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THE STRUCTURE
AND OTHER CHARACTERISTICS OF
COLORED BLOOD-CORPUSCLES

INVESTIGATIONS LAID BEFORE THE NEW YORK ACADEMY OF SCIENCES
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BY

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SYNOPSIS.

EXPLANATION OF ILLUSTRATIONS.

[Figs. 1 to 6 are included in Plate XII.]

Fig. 1, exhibits shape-changes of colored blood-corpuscles by indentation.

a, progressing and retrogressing furrowing.

b, indentations leading to irregular forms.

c, indentations leading to more or less regular forms.

d, instances of extreme and exceptional forms, especially the sharp-pointed stellated figure.

e, four phases of form-change, observed in one corpuscle, with separation of a constricted portion.

Fig. 2, shows knob-formation, principally by protrusion.

a, Nos. 1 and 2, progressive and retrogressive protrusion; No. 3, one pedunculated and three sessile knobs; No. 4, detachment of two knobs.

b, protrusion of knobs at the periphery and on the surface; in No. 3, the knobs surround the whole body of the corpuscle; and in No. 4, they are still more numerous.

Fig. 3, shows coalescence of two or more corpuscles, giving rise to chains and irregularly shaped compound bodies, with the net-work structure visible.

Fig. 4, represents vacuolized corpuscles.

In the upper line are seen three corpuscles, each with a differently sized central vacuole; in the middle line, the first figure shows three vacuoles in one corpuscle; these vacuoles are represented in the second figure to be close together, and in the third figure, the separating walls of apparently five vacuoles have broken down, and one irregularly shaped larger vacuole is seen. The lower line shows the appearance of vacuolized corpuscles seen on edge.

Fig. 5, shows the structure of five colored blood-corpuscles.

In the first, there is seen an encircling band of uniform thickness, in which are inserted numerous threads of a net-work; a number of knots are in the interior, which are seen to be the points of intersection of threads constituting a net-work; in the lower portion of the disk there is a larger knot, which may be called a nucleus. In the fifth corpuscle the complete net-work structure is best seen; in this corpuscle there is seen at the periphery, instead of an encircling band, a number of knots united by threads, having the appearance described as beads, each a little separated from its neighbors on the string. The second corpuscle shows the net-work and encircling band, as the majority of corpuscles show them. In the third, a lighter band is seen, and an irregular flap, produced by either indentation, or protrusion, or both. The fourth exhibits a large flap or knob at its lower portion, with a stretched or extended net-work.

Fig. 6, shows the final phases of colored blood-corpuscles treated with an appropriate solution of bichromate of potash.

In the upper left-hand figure there is a double-contoured ring, with irregularly massed matter and a central vacuole, showing traces of a net-work; in the lower right-hand figure this is less distinct; and in the two lower left-hand figures are represented two so-called "ghosts;" above these there is detritus, *i. e.*, two or three detached portions; and to the right-hand upper figure there is attached a mass which has apparently been extruded.

Fig. 7 (see p. 46), is a schematic drawing to illustrate the state of rest of the net-work; Fig. 8, illustrating the state of contraction; Fig. 9, that of extension; and Fig. 10 (see p. 47), that of layer-formation.

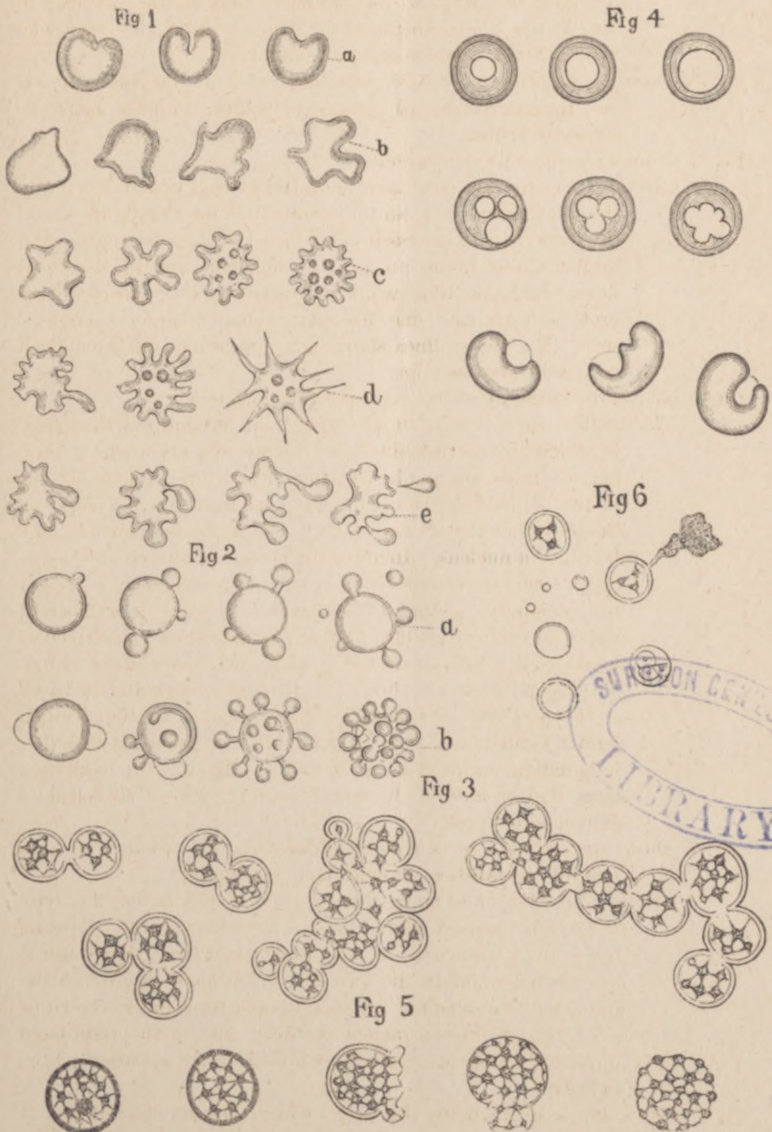
Fig 1
a
b
c
d
e
Fig 2
a
b
Fig 3
Fig 4
Fig 5
Fig 6

THE

STRUCTURE OF COLORED BLOOD-CORPUSCLES.

[From the Annals of the New York Academy of Science.]

The discovery of red corpuscles in the blood was one of the first results of microscopical study, over two hundred years ago. Since that time no other constituent of the body has been more frequently examined. Nevertheless, the structure of colored blood-corpuscles has not heretofore been ascertained.

I.

The examination of a small drop of fresh human blood, mixed with a drop of a from 40 per cent. to 50 per cent. saturated solution of bichromate of potash, and highly magnified,[1] reveals in the course of a few hours the following:

Perhaps the first thing noticed, is that the colored corpuscles vary in size.

Having made a number of measurements,[2] I can state that in every person's blood that I have examined, there are some as small as, or smaller than, the $\frac{1}{3875}$, and in nearly every person's some as large as, or larger than, the $\frac{1}{2767}$ of an inch in diameter (*i. e.*, .00655 and .00917 Mm.), with transitional sizes between these. The extremes are sometimes not met with in

(1) My investigations were made with a 1-12 immersion objective, manufactured by Tolles of Boston, and a No. 12 immersion made by Vérick of Paris, either of which with the eye-piece that was used, magnifies about 1090 times. An exceedingly thin cover having been oiled near the edges, the drop of blood obtained from a pin-prick in the palm of the hand, and transferred on a slide is mixed with a drop of the solution previously prepared, covered, and without delay placed on the microscope stage By a 50 per cent. saturated solution, I mean a saturated solution diluted with an equal quantity of distilled water; by a 40 per cent., one containing three-fifths water; by a 60 per cent., one containing two-fifths water, etc: I always prepare a saturated solution, and then dilute.

(2) I used with the Tolles' lens, and central illumination, in the eye-piece a micrometer-scale ruled with great exactness by Grunow of New York, each division of which was ascertained by the Standard Stage Micrometer of Rogers, N. S. No. 3, belonging to Mr. Fred'k Habirshaw, of New York, to measure, with the objective, eye-piece, and cover-adjustment employed, a 1-15,500, and each sub-division a 1-77,500 part of an inch.

each field of a drop, nor even in every drop of a person examined; but I have not found any adult of either sex, from whose blood the smaller extreme was absent, and only *very few* without the larger. I have repeated the measurements of blood-corpuscles without the addition of the reagent—both with and without oiling the edges of the covering glass, *i. e.*, with and without preventing the ordinarily rapid evaporation—with practically the same results; drying of course contracts blood-corpuscles,and corresponding variations are observed. Some of the disks are in outline not perfectly circular; by measuring the largest diameter of the largest, and the smallest diameter of the smallest disks, the extremes I have met with in one and the same specimen of human blood, are, as to the smallest, about the $\frac{1}{6000}$, and as to the largest, the $\frac{1}{2500}$ of an inch (*i. e.*, 0.00422 and 0.01016 Mm.). If the detached globules which I shall describe, be counted as blood-corpuscles, there are even still smaller ones. In each specimen of blood, the majority of red corpuscles, however, are of about one size, which differs in different specimens, but is most frequently between the $\frac{1}{3875}$ and the $\frac{1}{3100}$ of an inch (.00655.—00819 Mm.), or somewhere about the $\frac{1}{3370}$ of an inch (.0075 Mm.). The calculated average of the size of the red corpuscles in a drop, *i. e.*, the arithmetical mean of the measurements, is usually a little higher than the size of the majority of the corpuscles.

A very few, especially the smallest, but occurring exceptionally also among the larger, seem more or less globular; all others are bi-concave disks, the periphery being more shining and thick than the central portion.

So-called " rosette " and " thornapple " forms may be seen, either immediately or in the course of a little while. I have often watched the individual corpuscles while these forms, and many others, were being produced; and in Part III of this communication, I shall offer an explanation of their production.

Concentrating our attention upon the shape of the circular disks, we soon find that the round outline of a few (and the same is at times also true of the smooth surface), begins to be made irregular at one or more points. This occurs in either of two ways, viz.: by indentation and by protrusion: sometimes the one, sometimes the other, first takes place; frequently both appear in different corpuscles, at about the same time; occasionally both are met with in the same corpuscles; in different preparations either the one or the other predominates.

Firstly:—In from fifteen minutes to an hour, a very slight indentation may appear, and gradually deepen, so that the corpuscle be nearly cleaved through; then the clefts may gradually become shallower, so that again a mere indentation is seen; finally, even this may disappear, and the corpuscle be rounded again (see fig. 1, a.). Division into two separating halves, I have never observed under these circumstances, although I have often watched for it. The furrow of every corpuscle that I have caught nearly cleaved through, either remained stationary, or usually, retrogressed to a greater or less extent. The retrogression may stop at any point, and the furrowing again increase; and this going and coming of a cleft, though taking place slowly, may continue for some time, and then stop at any stage of indentation. Sometimes indentations appear at two or more points of the same corpuscle, and in their progress give rise to a great variety of angular, regular and irregular "rosette," "scolloped," "crenated," "thornapple," and "stellate" forms (see fig. 1, b, c, d.). The sharp pointed ends seen in the last figure of d are the extremes met with and exceptional; usually the ends are plump and rounded). These forms, as well as those of single cleft, after changing backward and forward, either persist or become finally rounded off to a greater or less degree; in some cases constriction of portions more or less minute occurs, with separation following constriction (see fig. 1, e). Sometimes constricted portions remain attached for a long time by a more or less long and slender pedicle. Transitionally or permanently, in any of the cases mentioned, the most curious and grotesque shapes may be met with. In the cases, too, of constriction and separation, the corpuscle, with the portions attached and unattached, sometimes gradually becomes rounded off so as to look like a parent globule surrounded by a number of little ones.

Secondly:—Usually in the course of half an hour, the protrusion of little round or roundish, more or less light colored knobs takes place. At first, only very few corpuscles show knobs, and the knobs are extremely small, and few in number, say only one, or at most two or three, on a corpuscle; but in the course of an hour or two, more corpuscles protrude knobs, more knobs are protruded from one corpuscle, and the knobs grow larger (fig. 2, a, Nos. 1 and 2). Occasionally a knob is drawn in again, and the former contour re-established. In some instances protrusion and retraction occur repeatedly, so that knobs appear and disappear, or become larger and smaller, very slowly, but repeatedly for some time. Occasionally a knob is pedunculated, and sometimes becomes detached from the corpuscle, while on the other hand some knobs are quite sessile (see fig. 2).

I have measured portions detached in either of the two ways described, and found them to vary from the $\frac{1}{30000}$ to the $\frac{1}{7500}$ of an inch (.00084–.00338 Mm.). All except the very largest may usually be seen in constant oscillatory (molecular) movement, and, unless entangled between larger stationary corpuscles, easily moving across the field (the latter probably caused by minute variation from absolute equilibrium level of the microscope stage).

In some dentated or so-called "mulberry" forms, knobs or small eminences protrude from the face of the disk, which may give to the inexperienced observer the impression of internal granules; but proper focussing corrects this impression, and shows the knobbed surface (fig. 2, b).

