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The Crescent Forms of the erythrocyte in normal and pathologic blood expressions.

Origin of
Red Blood Corpuscle
and Blood Plasm

BY
FRANK A. STAHL, M. D.
Rush 1887
Chicago

With Compliments of Author

THE CRESCENT FORMS OF THE ERYTHROCYTE IN NORMAL AND PATHOLOGIC BLOOD EXPRESSIONS.

ORIGIN OF RED BLOOD CORPUSCLE AND BLOOD PLASM

FRANK A. STAHL, M. D.
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The Predecessors, (Ancestors), normal,
of the pathologic crescentic forms of the erythrocyte as they occur in the various expressions of the Anæmias. An explanation for the origin of the Sickle-Cell Erythrocyte.

THE NORMAL CRESCENT-SHAPED ERYTHROCYTE.

In a research concerning Origin of Blood Corpuscle, and differentiations from the primary bloood corpuscle to the mature young erythrocyte, the red blood plastid of Minot; eight distinct forms of the erythrocyte developed in the metamorphosis from the large mono-nucleated erythroblast to the non-nucleated erythrocyte, the red blood corpuscle of maturity.

The material utilized were human ova from 2-8th week, in good histologic condition and all normal.

Of these eight forms, three belong to the characteristic, crescent-shaped or outlined erythrocyte.

The erythroblast, it will be remembered, is not of the primal blood corpuscle, predominant in the first or primal uncolored blood circulation; this primary uncolored circulation is predominant in character to the 6th week; then transition to the initial red blood colored circulation of the erythroblast.

In the secondary or red blood colored circulation there is at first a mixed type of uncolored primal blood corpuscles and of commencing predominant erythroblasts. Then again transition from the temporary erythroblast to the permanent non-nucleated erythrocyte of maturity. The permanent red blood circulation being referred to as permanent when the non-nucleated erythrocyte is predominant.

EXPLANATIONS OF FIGURES 1 AND 2.

FIG. 1.—The ancestor of crescent forms of erythrocytes, both normal and pathologic.

The normal nucleated pure crescent form of erythrocyte.

An example of intra-blood-vessel division, and multiplication differentiation from the erythroblast to the erythrocyte, in a blood vessel of the chorion of a 7-8th week human ovum.

Crescent.

Free nucleus below, slight blood-cell plasm still surrounding.

Erythrocyte.

Another free nucleus extruded into the general circulation, see Fig. 9 below; in pathology.

Erythroblasts.

FIG. 2.—Fig. 1 enlarged, the normal nucleated crescent erythrocyte, the better to show size and structure of crescent, with relationship to other contiguous corpuscles and nuclei; phases of blood-corpuscle intra-vessel differentiation.

