELATIONS OF MICRO-ORGANISMS TO THE DISEASE.

Read in the Section on Practice of Medicine, at the Forty-fifth Annual Meeting of the American Medical Association, held at San Francisco, June 5-8, 1894.

BY WASHINGTON AYER, M.D.

SAN FRANCISCO, CAL.

In the discussion of this question I shall assume the negative position. During the past ten years the medical mind has expended much of its force in the investigation of bacteriology, and no one in our country has more enriched the literature of this department of science than Dr. George Sternberg, and he is entitled to great consideration for the industry with which he has pursued his labors; yet I consider his efforts to be without practical results.

The subject of organisms is as familiar as household words and is filling the human mind with wonder, fear and amazement, and it is proper that the medical profession should pause for a season, take its reckoning and learn the true position it is occupying upon this question. We know much that was unknown to the founders of the healing art, and yet know but little of all that relates to the art and science of medicine; and the student at the close of his life-work will exclaim with Newton: "Alas! I have been but a child picking up pebbles upon the shore of the great ocean of truth!"

Like a dark shadow that creeps over a landscape, obscuring its beauty, transient causes stealthily invade the body until health vanishes into the gloom of disease with its true etiology unknown.

Fever is an important factor in nearly every form of disease, whether idiopathic or traumatic, and its various attendant phenomena can not be explained upon the germ theory, that microorganisms are the only true *materies morbi*. The ebbing of the tides of the ocean is influenced by planetary movements and changes, and so is lunacy, while the electric phenomena of the clouds and the seismic convulsions of the earth produce nervous prostration, fear and consequent disease.

Intelligence and learning are not evolved from any organisms, nor from light and heat, but spring into force and energy by individual application, and the maxim, *mens sana in corpore sano*, finds support in the world's philosophy and the sayings of men.

The different departments of learning belong to the different conditions of mind. We can not all think and reason alike, yet the healthy brain of the cadaver does not enable us to point out the specific differences in the quality and quantity of the minds of men.

Results of these conditions are the sequences of mental toil, as the harvest is gathered in by the strong arms of the yeoman and the charm of plenty fills the household.

So in the abstract does mental toil beget thoughts which enrich the world of learning and become our choicest companions, but the thinking and reasoning must be in the right direction to become profitable. Speculations mislead and error follows, and men of one idea cease to be useful.

"Nature is true to herself." Nature does not deal in fiction but in the great problems of reality, and the earnest medical student is willing to yield his life-work to add one more truth to human learning, still evolving and educating good, ever striving to relieve the sufferings of his fellow men.

While the literature upon the subject of fever is so great and so comprehensive as to appear nearly exhaustive, there yet lies much before us to be learned, and the physician who shall give to the world its positive cause and prevention will build to himself an enduring monument in the hearts and affections of the people, and they will be led upon the borders of the Utopia of human happiness by such a discovery.

Fever, in its generic acceptance, is an exalted or increased temperature of the blood coursing through the body, feeding the surface with accumulated heat as the result of friction and decomposition, and is attended with increased action of the heart, pain in the head and back, weariness in the limbs, a feeling of general exhaustion and great thirst.

By the increased heat of the blood the various functions of the viscera are changed, nutrition is interrupted and gradual decay follows, until the function of assimilation is restored to its normal condition by the slow processes of change in the multiple phenomena of life. Why the exaggerated mutations of temperature and restlessness are greater in one than in another person, in the same type of fever, is a subject which awakens a controversy in the minds of all diligent students of medicine. Here we may inquire what is the fuel, and where is the fire kindled that causes the increased temperature of the body, and why are not similar remedies always employed to extinguish this heat?

Were the theory of germs correct would they not continue to flourish, and why could not some germicide be employed to destroy the microorganisms at once, and place the patient on the highway to convalescence, and not allow him to waste away upon the bed of sickness for a period of three or six weeks?

When convalescence begins, does this change denote that the germs have ceased to proliferate, or that they have become alarmed at the fusillade of remedies that have been discharged into their ranks, and made their escape out of the mouth into the surrounding air to seek some new fields of operation and bring new subjects to the chamber of disease?

As all fevers have their periods of exacerbation, of pyrexia and anorexia, which may be determined at least twenty-four hours before their occurrence, what part of this program do the germs take? What are they doing during this interval? Are they waiting for some new neoplasm to spring up to feed upon?

Typhoid fever upon the Pacific coast is of a much milder type than is found upon the Atlantic seaboard, and, according to the Pasteur theory, the same class of typhoid bacillus is the *casus belli* here as there, when the body is invaded by the fever, and must be