In addition to the protean changes in shape initiated by indentation and protrusion, there are still others occasionally met with, due to combination or coalescence of two or more corpuscles. In the course of twenty-four hours or more—though this occurs in by far the smaller number of preparations of blood examined—two or more adjacent colored blood-corpuscles may, with a larger or smaller portion of their periphery, unite and form compound bodies, sometimes chains or other strange shapes (fig. 3).

Almost immediately on being ready for examination, a very few colored blood-corpuscles show a light central vacuole. In the course of the examination, a number of vacuoles, either of different sizes, or all of the same size, may appear in a corpuscle. Usually, a vacuole is round or roundish, but it may assume various irregular forms,—some of which, may perhaps have resulted from a union of several, and the breaking down of the separating walls, (see fig. 4. The three lower figures show appearance of vacuolized corpuscles seen on edge). Vacuoles sometimes persist and sometimes, after a longer or shorter continuance, suddenly disappear. They are either empty, or else contain one or more granules.

Soon after the corpuscles are studied, sometimes from the first, a difference is noticeable as to the intensity of their coloration : some are paler than others. Gradually a larger number of corpuscles becomes pale, and the degree of paleness, too, increases. There is a great difference in respect to the rapidity of "paling" of colored corpuscles, in blood taken from different persons, even in blood of the same person taken at different times, and with different strengths of the admixed solution of bichromate of potash.

Usually, in blood of healthy persons, examined as I have described, in about an hour from the time the drop of blood is placed on the slide, a few of the corpuscles that are least deeply colored appear to have become somewhat granular in their interior. Focussing shows that this is not the optical illusion alluded to in the case of knobbiness of the surface.

Soon the granules or dots seem more distinct; short conical thorns, or more delicate spines, appear to issue from one or two of the largest of them; and, on close inspection and focussing, some appear to be connected by irregularly concentric filaments. In the course of five minutes more, a complete network is distinctly seen in the interior of one or more corpuscles, and what at first appeared to be granules, turn out to be thickened points of intersection of the threads forming this reticulum. These points or dots are irregularly shaped, and vary in size (see fig. 5). Radiary threads of the network terminate at the periphery of the corpuscle, either with thickened ends connected by threads—giving an appearance of unevenness to the outer boundary, as though it were constituted by a wreath of beads, each bead separated from its neighbors on the string—or, far more frequently, with terminal points lost in an encircling band of a uniform thickness, often greater than either the interior threads or most points of intersection (compare Nos. 5 and 2 of fig. 5). From this appearance, as well as that of the so-called "ghosts," to be presently described, it is not to be wondered at that careful observers have ascribed to colored blood-corpuscles the possession of an investing membrane.

As the "paling" progresses, an increasing number of corpuscles shows the interior network, essentially as I have just described, and identical in construction with the network discovered by C. HEITZMANN in Amœba, colorless blood corpuscles, and other living matter of the body—("*Bau des Protoplasmas,*" *Sitzungsberichte der Kaiserlichen Akademie der Wissenschaften zu Wien*, vol. 67, division III, p. 100. *Vorgelegt in der Sitzung am* 17ten April, 1873)—a discovery which I have communicated to the American Medical Association more than three years ago.[1]

Gradually an interior network structure becomes visible, in nearly all the corpuscles in the field except the smallest, which appear more or less compact; and, occasionally a cor-

(1) "Notice of the Bioplasson Doctrine." Transactions of the American Medical Association, vol. XXVI (1875), p. 157.

puscle is met with having a central, or slightly excentric, dot of such relatively large size that it might be interpreted as a nucleus (see No. 1 of fig. 5).

Some movement takes place in the network; for sometimes the threads change in length, and perhaps in thickness, and the dots change their position and their size.[1]

In the course of another half hour or hour, the network becomes less distinct in the palest corpuscles; and in these gradually fades away. Then, for some time, the network remains visible in nearly all corpuscles except those that are too pale or too small: vacuoles, one or more, appear in many of the latter; while the former occasionally show indications of irregularly massed matter in their interior, though usually nothing is seen of them but double-contoured rings which have been called their "ghosts" (see fig. 6). During this time, also, a quantity, sometimes rather large, of detritus accumulates.

It appears as though the network is most plain in corpuscles that have suffered either not at all, or but little, from detachment of a portion of their substance. The active changes of indentation and protrusion have usually disappeared in a large number of corpuscles, by the time "paling" has sufficiently progressed to render the interior structure visible. As before stated, some corpuscles permanently retain scalloped and knobbed forms, while the majority are finally more or less rounded off; but the play of changing shape of many corpuscles is going on at the same time that this network is seen.

After a while, further "paling" stops, and the network structure of all corpuscles which show it, remains visible indefinitely long.

Blood-corpuscles, from hemorrhage in the bladder, in the

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(1) To make sure of the occurrence or non-occurrence of this movement, I used the micrometer scale, and, having, with great precaution as to entire rest of the microscope and the specimen, fixated by lines the position of the dots and length of the threads, the changes of position, size, and length became unmistakable.

urine of the late Dr. H****y, preserved with some bichromate of potash, still show the network after three years.

Specimens of blood taken from different individuals exhibited all the phenomena described, but with some slight differences among each other as to the order and time of appearance.

A 40 per cent. saturated solution of bichromate of potash, admixed with the blood, was found entirely satisfactory for the demonstration of all the phenomena; and some variation of strength, *i. e.* between the limits of a 35 per cent. and a 50 per cent. saturated solution, made no appreciable difference.

Of other solutions of bichromate of potash, it is sufficient to state the following:

With a 30 per cent. saturated solution, the phenomena are also to be seen, but appear more slowly, and quite a number of corpuscles usually remain more or less unpaled.

With a 20 per cent. saturated solution, the changes proceed still more slowly; comparatively few indentations occur; the network of the majority of corpuscles is visible after the lapse of 24 hours, but many remain entirely unaffected.

With a 10 per cent. saturated solution, vacuolization appears, also a little changing indentation and protrusion, but not sufficient "paling" to render the network visible even after several days.

With a 60 per cent. saturated solution, the majority of the corpuscles had already become pale by the time the specimen was in place for examination. Some showed interior network, some only double-contoured rings. Protrusions were seen, especially in the corpuscles not much paled; in one instance, a pale ring was also seen with a large pedunculated protrusion (fig. 6). During two hours, changes of scalloping and of knobs took place faster than is usual with blood mixed with a 40 per cent. or 50 per cent. saturated solution, but they could not be followed so distinctly. Extreme paling rapidly proceeded and much detritus filled the field, with only very few compact globules.

With a 90 per cent. saturated solution, the process of scalloping was completed in 20 minutes; and in 30 minutes a network was visible in a few roundish corpuscles, surrounded by masses of granular detritus. In addition, a large number of "ghosts" could be seen. Here and there a "ghost" would show a faint network.

With a saturated solution added undiluted, the network was after one hour visible in some corpuscles, but most of them were destroyed; of a few left intact, some looked homogeneous, and some vacuolized. The field was full of faint double-contoured rings, and a large quantity of granular detritus.

The network structure of colored blood-corpuscles is visible also in anatomical preparations which have been kept for a length of time in Müller's fluid (Bichromate of potash 100 parts, sulphate of soda 50 parts, and water 1000 parts).

In some of my examinations, especially the earlier, I used the heated stage; but as the phenomena described were seen at the ordinary temperature of a well-warmed room, I deem it best not to say anything here of variations of temperature.

I have made some micro-spectroscopic observations of blood, which I shall detail in another connection.

In this communication I omit the mention, also, of the remarkably varying amount of fibrine threads seen in different preparations of blood; nor do I enter at length into the question of "detritus formation," or as whatever else one may interpret the appearance in the field of an increasing number of free granules, and granular masses or plaques.[1] On both of these subjects, my Note-book relating to observations extending over two years, contains "minutes."

In addition to human colored blood-corpuscles, I have examined those of lower animals. Essentially the same intimate structure as that which I have described exists in all. As ex-

(1) Max Schultze, who saw some of these granules and granular plaques in healthy blood, prefers the designation "granule formation," as being non-committal.—*Archiv für Mikroskopische Anatomie*, vol. 1, p. 38.

amples, I will quote from my Note-book a few words referring to the examination of the colored blood-corpuscles of the ox and the newt—the one an example of the unnucleated, the other of the nucleated corpuscles.

A drop of fresh ox blood, mixed with a 50 per cent. saturated solution of bichromate of potash, and highly magnified (Tolles' $\frac{1}{12}$ immersion) exhibited, within 20 minutes, vacuolization beginning in several red corpuscles. Within 40 minutes, knobs were protruded, though not copiously. In the course of an hour, "paling" proceeded regularly, so that the network became visible in some, and within two hours, in a large number, of the corpuscles. After three hours, the network, the Note-book says, was very distinct in many corpuscles, with some detritus and a few "ghosts." Twelve hours later, about one-half of the whole number of corpuscles showed the reticulum, while the other half were either vacuolized or unchanged. No further change was observable for two days. After the third day, some few corpuscles, perhaps, that had not shown the network structure before, now did; but the paled ones had become too pale to do so, except a very few which showed it finally. The rest had become "ghosts," with much detritus. A week later, nearly all the corpuscles that had exhibited the network had become "ghosts," only in a very few of which, faint traces of the reticulum could be made out. The rest were still unchanged, as on the first day and remained so as long as the specimen was kept.

The red blood-corpuscles of the newt, examined in a 50 per cent. saturated solution of bichromate of potash, into which a drop of the blood from the freshly cut tail had been allowed to fall, presented peculiar changes of shape, consisting mainly in contractions of the body around the nucleus.

The nuclei always exhibited the network structure, either perfect, and more distinct than in specimens unmixed with the solution, or, when the nucleus was swelled to double or treble its original size, with the network torn. Just as in the case of the colorless corpuscles, there were seen two kinds of red corpuscles, finely granulated and coarse granular, the granules always being the points of intersection of the threads of the network. In both kinds the body as well as the nucleus exhibited the reticulum structure. The network of the body and that of the nucleus were connected by fine threads passing through the nuclear envelope. In many instances the body was reduced either to two polar flaps, bulging from each side of the nucleus, or to one flap, more or less colored, at the side of the nucleus; in other instances, it was uniformly contracted around the enlarged nucleus.

Many colored corpuscles contained vacuoles, in varying number, which were either empty or traversed by an exceedingly delicate, apparently stretched, reticulum, or else contained irregular accumulations of matter with remnants of the network.

II.

My observations as to amœboid movements of colored blood-corpuscles, as well as to varieties of size and shape,—observations which were really only incidental while investigating the structure, the main object of my researches,—have been anticipated by previous investigators. One saw and reported as an extraordinary finding, one or more forms or active form-changes like those I have described, another others; some a far greater number than I. "*Fehlt leider nur das geistige Band.*" The band which connects and explains the phenomena observed is the discovery of the structural arrangement.

In the following historical sketch of points bearing on my observations, I shall refer to a few only of the legion who have made colored blood-corpuscles the subject of their investigation.

More than a hundred years ago, *William Hewson*, after asserting that the red corpuscles are of different sizes in different animals, added: "I have likewise observed that they are not all of the same size in the same animal, some being a little larger than others,"[1] etc. Hewson's editor, *Gulliver*, who has made a very large number of measurements of red blood-corpuscles of different animals, and is "our highest authority upon the subject," said of his own elaborate tables: "We are only speaking now of the average size, for they vary like other organisms; so that in a single drop of the same blood you may find corpuscles either a third larger or a third smaller than the mean size, and even still greater extremes;"[2] and more recently,[3] "But as I have long since shown, the corpuscles in one species of the vertebrate class as seen in a single individual thereof, vary so much in size that their average dimensions cannot be determined with absolute precision; and were this fact kept in view much needless discussion might be spared."

Beale, also, long ago called attention to the fact that "corpuscles may be found which are not more than the fifth or sixth of the size of an ordinary blood-corpuscle."[4] Again: "the red corpuscles vary in size, and more than is usually supposed,"[5] and again: "It is generally stated that the red blood-corpuscles of an animal exhibit a certain definite size; but it will be found that they vary extremely, so that corpuscles exist of various dimensions."[6]

Welcker[7] found in the blood of Dr. Schweigger-Seidel colored blood-corpuscles as small as .0051, and as large as

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(1) Philosophical Transactions, vol. 63, Part 2, p. 320 (Read June 24, 1773). The works of William Hewson, F. R. S., Edited with an Introduction and Notes, by Geo. Gulliver, F. R. S. London. Published by the Sydenham Society. 1846 : p. 234.

(2) "Lectures on the Blood of Vertebrata." *Medical Times and Gazette*, vol. II of 1862, p. 157.

(3) "Comparative photographs of blood-disks." *Monthly Microscopical Journal.* November, 1876. p. 240.

(4) Archives of Medicine, vol II (No. VIII.) p. 236, and *Quarterly Journal of Microscopica Science.* April–May,' 1861 ; p. 249.