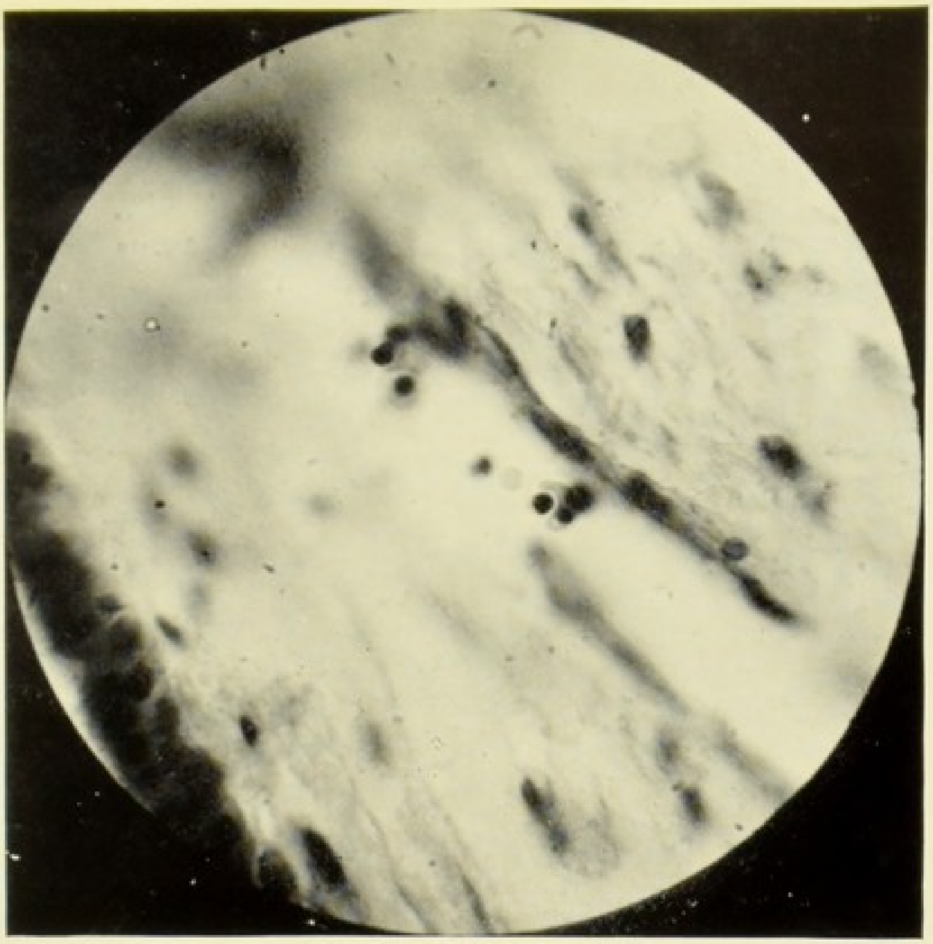

Fig. 1

Fig. 2

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Thus it will be seen there are three blood circulations characterizing the ovum; the one following the other; the first two being temporary in duration; the third being the permanent red blood colored circulation of the permanent erythrocyte, the erythrocyte not being subject to change. They are:

1—The primary uncolored blood circulation, where the uncolored primal blood nucleus-corpuscle is predominant and temporary; continues to about the 6-8th week.

2—The initial red blood circulation; where the red erythroblast becomes characteristic and temporary, and lends new red color to the blood circulation; continues beyond the third month.

3—The permanent red blood circulation where the mature non-nucleated red blood corpuscle, the erythrocyte becomes characteristic and remains so permanently; thus continuing the red color permanently to the blood circulation.

As is well known the crescent forms of erythrocyte occur in pathology, especially in the blood diseases of the anæmias. In the anæmias the crescents are easily recognized because of their numbers; they seem not so numerous or easy to find in the normal. This hesitancy might be explained in that, the normal blood corpuscle differentiation being unhindered by a dyscrasia from disease of blood or body, with consequent lowering of tone of blood corpuscle differentiation; the normal differentiation, therefore, is vigorously carried along by a normal 100% blood corpuscle differentiation, to completion of and without deformity of blood cell.

Whereas in the anæmias, there is hindrance and backwardness in differentiation; incompletion in blood cell outline and substance; a slower development in general process and continued metamorphosis; many times there is stasis. Therefore, the greater numbers and more easily recognized blood cell incompletion and deformity in pathology; proportionate to loss of physiology and function in blood cell and stream, there follow debility and death, as sequelæ.

Recognition of crescent shaped erythrocytes, in mature life, spells pathology in diagnosis.

Two of these crescent forms were found in the blood vessels of the chorion of a 7-8th week human ovum; the third in the Area Vasculosa in the same ovum, near the still open free inner margin of the chorion; before fusion of the amnion with the chorion.

CONCERNING ORIGIN OF THE BLOOD CORPUSCLE IN THE CHORION IN THE HUMAN.

It is a well known admission that blood corpuscle and blood circulation are extra-embryo in origin.

But from where primal blood corpuscle, plasm, and circulation; how developed and in and from what tissues have ever been open questions for difficult and original solutions; but not till today have they met with any happy results.

For origin of blood corpuscle, until today, especially, are mentioned Blood Islands and Yolk-Sac (potential yolk-sac); both, not primary but secondary auxiliary developments, depending upon the chorion for growth and development. But how does such growth and development occur, except through some afferent pabulum bringing circulation; surely not an autogenous growth! proving such (their) growth secondary to an anterior circulation. Also among such sources of origin may be mentioned the well known theory of the medulla. The medulla of the bone in this connection spells continuation, not origin of blood corpuscle.

Blood corpuscle, plasm, and circulation in origin, is in the chorion and is easy of histologic proof.

In a series of slides from a 2-3rd week ovum, the primary

EXPLANATIONS OF FIGURES 3 AND 4.