(5) "Observations upon the Nature of the Red Blood-Corpuscle." Transactions of the Microscopical Society of London (Read Dec. 9, 1863) vol. XII., N. S., p. 37. *Quarterly Journal of Microscopical Science*, Jan., 1864.

(6) The Microscope in its Application to the Practice of Medicine, 3d Edition. Republished in Philadelphia, 1867 ; p. 170.

(7) "Grösse, Volum und Oberfläche und Farbe der Blutkörperchen bei Menschen and bei Thieren." Zeitschrift für rationelle Medicin, S. III, vol. XX. (1863), p. 237.

.0085 Mm. Altogether, the minimum measurement recorded in his table is .0045 Mm., and the maximum, though not in the same specimen, .0097 Mm. He remarks: "I have always, both in animals and in man, found the transverse diameter of the blood-corpuscles of one and the same individual vary from $\frac{1}{4}$ to $\frac{1}{3}$ of the mean measurement; and it appears that all the sizes lying between the two extremes are present in tolerably equal numbers, with the exception of the smallest corpuscles, which occur for the most part singly and at intervals."[1]

Max Schultze distinguished in his own and other persons' healthy blood two forms of colored corpuscles, viz.: globular and disk-like; the globular, few in number, vary from .005 to .006 Mm. in size; and from these there are gradual transitions to the ordinary disks, which measure from .008 to .010 Mm.[2]

The smallest colored corpuscles which *Klebs* reported[3] having found in his own blood, varied from .0058 to .0066 Mm.; but in blood from the corpse of a leucæmic child he observed a few as small as .00416 Mm.

Woodward said: "The truth is that not only do the individual corpuscles in every drop of blood vary considerably in size, but as might be anticipated from this very fact, the average size obtained by measuring a limited number of corpuscles (50 to 175, still more in the case of but 10 to 50, as usually practiced) varies considerably, not only between different individuals, but also between different parts of the very same drop of blood." Both the maximum and the minimum which he found—viz.: the 396 millionths and the

(1) Cited by *Woodward* "On the similarity between the Red Blood-Corpuscles of man and those of certain other animals, especially the dog; considered in connection with the diagnosis of Bloodstains in criminal cases." *American Journal of Medical Sciences*, Jan., 1875. *Monthly Microscopical Journal*, February 1, 1875, p. 69.

(2) "Ein heitzbarer Objecttisch und seine Verwendung bei Untersuchungen des Blutes.' Archiv für Mikroskopische Anatomie, vol. I. (1865) p. 35.

(3) "Ueber die Kerne und Scheinkerne der rothen Blutkörperchen der Säugethiere." (Virchow's) Archiv für pathologische Anatomie and Physiologie und für Klinische Medicin: vol. XXXVIII, (1867), p. 195.

216 millionths of an inch, or .01005 and .00548 Mm.—were present in the same field of one drop.[1]

Berchon and Perrier[2] state that the colored blood-corpuscles of the fœtus and the newly-born are on an average smaller than those of adults. The extremes given are minimum .0031 to .0062 Mm. and maximum .0091 to .0093 Mm.; but they do not mention that the extremes occurred in one and the same case. More recently, Perrier[3] measured blood-corpuscles of 35 individuals of different ages, and found that those of .010 Mm. were very frequent in the first days after birth, while later they occurred much more rarely. After the first year, blood-corpuscles measuring .0093 Mm. were rarely present in greater proportion than 10 in a hundred; and in adults often absent. Such of .0043 Mm. occurred most often in the aged and in children. The diameter of the great mass at every age varies from .0050 to .0087 Mm.; within these limits, those of .0075 Mm. are most frequent and never absent. The form of the smaller is more or less globular; the larger are flattened.

According to *Hayem*,[4] the red blood-corpuscles in the newly born are much less uniform in size than in adults; corpuscles larger than the largest and smaller than the smallest adult corpuscles occur comparatively often. The size varies between .00325 and .01025 Mm. Hayem also calls attention[5] to the still smaller ones—measuring only .002 Mm.—which he considers young and growing blood-corpuscles, so called hæmatoblasts. He asserted having observed all transition sizes between these and the largest. He

(1) "The Application of Photography to Micrometry, with special reference to the micrometry of blood in criminal cases." Transactions of the American Medical Association, vol. XXVII. (1876), p. 303-315.

(2) "Note sur les globules du sang chez le fœtus." Bordeaux médical., p. 123 and 237; Canstadt's Jahresbericht for 1875, I., p. 46.

(3) "Sur les variations du diamètre des globules rouges du sang dans l'espèce humaine, au point de vue de l'expertise légale." Compt. rendus, tom. 84 (1877), No. 24, p. 1404.

(4) Des caractères anatomiques du sang chez le nouveau-né pendant les premiers jours de a vie." Compt. rendus, tom. 84 (1877), p. 1166.

(5) "Sur la nature et la signification des petits globules rouges du sang." *Ibid.* No. 22 p. 1239.

found hæmatoblasts increased whenever under physiological or pathological conditions a reparation of blood occurs, *e. g.* he found them more abundant in children than in adults, and more abundant during menstruation, and after losses of blood, also during reconvalescence after acute diseases.[1]

Netsvetzki reported[2] having found minute corpuscles moving in all directions, as constant constituents of normal human blood. [Although my observations as to the diversity of size of colored blood-corpuscles refer to healthy blood, I will not omit to mention here that *Vanlair* and *Masius*, having, in the blood of a patient who had symptoms of interstitial hepatitis, found a number of small globular corpuscles, gave them the name of microcytes, and called the patient's disease "microcythæmia," which they considered to be a peculiar alteration of the blood.[3] Cases of so-called microcythemia have since been reported by *Litten*, in a tuberculous individual;[4] by *Osler* in pernicious anemia[5]; and by *Lepine and Germont* in cases of cancer of the stomach. *Soerensen* distinguished in disease between Oligocythemia, in which the number of red blood-corpuscles is diminished, Achroiocythemia, in which their richness in coloring matter is diminished, and Microcythemia, in which their size is diminished. In a case of chlorosis observed by him, the average size of the colored corpuscles was

(1) "Note sur l'évolution des globules rouges dans le sang des vertébrés ovipares. Compt. rendus, tom. 85, No. 20, p. 907-909. "Sur l'évolution des globules rouges dans le sang des animaux superieurs (vertéb. ovipares) *Ibid.*, No. 27, p. 1285.

(2) "Zur Histologie des Menschenblutes. Kleine sich nach allen Richtungen hin bewegende Körperchen als constante Bestandtheile des normalen Menschenblutes" Centralzeitung für die Medicinischen Wissenschaften, 1873, No. 10.

(3) De la Microcythemie, Bruxelles, 1871 ; 101 pp.

(4) Aus der Klinik des Herrn Geh. Rath Prof. Frerichs "Ueber einige Veränderungen rother Blutkörperchen." Berliner Klinische Wochenschrift ; 1877, No. 1.

(5) "Ueber die Entwickelung von Blutkörperchen in Knochenmark bei perniciöser Anæmie." Centralblatt für die medicinischen Wissenschaften ; 1877, No. 28 ; 1878, No. 26.

(6) "Note sur la presence temporaire dans le sang humain d'un grand nombre de globules rouges tres petits (microcytes)." Gazette medicale de Paris ; 1877, No. 18, pp. 218 and 219 ; and "Note relative a l'influence des saignées sur l'apparition dans le sang humain d petits globules rouges (microcytes)." *Id.* No. 24, p. 296.

found to be only .0045, instead of the normal .006 to .0075 Mm.[1]

Hicks[2] found in the fluid from an ovarian cyst, small transparent colorless globular bodies which had been detached from red blood-corpuscles, and which were of a diameter of about the $\frac{1}{10000}$ of an inch.

Laptschinsky reported[3] finding very small corpuscles, only $\frac{1}{3}$ as large as the normal ones, in conditions of the body accompanied with high fever, especially in infectious diseases.

Hayem has come to the conclusion[4] that in anemia the blood-corpuscles are in general smaller than in normal conditions; but that the extremes which are met with are greater, viz. .0022 and .010 to .014 Mm.

Piper found in a case of "ulcerated scrotum and inflamed testicle, with apparently tuberculous deposit in the gland," "on one and the same slide, specimens which measure $\frac{1}{4085}$ of an inch; while on other parts of the same slide alike extensive fields of corpuscles which measure only a fraction less than the classic $\frac{1}{3200}$ of an inch."[5]

Ponfick,[6] *Osler*,[7] and *Obermeier*,[8] have reported other abnormities].

According to *Richardson*,[9] the variations above and below the standard size of corpuscles from any particular animal are

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(1) "Undersogelser om Antallet af rode og hoide Blodlegemer under forskjellige physiologiske og pathologiske Tilstande." Inaugural Dissertation, Kopenhagen; 1876, 236 pp.

(2) "Observations on Pathological Changes in the Red Corpuscle." Quarterly Journal of Microscopical Science, vol. XII, (1872), p. 114.

(3) "Zur Pathologie des Blutes." Centralblatt f. d. med. Wiss., 1874, No. 42, p. 658.

(4) "Des caractères anatomiques du sang dans les anemies.' Comptes rendus, tome 83 (1876), pp. 82, 85, p. 152, p. 230.

(5) "Contraction of Blood-corpuscles through the action of Cold." *New York Medical Journal*. March, 1877, p. 246.

(6) "Ueber das Vorkommen abnormer Zellen im Blute von Recurrenskranken." Centralblatt f. d. med. Wiss. 1874, No. 25.

(7) "An account of certain organisms occurring in the liquor sanguinis." *Monthly Microscopical Journal*, Sept. 1874, p. 141.

(8) "Vorkommen feinster, eine Eigenbewegung zeigender, Fäden im Blut von Recurrenskranken." Centralblatt f. d. med. Wiss, 1873, No. 10. Confirmed by Laptschinsky *Id.*, 1875, No. 9, p. 84.

(9) "On the value of high powers in the diagnosis of blood-stains." American Journal of the Medical Sciences, July, 1874; and London Monthly Microscopical Journal, September, 1874, p. 135.

comparatively slight in fresh blood, as proved by the following experiments, made with his $\frac{1}{05}$ inch objective, which gives with the micrometer eye-piece an amplification of 3,700 diameters. When thus magnified, the human red blood disks appeared about one inch and one eighth in diameter, so that even slight differences in their size could be accurately measured. Among one hundred red corpuscles freshly drawn from five different persons, the maximum and minimum diameters in parts of an inch, were as follows:—

Twenty from a white male aged	30,	maximum 1-3231,	minimum	1-3500
" " " " "	38,	" 1-3281,	"	1 3529
" " " female "	44,	" 1-3249,	"	1-3500
" " an African " "	50,	" 1-3182,	"	1-3559
" " a white male "	8,	" 1-3231,	"	1-3500

Moreover, the smallest red disks of man, as usually met with in mechanically unaltered blood, whether dry or moist, are according to him larger than the largest corpuscles of an ox, and *a fortiori* of a sheep.

More recently,[1] he measured corpuscles of individuals of fourteen different nations, one hundred of each. Of the 1400 corpuscles measured, the average was $\frac{1}{3224}$ (.007878 mm.) the maximum $\frac{1}{2777}$ and the minimum $\frac{1}{4000}$ of an inch; 1158, or 83 per cent., measured between $\frac{1}{3448}$ and $\frac{1}{3030}$ of an inch in diameter, and consequently under a power of two hundred would appear about the same magnitude; the total number of corpuscles of minimum measure was only six, or less than one half of one per cent.; and the total number which measured the maximum was ten, or less than one per cent.

All this is very remarkable, unless he measured mainly the majority, or average sized corpuscles. He made some selection, for he tells us, "Instead of measuring all corpuscles, deformed or otherwise, in two directions, as proposed by Dr. Woodward, (*Phila. Medical Times*, vol. VI. p. 457), I prefer to determine the size of unaltered, *i. e.* circular corpuscles *only*:" and

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(1) "On the Identity of the Red blood Corpuscles in different Races of Mankind." American Journal of the Medicafl Sciences, January, 1877, p. 112.

further, "I cautiously avoided recording those which manifested even slight departures toward an oval form;" but, on the other hand, "to secure the most infallible accuracy for my deductions, as the preparation was moved along, I measured *every isolated circular red disk* which came into the field of the microscope."

In the year 1761, Padre *Jo. Maria de Turre*, of Naples, made a present to the Royal Society of London of four spherical glasses for the microscope, made by himself, of which the diameters and magnifying powers were said to be as follows:

	Diameter.	Magnifying Power.
1.	Near 2 Paris points.	640 times, and upward, in diameter.
2.	1 Paris point.	1,280 " "
3.	1 " "	1,280 " "
4.	Half a Paris point, (1-144 of an inch.)	2,560 " "

Sir Francis Haskins Eyles Stiles, at the time in Naples, through whom the presentation was made, wrote several letters, in which he communicated Father de Turre's directions for the use of the glasses, as well as an account of some observations on the human blood, made by him, together with Turre, during July and August, 1761, and read before the Society during November, 1765. They saw in the blood globules the central depression, which had not theretofore been observed, and which carried with it so strongly the appearance of a perforation that they concluded the corpuscles to be rings. They also thought the rings to be articulated ("the transverse lines at the joints being very distinguishable").[1] As to their shape, "the figure of the rings, where they were free, and in their natural state, was circular; but where they were so crowded together as to compress one another in their passage, they assumed a variety of different figures, although they generally restored themselves to a circular figure again,

1) "An Account of some Microscopic Observations on the Human Blood." Philosophical Transactions, vol. lv. 1765), p. 254.

unless broken by the compression, which frequently happened, and then the broken parts floated separately; or, if they opened at a single joint only, the whole of the ring would float along, varying its figure occasionally from that of a portion of a circle, which it would first assume, to a straight line, an undulated one, or some other accidental incurvature.")[1]

Hewson[2] declared the so-called globules in the blood of man and all animals to be disks—"in reality, flat bodies," "as flat as a guinea." The dark spot in the middle, which Father di Torre had taken for a hole, he found "was not a perforation, and therefore that they were not annular." He denied that they were jointed, and inferred "they are not fluid, as they are commonly believed to be; but, on the contrary, are solid; because every fluid swimming in another, which is in larger quantity, if it be not soluble in that fluid, becomes globular." He also observed changes of shape; for, speaking of the blood-corpuscles of a lobster, he said: "But there is a curious change produced in their shape by being exposed to the air; for, soon after they are received on the glass, they are corrugated, or, from a flat shape, are changed into irregular spheres, as is represented in Plate XII, No. 12;"[3] and on turning to the plate we find represented "angular," "rosette," and "stellated" forms. He was the first who likened the appearance of corpuscles, with their external surface corrugated, to that of small mulberries.

It would be impossible for me, as well as useless, to give a list of all those who have described changes of form in red blood-corpuscles since Hewson's time. Different shapes—and some of them far more curious and irregular than those I have described—have been observed, under many physiological and pathological conditions, as well as on subjecting the blood to the action of various chemical and physical agen-

(1) *Ibid.* p. 256.

(2) "On the Figure and Composition of the Red Particles of the Blood, commonly called the Red Globules." Philosophical Transactions. Vol. LXIII Part II (1773). p. 303–323.

(3) *Ibid.*, p. 321. Opus posthumum, p. 19, 20; Collected Works, edited by Gulliver, *cit.*, p. 234.

cies. Text-books and monographs give sufficient information on this point, especially the article on the blood by *Alexander Rollett*, in Stricker's "*Handbuch der Lehre von den Geweben des Menschen und der Thiere*," which has been translated by Henry Power and published by the London New Sydenham Society, and which has been republished in this country.[2]

Since that article was written the following observations have been made:

Langhans,[3] in experiments on rabbits, saw, in extravasated blood, red corpuscles with numerous fine projections, and, in pigeons' red blood-corpuscles, also, observed morphological changes.

Lieberkühn[4] described remarkable form-changes in the red corpuscles of the blood of salamanders and of pikes.

Wedl[5] observed changes of shape in human and frog's red blood-corpuscles on adding a drop of concentrated aqueous solution of pyrogallic acid to a drop of fresh blood.

Ray Lankester[6] found in his own healthy blood, in addition to the ordinary biconcave forms, "thorn-apple" and "single and double watch-glass" forms. In the two latter there is, when the corpuscle is seen on edge, instead of a concavity, a convexity on either one or both sides. He also described and figured varieties of shape in both human and frog's colored blood-corpuscles subjected to the action of various reagents. Of these I shall cite, later on, the effects of very dilute ammonia gas and acetic acid vapor.

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(1) *Ibid*. p. 313, etc.

(2) A Manual of Histology. By Prof. S. Stricker. American Translation edited by Albert H. Buck. New York: Wm. Wood & Co., 1872.

(3) "Beobachtungen über Resorption der Extravasate und Pigmentbildung in denselben." Virchow's Archiv, Vol. 49 (1870), p. 66–116.

(4) "Ueber Bewegungserscheinungen der Zellen." Schriften der Gesellschaft zur Beförderung der gesammten Naturwissenschaften zu Marburg. Vol. IX (1870), p. 335.

(5) "Histologische Mittheilungen: Ueber die Einwirkung der Pyrogallussäure auf die rothen Blutkörperchen." Sitzungsberichte der Wiener Akademie der Wissenschaften, Vol. 64 (1871), I Div., p. 405.

(6) "Observations and Experiments on the Red Blood-corpuscle, chiefly with regard to the Action of Gases and Vapours." Quarterly Journal of Microscopical Science, October, 1871, p. 361–387.

Braxton Hicks[1] observed colored blood-corpuscles of various shapes in fluid from an ovarian cyst, and in blood in other pathological conditions.

Huels[2] described frog's red blood-corpuscles acted on by carbolic acid.

Faber[3] observed, in the urine of a patient with Bright's disease, colored blood-corpuscles of a great variety of different shapes, some of which showed him phenomena of contractibility and amœboid movement, "very similar" to those of colorless blood corpuscles.

Hüter[4] reported seeing in the capillaries of the frog lung a few red blood-corpuscles adhere to the sides by means of a drawn-out pedicle, with half the body on each side, having a saddle-bag like shape ("*zwergsackähnlich*").

Laptschinsky described and figured[5] the effects of various reagents, among them aniline blue, magenta, and tannin, on the red blood-corpuscles of triton and man. He confirmed and enlarged the older observations of *Roberts.*[6] *Laptschinsky*[7] also described some variations of shape which he met with on examining human blood in different diseases.

Arnold[8] in the course of his observations on diapedesis of colored blood-corpuscles after ligating the median vein of the frog's tongue, saw that in the various phases of transit these corpuscles assumed various shapes, sometimes pear-shaped, with slender stem, sometimes caudated, oval, etc. Similar shapes have under similar circumstances been described by others.

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(1) Observations *cit.* Quart. Journ. Microsc. Science. vol XII. (1872), p 114.

(2) "Wirkung der Carbolsäure auf rothe Froschblutkörperchen." Inaug. Dissertation, Greifswalde 1872 43 pp.

(3) "Ueber die rothen Blutkörperchen." Archiv der Heilkunde. 1873, XIV. p. 481–511.

(4) "Ueber den Kreislauf und die Kreislaufstörungen in der Froschlunge." Centralblatt für die Medicinischen Wissenschaften. 1873 No 6 p 82.

(5) "Ueber das Verhalten der rothen Blutkörperchen zu einigen Tinctionsmitteln und zur Gerbsäure." Sitzungsberichte der Wiener Akademie. Vol. 68 (1873) Div III, p 148.

(6) "On peculiar appearances exhibited by blood corpuscles under the influence of solution of magenta and tannin" Quarterly Journal of Microscopical Science 1863 p. 170.

(7) "Zur Pathologie des Blutes," Centralblatt f. d. med. Wiss., 1874, No. 42, pp. 660 and 661.

(8) "Ueber Diapedesis." Virchow's Archiv, vol. 53 (1873), pp. 203-254.

Hiller[1] refuted the supposition of Hüter (II. Deutscher Chirurgen Congress, April 18, 1873), that the stellate and thorn-apple forms of red blood-corpuscles are due to immigration of monads into the substance of the corpuscles. He found such forms in blood during febrile and non-febrile diseases; they were absent in some cases in which large quantities of monads had been injected into the blood of animals; and he observed in many cases their development directly under the microscope.

Rommelaere,[2] observed in various diseases, changes of shape of the red blood corpuscles.

Landois,[3] saw corpuscles assume, before their dissolution, a spherical form with exceedingly fine points.

Ebert,[4] *Böttcher*,[5] *Fuchs*,[6] and *Schmidt*, have reported variations of the ordinary shape. The latter has also called attention to the fact that human red blood-corpuscles seen in exact profile, and closely examined, are represented by two straight and parallel lines connected at their extremities by two semicircular ones, and not showing merely their central concavity as usually represented.

The question whether or not colored blood-corpuscles possess an investing membrane, has been much discussed. *Hewson*, who, as I have already stated, showed that these corpuscles are not perforated, contended that the dark spot in the middle believed by Torre to be a perforation, "is a solid particle contained in a flat vesicle, whose middle only it fills, and

(1) "Ueber die Veränderungen der rothen Blutkörperchen nebst Bemerkungen über Microcyten." Centralblatt f. d. med. Wiss. 1874. Nos. 21-25.

(2) "De la deformation des globules rouges du sang." Bruxelles 1874. 47 pp.

(3) "Auflösung der rothen Blutzellen." Centralblatt f. d. med. Wiss. 1874. No 27. p. 419

(4) "Ueber Formveränderungen der rothen Blutkörperchen." Greifswald 1875.

(5) "Ueber einige Veränderungen welche die rothen Blutkörperchen in Extravasaten erleiden." Virchow's Archiv. vol 69, (1876), p. 295-307. Also in other articles which I quote in this review.

(6) "Beitrag zur Kenntniss des Froschblutes und der Froschlymphe." Virchow's Archiv, vol. 71, (1877) p. 78-107.

(7) "The structure of the colored Blood-corpuscles of Amphiuma tridactylum, the Frog, nd Man." Journal of the Micr. Soc. of London, May and July, 1878, pp. 66, 68, 110, etc.

whose edges are hollow, and either empty, or filled with a subtile fluid."[1] He detailed the following experiments:—"Take a drop of the blood of an animal that has large particles, as a frog, a fish, or what is still better, of a toad; put this blood on a thin piece of glass, as used in the former experiment, and add to it some water, first one drop, then a second, and a third, and so on, gradually increasing the quantity; and in proportion as water is added, the figure of the particle will be changed from a flat to a spherical shape, * * * * * it will roll down the glass stage smoothly, without those phases which it had when turning over when it was flat; and, as it now rolls in its spherical shape, the solid middle particle can be distinctly seen to fall from side to side in the hollow vesicle, like a pea in a bladder." He added: "From the greater thickness of the vesicles in the human subject, and from their being less transparent when made spherical by the addition of water, and likewise from their being so much smaller than those of fish or frogs, it is more difficult to get a sight of the middle particles rolling from side to side in the vesicle which has become round; but with a strong light (these experiments were all made with daylight, in clear weather), and a deep magnifier, I have distinctly seen it in the human subject, as well as in the frog, toad, or skate." Another experiment he describes thus: "If a saturated solution of any of the common neutral salts be mixed with fresh blood, and the globules (as they have been called, but which for the future I shall call flat vesicles) be then examined in a microscope, the salt will then be found to have contracted or shriveled the vesicles, so that they appear quite solid, the vesicular substance being closely applied all around the central piece." Furthermore, "the fixed vegetable alkali, and the volatile alkali, were tried in a

(1) "On the Figure and Composition of the Red Particles of the blood, commonly called the Red Globules." Philosophical Transactions vol. 63, Part II, p. 310 *et seq*. (Read June 17th and 24th, 1773.) "A Description of the Red Particles of the Blood in the human subject and in other animals, being the remaining Part of the Observations and Experiments of the late Wm. Hewson." By Magnus Falconer, London, 1777, p. 221 *et seq*.

pretty strong solution, and found to corrugate the vesicles."

The vesicular nature of colored blood corpuscles, thus announced more than sixty years before the publications of Schleiden and Schwann, so perfectly fits into their cell-schema, that many suppose that they have originated this view of the constitution of the corpuscles. But in point of fact they have in this respect followed Hewson. According to *Schwann*,[1] the red blood-corpuscle is a cell and consists, like every other cell of the body, of a membranous envelope, a nucleus, and liquid contents; the credit of the observation of the "rolling around" of the nucleus is given by Schwann to *C. H. Schultz*, who, however, has only repeated and confirmed[2] the experiments of Hewson.

Although not accepted without some opposition, it was not until the year 1861 that the existence of a cell-wall was positively denied. *Beale* declared:[3] "I have never succeeded in seeing the cell-wall said to exist, neither have I been able to confirm the oft-repeated assertions with regard to the passage of liquid into the interior of the corpuscle by endosmose, its bursting and the escape of its contents through the ruptured cell-wall. When placed in some liquids, many of the corpuscles swell up and disappear; but I have never seen the ruptured cell walls." He also published observations which he considered "fatal to the hypothesis that each corpuscle is composed of a closed membrane, with fluid contents."[4] *Brücke* expressed the opinion that the rolling around of the nucleus is illusory, that other phenomena do not conclusively prove the presence of a membrane, and that "the unanimity with which the vesicular nature of blood-corpuscles had for a long

(1) Mikroskopische Untersuchungen über die Uebereinstimmung in Structur und Wachsthum der thierischen und pflanzlichen Organismen Berlin 1839 pp 74 und 75.