FIG. 3.—The normal non-nucleated crescent, found in another blood vessel of the chorion of 7-8th week human ovum. Another example of intra-blood vessel differentiation. Note the delicate nucleus, apparently just extruded into the hollow of the crescent.

1. Non-nucleated crescent typed erythrocyte with extruded nucleus in hollow of crescent.

2. Inwandering elongated or spindle-shaped nuclei undergoing division and multiplication differentiation from the large round nucleus of the second row; they enter blood stream and metamorphose into erythroblasts. Margin of blood space vessel seems endothelial, but not so, they are concentrically arranged spindle-shaped nuclei only, ready to enter blood stream. This picture lends explanation to the theory formerly held, that endothelial proliferation affords origin to red blood corpuscle, the erythroblast. Refer to Fig. 10 below, where vessel wall lumen again is seen without endothelium. This, no endothelium, feature is also seen in so important vessels as the umbilical arteries and vein of the umbilical cord at the 5-6th week; human ovum.

3. Erythroblasts in villus stroma blood space.

4. Elongated blood space vessel with erythroblasts within; no endothelium.

5. Spindle nuclei ready to subdivide into several offspring and enter blood stream.

FIG. 4.—The normal cup-shaped erythrocyte, found in the Area Vasculosa of a 7-8th week human ovum. An example of blood corpuscle division and multiplication differentiation in the delicate arachnoidal connective tissue from the area vasculosa.

Cup-shaped crescent.

In surrounding meshes of area vasculosa, many young mature non-nucleated erythrocytes.

To the left large erythroblasts with several nuclei; pre-multiple division by amitosis, into several offspring; one offspring for every nucleolus.