(2) Das System der Circulation. Stuttgardt and Tübingen. 1836 p 19 *et seq.*

(3) "Lectures on the structure and growth of the tissues of the human body. Delivered at the Royal College of Physicians. Lecture III. April 22nd 1861." Archives of Medicine, vol. II. No. 8 (May, 1861). p 236 Re published in Quarterly Journal of Microscopical Science vol I N. S. (April–May, 1861). p. 240.

(4) Observations upon the nature of the red blood-corpuscle." Transactions of the Micr. Soc., vol. XII. N. S. p. 37. Quarterly Journal of Microscopical Science, Jan., 1864.

time been taught, was owing more to the silence of the opponents than to the force of the arguments of the believers."[1] *Vintschgau*[2] and *Rollett*[3] also argued against the existence of an investing membrane; and the opinion seemed doomed.

But before the end of the year in which Beale and Brücke contested the existence of an investing membrane, *Hensen* defended it.[4] He reports having observed in the blood of frogs both in fresh preparations,—*i.e.*, in red corpuscles examined without the addition of any reagent,—and in corpuscles placed in various mixtures, especially a solution of sugar, that sometimes the membrane, as a distinct outer contour, is lifted up from the interior contents at one or more points of the circumference, these interior contents being retracted more or less densely upon the nucleus. A few years later[5] Hensen reiterated his conviction as to the presence of a membrane; it is certain, therefore, that Lankester[6] has misapprehended his meaning. *Köllicker*, who had previously asserted that the red blood-corpuscle possesses "a very delicate but nevertheless tolerably firm and at the same time elastic colorless cell-membrane, composed of a protein substance closely allied to fibrin,"[7] continued to uphold their vesicular constitution.[8] *Preyer* reported that the early observation of the rolling nucleus (erroneously ascribed by him, after Schwann, to Schultz instead of to Hewson), agreed with what

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(1) "Die Elementarorganismen." Sitzungsberichte der Wiener Akademie, vol. 44, Div. II, p. 389 (Read Oct. 17th, 1861).

(2) "Sopra i corpusculi sanguigni della rana." Atti del Istituto Veneto, vol. VIII, Ser. III.

(3) "Versuche und Beobachtungen am Blute." Sitzungsberichte der Wiener Akademie, vol. 46 (1862), p. 65.

(4) "Untersuchungen zur Physiologie der Blutkörperchen sowie über die Zellennatur derselben." Zeitschrift für wissenschaftliche Zoologie, vol. XI, Heft 3 (Ausgegeben Dec. 23, 1861), pp. 253-278.

(5) In a foot note of an article entitled "Ueber das Auge einiger Cephalopoden." Ibid., vol. XV, Heft 2 (April 1, 1865), p. 170.

(6) Lankester, in his article on the red blood-corpuscle in the Quarterly Journal of Microscopical Science, Oct., 1871, already cited, says, p. 366, that Hensen "distinguishes a layer of fluid protoplasm surrounding the colouring matter, by cadaveric alteration of which he believes the supposed membrane of the corpuscle to be formed."

(7) Manual of Human Histology. Translated and edited by Geo. Busk and Thos. Huxley, London, Sydenham Society, 1854, vol. II, p. 326.

(8) Handbuch der Gewebelehre, 1863, p. 627.

he himself had seen, and at least so far as red corpuscles of the blood of salamanders are concerned, positively declared a membrane normally to exist.[1] As proof of the existence of a membrane and of its taking no part in the formation of blood-crystals, *Bryanowski* refers to his success in demonstrating it by means of distilled water.[2] *Owsjannikow* says: "To prove with certainty the existence of the membrane is no easy task. Preparations occur which seem to be convincing that there is no membrane; but other preparations show it without the addition of any reagent. The interior contents retract away from it, so that between it and the yellowish colored contents an empty space remains. Still more distinctly than in pure blood is the membrane seen on the addition of a weak solution of sugar, either without or with admixture of a little alcohol. Then it appears in many or perhaps in most of the blood-corpuscles." Furthermore, he describes interior crystallization in which he has seen the membrane pushed out lengthwise by a crystal, and other cases in which "the membrane becomes very distinctly visible as it passes from nucleus to crystal." With high magnifying power, he says, human red blood-corpuscles not seldom show a very delicate membrane; and one of his conclusions is: "In the blood corpuscles of most animals an independent membrane can be proved to exist, which behaves toward serum, water, etc., differently than the cell contents and which occasionally possesses considerable firmness."[3] *Richardson* argued[4] in favor of the same view, mainly on account of experiments upon the gigantic blood disks of the Menobranchus, in which "crystals of hæmato-crystallin were seen to prop out a visible membranous capsule." More recently, Richardson exhibited before the members of the Section on

(1) "Ueber amoeboide Blutkörperchen." Virchow's Archiv, vol. 30 (1864), p. 437.

(2) "Beobachtungen über die Blutkrystalle." Zeitschrift für wissenschaftliche Zoologie, vol. XII, Heft 3 (Nov. 17, 1862), p. 317.

(3) "Zur Histologie der Blutkörperchen." Bulletin de l'Academie des Sciences de St. Petersbourg, t. VIII. (1865), pp. 564, 568, 569 and 570.

(4) "On the Cellular structure of the red blood-corpuscle." Transactions of the American Medical Association for 1870, pp. 259-271.

Biology of the International Medical Congress of Philadelphia, a slide with a colored blood-corpuscle of the Amphiuma tridactylum, of which it is reported that "the imperfectly crystallized cell-contents occupy the upper end, while the oval granular nucleus fills the inferior extremity, leaving the membranous capsule relaxed and wrinkled longitudinally, hanging like part of a half-flaccid balloon between them."[1] *Arloing*, as the result of his observations,[2] ascribed a membrane to red blood-corpuscles. *Kollmann*, after expressly declaring that when he uses the word membrane in relation to red blood-corpuscles, he means to speak of what may be called an "artefact," *i. e.* "that apparent membrane which is made visible by the action of reagents,"[3] discusses the arguments pro and con, and concludes that "the adherents of a membrane have for their opinions, at least as many reasons as the opponents."[4] He himself believes in "the existence of a membrane in the fresh condition, which can be made visible by the action of reagents by depriving the corpuscle of coloring matter, and which, when it does not become visible, has been destroyed by the reagent."[5] According to *Böttcher*, the outer layer of the same blood-corpuscle is not the same at all times and under all circumstances. He seems to regard the appearance of a distinct membrane as an artificial production; but considers "the cortical layer as the result of a process of development which deprives the blood-cells more and more of their protoplasm, and finally converts them into homogeneous bodies." He, therefore, classes it "with the capsule of cartilage cells, and with the cellulose membrane of vegetable cells."[6] *Fuchs* observed a membrane

(1) Transactions of the International Medical Congress of Philadelphia held in 1876. Philadelphia 1877. p. 488.

(2) "Recherches sur la nature du globule sanguin." Compt. rendus, t. 74 (1872), No. 19, pp. 1256-1 59.

(3) "Bau der rothen Blutkörperchen." Zeitschrift für wissenschaftliche Zoologie, vol. XXIII. Heft 3 (Nov. 18, 1873). p. 467.

(4) *Ibid.*, p. 482.

(5) *Ibid.*, p. 480.

(6) Compare "Neue Untersuchungen über die rothen Blutkörperchen." Mémoires de l'Academie Imperiale des Sciences de St. Petersbourg, VII Serie, t. 22 (1876), No. 11, p. 8:

of a certain power of resistance in frog's red blood-corpuscles after keeping them a few days on the slide without addition of any reagent, which membrane was particularly obvious when the nucleus made its exit out of the corpuscular mass.[1] According to *A. Bechamp*,[2] and *J. Bechamp and Baltus*,[3] the red blood-corpuscles of mammals, birds and amphibia, possess a distinct membrane which can be thickened by adding a solution of starch to the blood and then becomes more resistant to the action of water.

It has even been supposed that blood-corpuscles had more than a single membrane; thus *Roberts* said[4] his observations had led him "to the belief that the envelope of the vertebrate blood-disk is a duplicate membrane; in other words, that within the outer covering there exists an interior vesicle which encloses the colored contents, and in the ovipara, the nucleus." Böttcher has refuted this notion,[5] and it is characterized by *Wedl*, too, as incorrect; according to Wedl, when the cortical layer becomes swelled and condensed, the double contour which is seen indicates its thickness—but he is "quite certain that whether it be called membrane or not, it is not simply an artificial product."[6] *Lankester*, in his conclusions regarding the vertebrate red blood-corpuscle, says: "its surface is differentiated somewhat from the underlying material, and forms a pellicle or membrane of great tenuity, not distinguishable with the highest powers (whilst the corpuscle is normal and living), and having no pronounced inner limitation."[7] *Ranvier* thinks that the double contour

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and the "Untersuchungen" in Virchow's Archiv vol. 36, (1866) pp. 357, 383, 387-8, 389 and 404, with Archiv für Mikroskopische Anatomie, vol. XIV (1877), p. 93, or "On the minute structural relations of the red blood-corpuscles," (translated from the preceding in) Quarterly Journal of Microscopical Science, Oct., 1877, p. 392.

(1) "Beitrag zur Kenntniss des Froschbluts," etc., *l. c.*, p. 91

(2) "Recherches sur la constitution physique du globule sanguin." Compt. rendus t. 85, (1878), No. 16, pp. 712-715.

(3) "Sur la structure du globule sanguin et la résistance de son envelloppe à l'action de l'eau." *Ibid.*, No. 17 p. 761.

(4) *L. c.*

(5) *Op. cit.* Virchow's Archiv, vol. 36, (1866), pp. 392-395.

(6) *L. c.*, p. 408.

(7) *L. c.*, p. 386.

—the effect of dilute alcohol—"proves the existence if not of a membrane, at least of a differentiated cortical layer."[1]

Schmidt[2] calls attention to the double contour as being "the only proof of the presence of a membrane, whether pre-existent or artificially produced." In fresh blood of Amphiuma he has observed colored blood-corpuscles with a greenish border, indicating "the existence of a thin layer at the surface, differing if not in chemical composition at least in density from the substance of the disks." He has frequently met with "specimens of blood-corpuscles, on which, by a contraction of the protoplasm representing the greater portion of the whole body, the pellicle in question appears separated from the latter." Once he saw a fragment of a corpuscle on which "the membranous layer was seen projecting on the torn surface;" and at another time he found "a fresh blood-corpuscle of the Amphiuma on which the membranous layer had apparently burst and retracted, leaving a portion of the underlying material, the protoplasm, exposed." He says: "The changes taking place in these blood-corpuscles, when treated with the solution of the hydrate of chloral, are very interesting and important; as they manifestly show the existence of the membranous layer of these bodies, such as I have described it. Thus, after the solution has been applied, the protoplasm of the blood-corpuscle, without much or any alteration of form, gradually contracts upon the nucleus. As the result of this contraction, it becomes entirely separated from the membranous layer, which manifests itself in the form of a delicate double contour. The interspace left between the contracted protoplasm and the double contour, representing the membranous layer, is very considerable, as will be seen from the drawings; and it seems to me

(1) "De l'emploi de l'alcool dilué en histologie." Archiv de physique 1874. pp. 790-793. And again. "Recherches sur les éléments du sang." *Id*, 2. Serie. vol. II, 1875 pp. 1-15.

(2) "The structure of the Colored Blood-corpuscles of Amphiuma tridactylum the Frog. and Man." Journal of the Royal Microscopical Society; containing its Transactions and Proceedings, with other Microscopical Intelligence. London, Vol. I, No. 2 (May, 1878), pp. 57-73; No. 3 (July, 1878), pp. 67-120.

should be sufficient evidence to prove the existence of such a layer to an unbiassed mind." In the colored blood-corpuscles of the frog, he has also seen a distinct stratum, or membranous layer.

"The colored blood-corpuscles of man show a double contour under various circumstances and conditions, indicating the existence, if not of an enveloping membrane, at least of a membranous layer on its surface." As one proof, Schmidt recommends the experiment of pressing down, by means of the point of a forceps, a *small* round covering glass upon a very small drop of fresh human blood placed upon the slide, "with the object of compressing or crushing the blood-corpuscles as far as possible." "Carefully examined with a first-class objective of sufficient amplification, it will be found that they have not run into each other; but that, on the contrary, the outlines of almost every individual may be discerned, however distorted they may be."

Almost all investigators nowadays agree that the colored blood-corpuscles of birds, reptiles, amphibia, and fishes, have a nucleus; while in those of man and other mammalia, except in developmental forms, a nucleus does not occur. On this difference, *Gulliver* has founded his division of all vertebrate animals into Pyrenæmata and Apyrenæmata.[1] But the existence of a nucleus in living corpuscles of oviparous vertebrata has been denied on the one hand; while, on the other, the opinion has been advanced that the mammalian red corpuscles, as well as those of other vertebrata, are in reality nucleated.

Not to cite older authors, I will mention that *Funke*[2]

(1) "Lectures on the blood of vertebrata" *l. c.*; in "Journal of Anatomy and Physiology, vol. II; Proceedings of the Zoological Society of February 25, 1862; and Hunterian Oration, 1863, referred to in "Observations on the sizes and shapes of the red corpuscles of the blood of vertebrates, with drawings of them to a uniform scale and extended and revised Tables of Measurements." Proceedings of the Zoological Society of London, for the year 1875. Part III, p. 479.

(2) Lehrbuch der Physiologie. Leipzig, 1863, vol. I, p. 17.

asserts that the nucleus of nucleated blood-corpuscles does not exist during life, but is a product of decomposition after death. Likewise *Savory*, in a paper[1] read before the London Royal Society, urged that "when living, no distinction of parts can be recognized; and the existence of a nucleus in the red corpuscles of ovipara is due to changes after death, or removal from the vessels;" and furthermore, "the shadowy substance seen in many of the smaller oviparous cells after they have been mounted for some time, is very like that seen under similar circumstances in some of the corpuscles of mammalia." But *Böttcher* has reported[2] seeing nucleated blood corpuscles in the capillaries of living frogs, and more recently *Hammond* saw a nucleus in the red blood-corpuscles of young trout, varying as to age from a day to three weeks, swimming in a cell full of water[3]; and, afterward, also in those of the tail of frog-embryos and in other animals[4].

Böttcher has by numerous methods and for a long time sought to demonstrate the existence of a nucleus in mammalian red blood-corpuscles. In his first publication[5] he gave a historical sketch of the literature of the subject, and described the effects of chloroform, magenta, tannin, and other reagents. He also treated corpuscles with serum of other blood; next[6] he placed them in aqueous humor ("methods which alter the red blood-corpuscles as little and as slowly as possible"); afterward[7] he treated them with alcohol and acetic acid, and

(1) "On the Structure of the Red Blood-corpuscle of Oviparous Vertebrata." Proceedings of the Royal Society, XVII, 1868, 1869. (Read March 18, 1869.) Monthly Microscopical Journal, April, 1869, p. 235.

(2) "Untersuchungen über die rothen Blutkörperchen der Wirbelthiere." Virchow's Archiv, vol. 36 (1866), (pp. 342-423), p. 351.

(3) "Observations on the structure of the red blood-corpuscles of a young trout." Monthly Microscopical Journal, June, 1876, pp. 282-283.

(4) "Observations on the structure of the red blood-corpuscles of living pyrenæmatous vertebrates." *Id.*, September, 1876, p. 147.

(5) The "Untersuchungen" just cited, pp. 359, 363, 367, etc., and 376.

(6) "Nachträgliche Mittheilung über die Entfärbung rother Blutkörperchen und über den Nachweis von Kernen in denselben." Virchow's Archiv, vol. 39 (1868), pp. 427-435.

(7) "Neue Untersuchungen über die rothen Blutkörperchen." Mémoires de l'Acad. Imp. des Sci. de St. Petersbourg, VII Ser., t. 22, No. 11.

still more recently[1] by means of a concentrated alcoholic solution of corrosive sublimate (methods of "hardening the blood-corpuscles and then extracting the hæmatin from them"). *Freer*, using reflected instead of transmitted light (by means of Wales' Illuminator) affirmed[2] independently of *Böttcher*, the existence of a nucleus in human blood; and *Piper*[3] seems very desirous to confirm *Freer*. *Brandt*, having[4], in the red blood-corpuscles of living Sipunculus, occasionally found a nucleus, though usually there is none, thought that perhaps the nuclei are unstable formations which by slight influences are produced or made visible, and by others are destroyed or made invisible; on examining a drop of blood from his finger, on which he had before pricking placed a little fresh chicken albumen, he usually found in many red corpuscles what he was inclined to interpret as a central nucleus, in confirmation of the observations of *Böttcher*[5]. More recently *Stowell* has written a communication to corroborate *Böttcher*[6]. And *Stricker* has expressed the opinion that the nuclei of embryonal colored blood-corpuscles of mammals persist as circular thin disks; he argues that these "disks are so large that the body proper of the corpuscle appears on a surface view as only a narrow zone: and that, therefore, except with high powers, the existence of a nucleus is easily overlooked: and he asserts that, by means of objective No. 15, he has in the blood-corpuscles of man, dog, rabbit, and cat, seen the nucleus in both surface and profile views.[7]

(1) "Ueber die feineren Structurverhältnisse der rothen Blutkörperchen." Archiv für Mikrosk. Anatomie, vol. XIV (1877), pp. 73-93.

(2) "Discovery of a new anatomical feature in human blood-corpuscles." Chicago Medical Journal, May 15, 1868, and April 15, 1869.

(3) "Contraction of Blood-corpuscles through the action of Cold." New York Medical Journal, March, 1877, p. 244.

(4) "On the nucleus of red blood-corpuscles." Arbeiten der St. Petersb. Gesellsch. d. Naturf., vol. VII (1876), p. 129. (In the Russian language.)

(5) "Bemerkungen über die Kerne der rothen Blutkörperchen," Archiv. für Mikrosk. Anatomie, XIII, 2 (1876), p. 392.

(6) "Structure of blood-corpuscles." American Journal of Microscopy and Popular Science, New York, June, 1878, p. 140.

(7) Vorlesungen über allgemeine und experimentelle Pathologie, II Abtheilung. Wien, 1878, p. 438.

On the other hand, *Schmidt* and *Schweigger-Seidel*, who repeated *Böttcher's* early methods, using especially chloroform as he had done, failed in finding nuclei, and suspected optical illusion[1]. *Klebs* contradicted *Böttcher's* statements as to the presence of nuclei in normal mammalian red blood-corpuscles; but described the occurrence of nucleated red corpuscles in blood taken from the corpse of a child who had suffered from leucæmia, agreeing in so far with a like observation of *Böttcher*[2]. *Brunn* said[3] that he had convinced himself that the appearances produced by both of *Böttcher's* later methods are artificial and optical effects, due to action of the re-agents on the substance of the corpuscles. And, similarly, *Eberhardt* has come to the conclusion that the remains after the action of different decolorizing reagents, are not nuclei, but stromata deprived of coloring matter; and that a formation, unmistakably a nucleus, has not yet been demonstrated in adult human and mammalian red blood-corpuscles."[4]

Among other questions as to the red blood corpuscle stated by Beale,[5] he asks: "Is it a living corpuscle that distributes vitality to all parts of the organism, or is it simply a chemical compound which readily absorbs oxygen and carbonic acid gases and certain fluids? Is it composed of formative living matter, or does it consist of matter that is inanimate? Does it absorb nutrient matter, grow, divide, and thus give rise to other bodies like itself, or does it consist of passive material destitute of these wonderful powers and about to be dissolved into substances of simple composition and more nearly related to inorganic matter?"

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(1) "Einige Bemerkungen über die rothen Blutkörperchen." Bericht der Königl. Sächsischen Gesellschaft der Wissenschaften, 1867. p. 190.

(2) "Ueber die Kerne und Scheinkerne der rothen Blutkörperchen der Säugethiere." Virchow's Archiv, vol. 38 (1867), p. 200.

(3) "Ueber die den rothen Blutkörperchen der Säugethiere zugeschriebenen Kerne." Archiv für Mikroskopische Anatomie, vol. XIV, Heft 3 (1877), pp. 333-342.

(4) Ueber die Kerne der rothen Blutkörperchen der Säugethiere und des Menschen. Inaugural-Dissertation der medizinischen Fakultät zu Königsberg. April, 1877, p 30.

(5) Observations upon the Nature of the Red Blood-corpuscle; *l. c.*, p. 32.

He answers the first parts of these interrogatories in the negative, and holds that it is "not living, but results from changes occurring in colorless living matter, just as cuticle, or tendon, or cartilage, or the formed material of the liver-cell, results from changes occurring in the germinal matter of each of these cells." He says, "The colorless corpuscles, and those small corpuscles which are gradually undergoing conversion into red corpuscles, are living, but the old red corpuscles consist of inanimate matter. They are no more living than the cuticle or the hard horny substance of nail or hair is living."[1] He therefore denied the contractility and amœboid movement of colored blood-corpuscles.

Klebs was the first who accorded them life and contractility.[2] He did this because, on preventing evaporation and raising the temperature of blood, he noticed, aside from motion of the corpuscles, the protrusion and retraction of knobs, and the formation and disappearance of scallops. But, though the correctness of his observation was not doubted, his inferences were strenuously contradicted by Rollett and others.[3] *Lankester* observed "amœboid figures" when colored blood-corpuscles had been subjected to the action of dilute ammonia and acetic acid, of which he says:[4] "The behaviour of these corpuscles under alternate weak ammoniacal and acid vapors furnished a very curious parallel to the movements of amœboid protoplasm, and a careful consideration of the phenomena may throw some light on the nature of protoplasmic contractility." *Böttcher* admits the possibility of vital contractility, but thinks it cannot be compared to that of colorless blood-corpuscles."[5] *Brücke,*[6] also, admits cautiously this possibility. *Preyer*[7] uses many qualifying expressions, such as "only in part," "under certain circumstances," "in some degree," "temporarily," "at certain times."

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(1) *Idem.* p. 43.

(2) Centralblatt für medizinische Wissensch. 1863. No. 514, p. 851.

(3) For the views of Rollett, Max Schultze. Kühne, etc., see *Stricker's Handbuch, cit.*, Leipzig (1869) Edition, p. 297; American Reprint (1872), p. 286.

(4) *Op. c.*, p. 378.

(5) Archiv für mikr. Anat., vol. XIV, *cit.* p. 91: translated in Quart. Journ. of Microsc. Sci., Oct., 1877, p. 391.

(6) *L. c.*

(7) *Op. c.*, p. 417, *et seq.*

He observed active form-changes of red corpuscles in extravasated amphibian blood, examined in the moist chamber, which led him to the conclusion that "the substance of these corpuscles consists of dissolved coloring matter and a colorless material (protoplasma) which, both when still in connection with the coloring matter and when free from this, shows under certain circumstances phenomena of contractility similar to those observed in many lower organisms." He adds, "As a rule it evinces no contractility, and constitutes, as modified protoplasm, the stroma of amphibian blood-corpuscles."[1] *Max Schultze*, who denied the contractility of red blood-corpuscles of man and mammals, (although when subjected to a very high temperature —50 to 52° C., nearly enough to kill them—he saw protrusions and detachments of portions,) admitted that the red blood-corpuscles of very young chicken-embryos are contractile.[2] *Friedreich*[3] observed in an enfeebled anæmic patient polymorphous red blood-corpuscles with active though very slow form-changes, which he could not but interpret as the result of contractility. In the *post-mortem* blood of a woman who had been leucæmic he saw similar polymorphous corpuscles; and in a case of albuminous urine he repeatedly observed colored blood-corpuscles from which minute portions became constricted and separated, as well as such which exhibited amœboid protrusion and retraction of short blunt projections, whereby a slow locomotion of the corpuscle was accomplished. He assumed that the contractility which the colorless corpuscles possess in so high a degree is preserved in undiminished strength in the red corpuscles in certain pathological cases. According to *Charlton Bastian*,[4] red blood-corpuscles leave under certain circumstances the vessels by virtue of active amœboid movements; and he thinks it would be well if "the attention of future observers should be directed to these peculiarities, and to the particulars above mentioned, in order

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(1) *Ibid.* p 440.

(2) Verhandlungen der Niederrheinischen Gesellschaft für Natur und Heilkunde in Bonn, am 8 Juni, 1864: Berliner Klinische Wochenschrift, 1864 No 36, p. 358.

(3) "Ein Beitrag zur Lebensgeschichte der rothen Blutkörperchen;" Virchow's Archiv, vol. 41 (1867), p. 395.

(4) "Passage of the Red Blood-corpuscles through the walls of the Capillaries in Mechanical Congestion." British Medical Journal, May 2, 1868 pp. 425, 426.

to determine more certainly than has yet been done how far amœboid movements and contractions do take place in the much-examined and much-written about red blood-corpuscles."

Lieberkühn observed in the red corpuscles of salamandra and pike's blood active protrusion and retraction of bead-like processes. He also saw movements of granules or small molecules in the interior of the red blood-corpuscles of living frog embryos.[1]

Faber,[2] in addition to his own observations of contractility and spontaneous locomotion of colored blood-corpuscles in albuminous urine—phenomena which continued to be manifested for a longer time in colored than in colorless corpuscles—has given a rather complete account of the literature of these phenomena, including the reports of *diapedesis* observed by Virchow, Stricker, Cohnheim, Prussak and Hering. The observations of amœboid movements by *Bastian* (just cited), *Owsjannikow,*[3] *Winkler*[4] and *Brandt,*[5] seem to have escaped him; *Arnold's* experiments concerning diapedesis,[6] and Belfield's observation of emigration of certain small-sized red corpuscles of the frog,[7] were published more recently. Since the publication of Faber's article, furthermore, *Rommelaere* has described amœboid movements of colored blood-corpuscles;[8] *Brandt*[9] has spoken of the peculiar forms of the red blood-corpuscles of Sipunculus and Phascolosoma referable to amœboid movements, and of the fact that occasionally in the temperature of an ordinarily warmed room considerable movements are accomplished; and *Schmidt* has observed spontaneous motion (expansion and contraction) in a fresh colored blood-corpuscle of Amphiuma in one instance,[10] and

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(1) "Ueber Bewegungserscheinungen der Zellen." Schriften der Gesellschaft zur Beförderung der gesammten Naturwissenschaften zu Marburg, vol. IX (1870), p. 335.

(2) "Ueber die rothen Blutkörperchen." Archiv der Heilkunde. XIV (1873), pp. 481–511.

(3) *Op. cit.*, p. 563.

(4) Textur, Structur und Zellleben in den Adnexen des Menschlichen Eies. Jena, 1870, p. 33.

(5) "Anatomisch-hist. Untersuchungen über d. Sipunculus nudus, L." Mémoires de l'Académie Imperiale des Sciences de St. Petersbourg, VII. Serie, t. XVI, No. 8.

(6) *Loc. cit.*

(7) "Emigration in passive hyperæmia." American Quarterly Microscopical Journal, October, 1878, p. 39.

(8) De la déformation des globules rouges du sang. Bruxelles, 1874, p. 47.

(9) In a foot-note to his "Bemerkungen über die Kerne der rothen Blutkörperchen," *l. c.*, pp. 391, 392.

(10) *Op. cit.*, p. 67.

in those of man in a number of instances. He reports that he had witnessed the phenomenon in the colored blood-corpuscles of man as early as the summer of 1871. He says, "In examining a specimen of human blood, and whilst my attention was directed to the colored corpuscles as they were carried along by a moderate current of the liquor sanguinis under the covering glass, I noticed on some of them the projection and immediate withdrawal of minute, conical, thorn-like processes, whenever one blood-corpuscle came into the vicinity of another, without, however, actual contact. It seemed almost as if one corpuscle were attracting or drawing out the thorn-like process from the surface of the other. In other instances, however, I observed the shooting forth and quick withdrawal of these processes from the margins of corpuscles not in close vicinity to others. As these processes appeared at the marginal surfaces of the blood-corpuscles, before the latter had come in contact with other of their fellows, I naturally regarded the phenomenon as one of spontaneous motion, manifested by the colored blood-corpuscle. But as in most instances the phenomenon was observed in corpuscles passing near each other, I was inclined to attribute it to a certain power of mutual attraction, residing under certain conditions in the colored blood-corpuscles. Having taken the precaution of slightly warming the glass slide before putting the blood, quickly taken from the vessels of the skin of a vigorous young man, upon it, and the temperature of the surrounding air being 96° F., or even more at the time, I also considered a certain amount of heat, at least 98° F., as essential to the manifestation of the phenomenon. This view, however, proved to be erroneous, as I shall show directly. Although I have witnessed this phenomenon on blood-corpuscles when in a state of rest, it nevertheless is more frequently observed on blood-corpuscles in motion, as when they are carried along by a current, arising in the specimen under the covering glass, and resembling in character the current in the capillary vessels. With this view, the drop of blood should be thinly spread upon the glass slide, and quickly covered with the thin plate of glass. While the blood-corpuscle is projecting the thorn-like process, its body elongates, resembling a unipolar cell; but with the withdrawal of the process, generally assumes its original round form; bipolar or lemon-shaped corpuscles are also very frequently met with in specimens of human blood. The same process is also observed when the margins of two corpuscles actually touch each other very slightly, and then slowly separate again. While separating, the thorn-like processes will be drawn out at the exact place of contact, and either remain permanent or disappear again after the separation has taken place.

That the normal heat of the human blood is not essential to the manifestation of spontaneous motion in the colored corpuscles, I discovered during the past winter, while repeating my examinations of the structure of these bodies. I then witnessed the phenomenon above described, without having warmed the glass slide and covering glass, and at the temperature of a moderately warmed room. However, I observed a colored corpuscle of a constricted form, similar to a figure of eight, slowly expanding, and finally resuming its original round form.

From this we may conclude that the colored blood-corpuscle of man possesses not only a certain inherent power of contracting its body, but also of resuming its original form by a subsequent expansion, a characteristic property of the living protoplasm, enabling the colored corpuscle to manifest spontaneous motions, though not to so great an extent as is seen in the colorless."[1]

In his "General Conclusions and Summary," *Lankester*[2] says, that the viscid mass constituting the red blood-corpuscles of the vertebrata "consists of (or rather *yields*, since the state of combination of the components is not known) a variety of albuminoid and other bodies, the most easily separable of which is hæmoglobin; secondly, the matter which segregates to form Robert's macula; and thirdly, a residuary stroma apparently homogeneous in the mammalia (excepting so far as the outer surface or pellicle may be of a different chemical nature), but containing in the other vertebrata a sharply definable nucleus; this nucleus being already differentiated, but not sharply delineated during life, and consisting of (or separable into) at

(1) *Op. cit.*, pp. 113, 114, 115.
(2) *Op. cit.*, p. 386.

least two components, one (paraglobulin) precipitable by CO_2, and removable by the action of weak NH_3; the other pellucid and not granulated by acids."

A residuary stroma, such as Lankester here speaks of, seems to have been first recognized by *Nasse*, who said[1] that the red blood-corpuscle "consists of a basis tissue, insoluble in water, which is penetrated by a red substance, probably dissolved, or at least in water easily soluble (the red coloring matter of the blood), and some water, and within which there is an aggregation of solid granules not connected with the coloring matter." *Rollett*,[2] also, assumed that a stroma or matrix enters into the structure of the colored elastic extensible substance of the red blood-corpuscle, to which the form and the peculiar physical properties of the corpuscle are due. This stroma is, however, according to *Böttcher*, an artificial product, "nothing more than a residue of the colorless part of the red blood-corpuscles, varying much in form and extent, which remains after the dissolution of the original structural relations."[3] *Brücke* considered the most probable interpretation of the forms of colored blood-corpuscles, based on their appearances after the addition of boracic acid, to be the existence of a porous mass of motionless, very soft, colorless, hyaline substance, which he calls œcoid, in the interspaces of which is imbedded the living body of the corpuscle; which body he calls zooid, and which consists of the nucleus (where that exists) and all the remaining part of the corpuscle containing the hæmoglobin.[4] But Rollett insisted that the forms on which Brücke based this interpretation are products of decomposition.[5] *Stricker* agrees with Brücke as to the existence of the œcoid, but separates, in oviparous

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(1) "Blut." R. Wagner's Handwörterbuch der Physiologie. Braunschweig, 1842, vol. I, p. 89.

(2) "Versuche und Beobachtungen am Blute." Moleschott's Untersuchungen. IX; also, Sitzungsberichte der Wiener Akademie, vol. 46, Div. II (1862), pp. 65–98; and Stricker's Handbuch, cit. Leipzig Edition, 1869, p. 295; American, p. 284.

(3) *Op. cit.*, Archiv f. Mikrosk. Anatomie, p. 90, translated in Quarterly Journal of Microscopical Science, October, 1877, p. 390.

(4) Ueber den Bau der rothen Blutkörper;" Sitzungsberichte der Wiener Akademie, vol 56, Div. II (1867), p. 79.

(5) "Ueber Zersetzungsbilder der rothen Blutkörperchen;" Untersuchungen aus dem Institute der Physiologie und Histologie in Graz. Leipzig, 1870, p. 1.

corpuscles, the remaining portion into nucleus and body.[1] Of the three views thus presented, Lankester gives, after Stricker, the following tabular statement :[2]

Red blood-corpuscles of ovipara, divisible into	Stroma. Coloring matter.	According to Rollett.
	Œcoid=outer part of stroma. Zooid=rest of stroma plus hæmoglobin.	According to Brücke.
	Membrane=œcoid. Body=zooid minus nucleus. Nucleus=zooid minus body.	According to Stricker.

If it had not been for the deserved eminence in other respects of the three investigators, Rollett, Brücke and Stricker, these notions of the structure of colored blood-corpuscles would probably never have attracted any attention.

Laptschinsky[3] considered colored corpuscles to consist of two kinds of substance, viz., one which appears smooth, soft, extensible, assumes mostly a roundish form, and, altogether, possesses some if not all of the properties of the so-called stroma; the second, visible under the microscope only, when through the action of different re-agents it is precipitated, or swelled, or both. It is this second substance which, on staining, takes up the coloring matters, and, by separating in the interior of the corpuscle from the first substance, or protruding from it, gives rise to the various shapes observed. At present it cannot be determined in what relation these two substances stand to each other previous to the precipitation of the stainable portion. The separating the blood-corpuscles into the two substances mentioned, is brought about by various external influences.

In amphibian, *i. e.*, frog's and salamander's, red blood-corpuscles, *Hensen*, *Böttcher*, *Kollmann* and *Fuchs* have seen a network; and although they have failed to interpret it correctly—

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(1) Mikrochemische Untersuchungen der rothen Blutkörperchen;" Archiv für die gesammte Physiologie des Menschen und der Thiere (Pflüger's), vol. I (1868), p. 592.

(2) *Op. cit.* in a foot-note to p. 374.

(3) "Ueber das Verhalten der rothen Blutkörperchen;" *loc. cit.*. pp. 173, 174.

as is evident from the context of their descriptions—I beg to call special attention to their observations.

Hensen ascribed to the corpuscle the possession of protoplasm accumulated at the nucleus and at the inner surface of the membrane; the two being connected by delicate radiating filaments, in the spaces between which the colored cell-liquid lies.[1]

Böttcher, from his observations, "inferred that around the nucleus of the amphibian blood-corpuscles a mass of protoplasm is collected, which radiates in the form of filaments into the homogeneous red substance. * * * * The protoplasm appears sometimes collected uniformly round the nucleus, at other times it is accumulated more to one side of it. It is either provided with only a few processes, or is arranged round the nucleus in the shape of an elegant star, whose points extend to the margin of the corpuscle, or else it forms round the nucleus a peculiar lobed figure. Very often it appears beset on one or all sides with fine hair-like processes. Then, again, it may represent a sort of net-work, which either appears separated from the less darkly colored cortical layer and more contracted, or else it throws out into the cortex innumerable very fine radiating filaments, so that its processes approach the extreme periphery of the blood-corpuscles. In this case, therefore, the whole blood-corpuscle is permeated by a net-work of fine filaments."[2]

According to Kollmann, the membrane encloses a net-work of delicate slightly granular albumen threads. These in their totality constitute the stroma, and in the small spaces between the threads of the stroma lies the hæmoglobin. The soft elastic albumen threads are stretched between membrane and nucleus. Only by a certain degree of their tension is the characteristic form of the blood-corpuscle possible. The hæmoglobin in the meshes counteracts excessive shortening of the threads."[3]

Fuchs expresses himself similarly as to the net-work of fibers

(1) "Untersuchungen," *l. c.*, p. 261.

(2) "On the Minute Structural Relations of the Red Blood-corpuscles," Quarterly Journal of Microscop. Science, Oct., 1877, pp. 388, 389, 390.

(3) "Bau der rothen Blutkörperchen;" *l. c.*, p. 482.

emanating from the nucleus, and going to the periphery of the frog's red blood-corpuscle. He adds that the net-work gives the corpuscle its shape, and fixates the nucleus in the centre. Death of the corpuscle produces first coagulation, afterward liquefaction of the fibers of the net-work. Whenever the fibers are coagulated they are shortened, and produce indentations at the surface by drawing upon the points where they are attached; when the shortening proceeds too far, the fibers are torn off from the membrane, and in both cases of shortening there are places at the surface which look protruded. Liquefaction of the fibers is assumed when the corpuscle has a vesicular appearance, when it seems to contain a semifluid mass in which the nucleus may take any position, and from which it sometimes exudes, proving in exuding the existence of a membrane as already described.[1]

Schmidt seems to have seen something like an arrangement of filaments, but if so, has misinterpreted it entirely. He has reported observing in blood of amphiuma treated first with water under the microscope, and then with a very weak solution of chromic acid (strength not ascertained), "a series of fine lines, radiating from the periphery of the nucleus through the protoplasm to the inner surface of the membranous layer of the blood-corpuscle." He remarks: "Now this picture would almost seem to corroborate the theory of Hensen, as well as that of Kollmann; the fine double lines representing the filaments, which they suppose to radiate from the nucleus to the enveloping membrane. But this is not the case; for a closer examination reveals that these lines represent nothing but fissures in the protoplasm, which appears to have assumed some form of crystallization. This becomes more evident by observing some of these fissures, deviating from their course and giving rise to subordinate branches."[2] He has also reported a somewhat analogous appearance in the colored blood-corpuscles of the frog, both fresh and treated with the same reagents. This he explained by contraction of the interior mass. He says: "The protoplasm in such a case retracts upon the nucleus, which it

(1) *Op. cit.*, p. 95.
(2) *Op. cit.*, p. 72.

completely surrounds, while the membranous layer appears isolated, manifesting itself by a double contour. And again, if the same process should take place without entirely separating the protoplasm from the membranous layer, but leaving at certain small points a union between the two parts, the result must be the production of a number of filamentary processes, arising from the main bulk of the protoplasm, and passing to those points of the membranous layer."[1]

Kneuttinger considered the two surfaces of the biconcave disk of blood-corpuscles to be connected at the place of the depression by protoplasma threads; if these tear, the biscuit form changes to a sphere.[2]

According to *Krause*, the red blood-corpuscle consists of—1. A colorless stroma formed by a solid albuminous matter arranged into radial fibers, and—2. Hæmoglobin, which is a colored fluid albuminous matter lying in the interspaces of these fibers.[3]

Lieberkühn has found that the free nuclei of red blood-corpuscles of salamandra and tritons (the blood having been kept for some time in colored glass tubes) consists of two substances, of which one forms the envelope and septa or threads passing more or less regularly through the interior; the other being contained between these septa.[4]

In the nuclei of colored blood-corpuscles *Bütschli*, *W. Flemming* and *Klein* have reported the existence of a net-work, viz.:

In the nuclei of red blood-corpuscles of frog and newt, Bütschli observed fibrils, with granular thickenings, traversing the nucleus and passing to and connecting with its envelope.[5]

Flemming saw a very delicate and dense network of fibers pervading the interior of the nucleus, and attached to the nuclear membrane in many so-called cellular elements of the bladder of curarized salamandra maculata. He inferred that the net-work

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(1) *Ibid.* p. 106.

(2) Zur Histologie des Blutes. Würzburg, 1865, p. 22.

(3) Allgemeine und Mikroskopische Anatomie, p. 325—334.

(4) *Loc. cit.*

(5) "Studien über die ersten Entwickelungsvorgänge der Eizelle, die Zelltheilung und die Conjugation der Infusorien." Abhandlungen der Senckenbergischen Naturforschenden Gesellschaft, vol. X, Heft 3, 4 (1876), p. 2C0.

is present also in the nuclei of the red blood-corpuscles, though he did not see it there.[1]

Speaking of some capillary blood-vessels of a newt, Klein said: "Some such capillaries contained blood-corpuscles, and the nuclei of these showed a very distinct net-work."[2] Also, "The examination of the nuclei of fresh epithelium of frog, toad or newt, the nuclei of fresh colored corpuscles of these animals, especially of toad, with a Zeiss's F Lens, or a Hartnack's Immersion, No. 10, reveals fibrils in the nucleus, and also shows that the 'granules' are due to the twisted or bent condition of them."[3]

III.

The method employed in my investigation, viz.: treatment of fresh blood with solution of bichromate of potash, and examination with high magnifying power, has revealed certain appearances as the structural arrangements of colored blood-corpuscles. Do these arrangements exist in the living corpuscle, or are they artificial productions of the reagent?

Dilute solutions of bichromate of potash and Müller's fluid are known as the best preserving media for the most delicate animal structures: Nervous tissue, the eye, embryos, etc., are kept in them unchanged for any length of time. In the fecundated chicken-egg of only twenty hours, placed in such a solution, the heart, but just formed, has been known to continue for a time to beat. Rollett has investigated the influence of bichromate of potash on "protoplasm," and found that no alterations were produced. In my series of observations, the weakest solutions (10 *per cent.* saturated solution or less) produced no paling of the colored corpuscles; while, on increasing the strength up to a certain point, paling occurred in an increasing degree, and a morphological structure became visible at the same time that the manifestations of life (contraction and amœboid movement) continued.

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(1) "Beobachtungen über die Beschaffenheit des Zellkernes." Archiv für Mikroskopische Anatomie, vol. XIII (1876), p. 693, *et seq.*

(2) "Observations on the Structure of Cells and Nuclei." Quarterly Journal of Microscopical Science, July, 1878, p. 337.

(3) *Ibid.* p. 332.

From this, we certainly may infer that the reagent has not altered, at all events not seriously impaired, the living matter; and when we find that the structural arrangements thus revealed are the same as those demonstrable without reagents in other living matter, the inference that they were pre-existing and not artificially produced by the reagent becomes a certainty.

The knowledge of the structure of colored blood-corpuscles will not enable us to solve all the problems regarding their nature; but some questions are answered pretty conclusively by my investigation.

The colored blood-corpuscle is not a cell in any proper sense of that word, but, like the colorless corpuscle, is an unattached portion of the living matter (bioplasson[1]) of the body. Broadly speaking, the essential difference[2] between the two kinds of corpuscles is the presence of hæmoglobin, using this term to designate the substance or substances—no doubt chemically very complicated—constituting the coloring matter under all the varying physiological circumstances.

In size, human colored blood-corpuscles vary so much, that claims to be able to distinguish them by their size from certain other mammalian colored blood-corpuscles are inadmissible.

The colored blood-corpuscle has no separate investing membrane; nevertheless, the outer portion, essentially like the inner substance forming the net-work, may be considered to be differentiated from the latter, especially at the periphery of the disk, where it constitutes an encircling band of uniform thickness, or occasionally of a wreath-of-beads appearance. In the colored blood-corpuscles of the lower classes of vertebrate animals there is usually a nucleus to be seen, which is not the case as a rule in those of man and other mammalians; but there is in the interior of these an accumulation of matter occasionally met with, which may be interpreted as a nucleus.

In the communication to the Vienna Academy, cited in Part I,

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(1) I use the word bioplasson as synonymous with "living matter" in preference to the better known word "protoplasm," because the former is etymologically more correct, and also because the latter has been used with other meanings attached to it than the one alone intended here, viz., living matter.

(2) The differences in the possession of nuclei I shall discuss on another occasion.

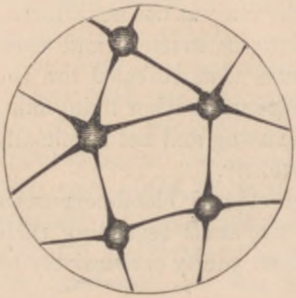

Fig. 7.

Heitzmann demonstrated the existence of a net-work in amœbæ, blood-corpuscles of astacus and of triton, human colorless blood-corpuscles and colustrum corpuscles; and, from direct observation of the changes in the reticulum during the contraction of the living body, announced that the substance constituting the net-work is itself the living matter or bioplasson, *i. e.*, "the nucleolus, the nucleus, the granules with their threads, are the living contractile matter proper."[1] Aside from some conditions which do not here concern us, he described, and illustrated by the accompanying schematic drawings, three states of the net-work, viz.: that of rest (fig. 7), that of contraction (fig. 8), and that of extension (fig. 9).

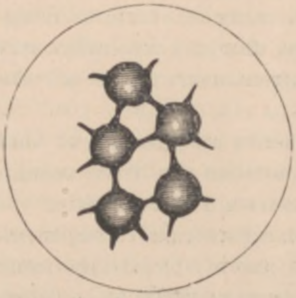

Fig. 8.

In the state of rest, the granules or points of intersection of the threads of the reticulum are in equilibrium, and the meshes holding the lifeless "protoplasmic fluid" are uniformly distributed. In the state of contraction, the granules increase in size at the expense of the length of the uniting threads; the granules approach each other, and as the meshes between them become smaller, the fluid therein contained is forced toward the part not subjected to contraction. In the state of extension, the points of intersection decrease in size and move apart; the uniting threads become elongated, while the lifeless fluid is forced into the meshes from the contracting portion.

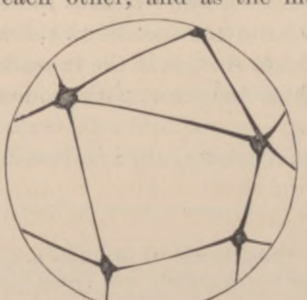

Fig. 9.

A fourth state of the living matter is assumed (hypothetically) by

(1) Sitzb. d. Wien. Akad., vol. 67, div. 3, p. 110.

the same investigator,[1] to account for the formation of a flat layer of living matter, such as forms the walls of a vacuole, the membrane of a nucleus, or the outer layer of the whole bioplasson mass; this is the protruding by a granule (which itself thereby loses its bulk and becomes flattened) of innumerable pseudopodia or offshoots, which unite laterally with each other, and with offshoots from neighboring granules. This is illustrated by Fig. 10.

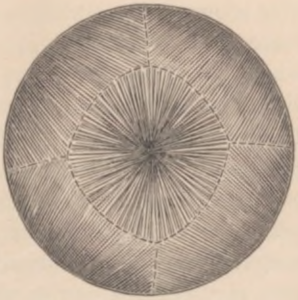

FIG. 10.

Heitzmann believes that each of these states may at any time change into the other, *i. e.*, that the network may from the condition of rest be transformed into that of contraction, or of extension, or of flattening, and from each of these into either of the others. At all events, there may arise in the bioplasson body a vacuole having a continuous thin wall, and containing lifeless fluid and detached particles of the living matter; the latter may send delicate offshoots to the wall of the vacuole, and suddenly the vacuole disappears and the network is re-established throughout the whole body. Or, a bioplasson mass may take into its interior foreign bodies by forming around them a *cul-de-sac*, which then opens toward the centre and closes at the periphery, and the net-work, rent during the process, re-establishes itself. Again, a bioplasson body, which by flap or knob protrusion and separation has lost a portion of its substance, as well as the portion detached, may become rounded off—the rupture at the place of detachment healing in each case without loss of life. And further, two bioplasson bodies may coalesce, and a portion of the periphery of each be transformed into the uniting net-work.

By adopting these views, and applying them to the living matter of colored blood-corpuscles, we may explain the changes which they have been observed to be subject to. What are the changes

(1) "The Cell-Doctrine in the light of recent investigations." New York Medical Journal, April, 1877.

that occur on the addition of a 40% saturated solution of bichromate of potash? I have described indentions and protrusions which either persist or are levelled again; protrusion of knobs, either pedunculated or sessile, which sometimes are so numerous that they surround the body of the corpuscle like a wreath; decrease of the size of the main body by detachment of knobs; appearance of net-work structure, most marked in the corpuscles which have not lost much of their substance; vacuolization of corpuscles, and transformation of many of the portions detached into vacuolized globules which increase in size; finally, change into faint, almost structureless disks, the so-called "ghosts."

The regular rosette, stellated, and thorn-apple shapes are caused by a uniform concentric contraction of the living matter;—the fluid in the interior, being pressed toward the outer layer between the points of attachment of the threads, will produce a bulging out at the periphery. Irregular contractions of the living matter will give rise to irregular flaps at the periphery.

An indentation is due to locally limited contraction of the net-work in the interior of the corpuscle. Contraction of the living matter at one part of the periphery will bring about a protrusion of a flap at another, the flap being bounded by the outer layer of the corpuscle.

Segmental contraction of the net-work will produce a rupture of the outer layer of the corpuscle, with projection of a pedunculated granule or knob, formerly a part of the interior net-work. Continued contraction will be followed by the rupture of the pedicle, and the production of either so-called detritus or small granules, or when the protruded knob is larger, or has become swelled, of a pale grayish disk.[1]

Lastly, a large amount of the net-work having been separated

(1) The peculiar corpuscles believed to be characteristic of syphilis by Lostorfer, and proved by Stricker, to be present in the blood of individuals broken down by that and various other diseases, are nothing but such disks, *i. e.*, portions of the colored blood-corpuscles protruded from the interior, detached and more or less swelled. As persons in low states of health have a relatively small amount of living matter in the same bulk, or, in other words, only a delicate network within the bioplasson body or plastid (the so-called "cell"), such a network suspended in a relatively large amount of fluid can much more easily contract and bring about a rupture of the outer layer, than in the case of healthy persons within whose plastids there is relatively less room for contraction to take place.

from the parent body, the latter becomes transformed into a pale disk, in which no traces of a net-work, or but very indistinct ones, are visible, a so-called ghost.

At every stage of the protrusion of either flaps, or pedunculated knobs, or granules, the living matter may be overtaken by death, and the contraction become fixed by cadaveric rigidity. It may perhaps be worth while to notice that irregular contractions have a somewhat greater tendency to such permanency than regular ones; these more frequently yielding, by relaxation of the net-work, or re-establishment of the state of rest, at impending death. But in the blood-corpuscles kept for over two years in bichromate of potash, all the described forms can be observed just as well as in freshly made specimens.

The reason why the corpuscles of the smallest size do not change in the solution of bichromate of potash of medium concentration, is, perhaps, that, being compact masses of living matter in which the hæmoglobin is not as yet accumulated within meshes, the solution does not reach and cannot extract the hæmoglobin. These small globules are probably intermediate stages of development of colored blood-corpuscles, or the so-called hæmato-blasts of Heitzmann[1] and of Hayem.[2]

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(1) "Studien am Knorpel und Knochen" Med. Jahrbb., 1872.

(2) "Sur l'évolution des globules rouges dans le sang des vertébrés ovipares." Compt. rend. Acad. des Sci., Nov. 12, 1877; *Idem*, Soc. de Biologie, Nov. 24, 1877. "Sur l'évolution des globules rouges dans le sang dés animaux supérieurs." Compt. rend. Acad. des Sci., Dec. 31, 1877.