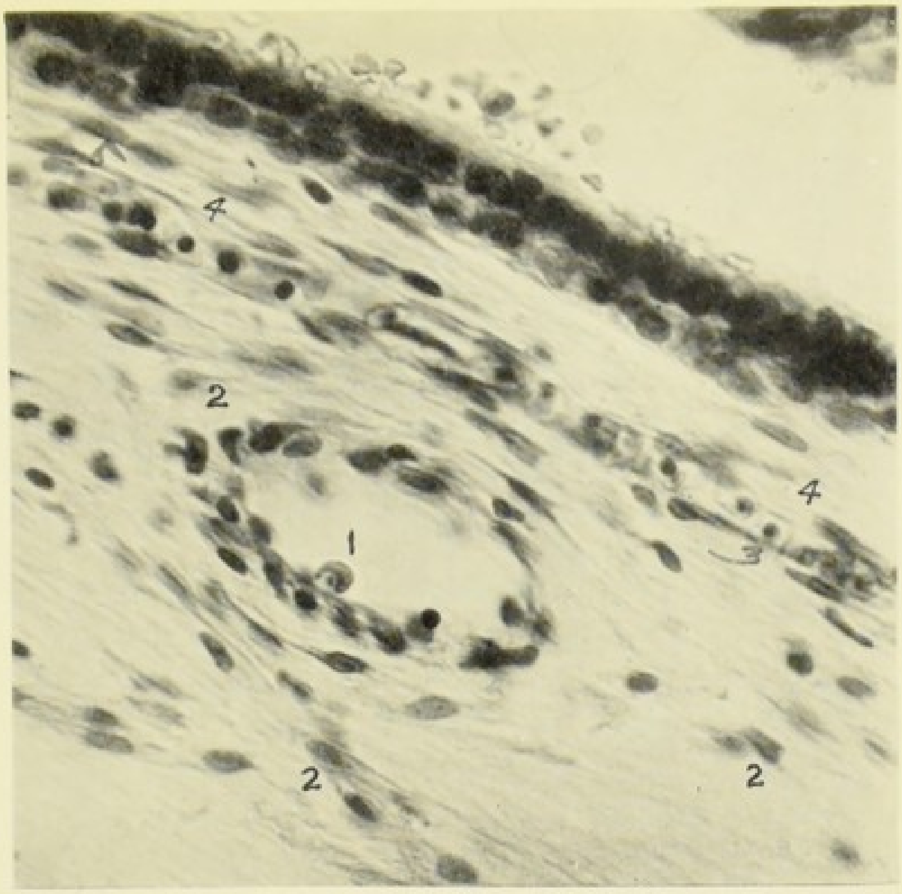

FIG. 3

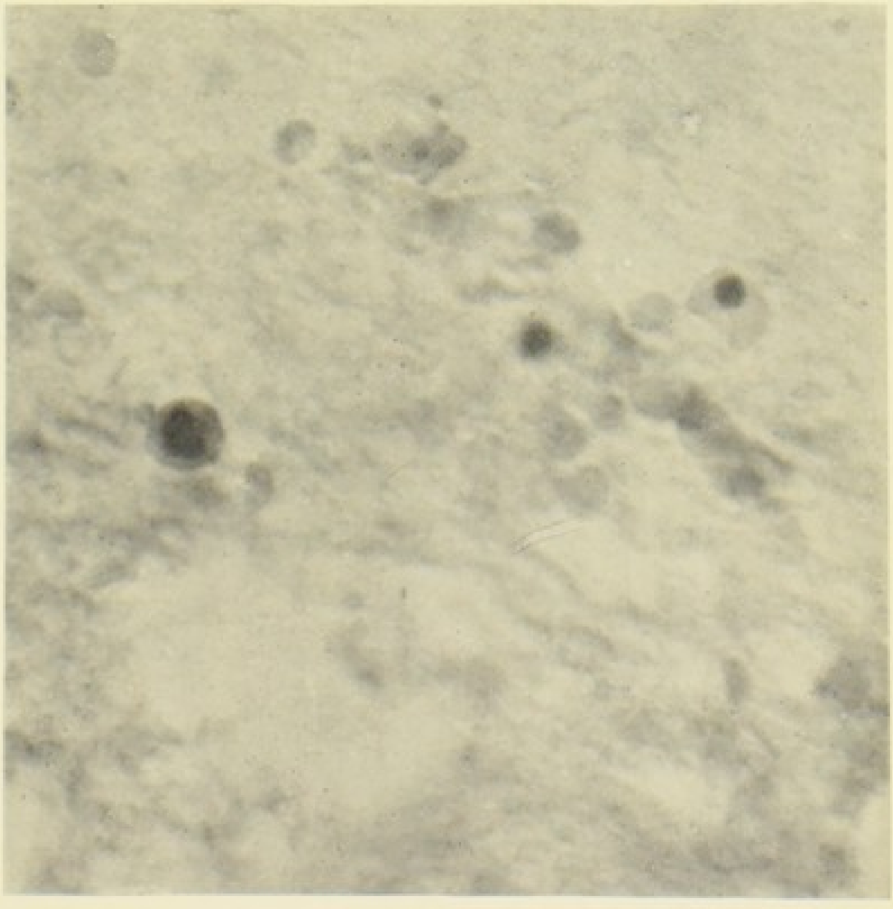

FIG. 4

THE CRESCENT FORMS OF THE ERYTHROCYTE
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blood-nucleus-corpuscle may be traced from the syncytium into the stroma, blood space and vessel of the villus; through the course of the vilus to empty into the blood space and vessel of the chorion.

Likewise through the trophoblast and syncytium of the chorion and villus, is the origin of the primal blood plasm.

In another series of slides from a 3-4th week series, the blood nuclei-corpuscles from the inner row of the syncytium, and which form the primal uncolored multinucleated nucleus-blood-corpuscles, characteristic of and giving color to the primal uncolored blood circulation, can readily be traced: (1) the nucleus-cell leaving the 2nd row of the syncytium; (2) to enter a primal blood space-vessel of the villus; (3) such a blood space-vessel can be traced throughout the length of the villus; (4) to empty and pass through the chorion into a blood-island in the area vasculosa, just within the inner free margin of the chorion; (5) from this blood island anastomosing blood circulation divisions radiate to the right and left, in the area vasculosa in the cavity of the chorion; (6) blood nucleus-corpuscle differentiation is clearly shown from the large round multinucleated nucleus of the 2nd row to its spindle shaped elongated form, where the metamorphosing nucleoli of the original nucleus of the syncytium cling together in an elongated spindle form, just ready to break up and divide into several offspring; one offspring for each nucleolus.

This multiplication and division of primal nucleus-blood-corpuscle differentiation, may easily be traced into and through the villus, chorion and area vasculosa, and distinctly so, as mentioned, in the slides of the 3-4th week series.

This offspring differentiates into the mono-nucleated red erythroblast, in blood space and vessel of the adolescing blood stream; where primary hematinization occurs, thus the primal uncolored blood circulation gives way to the 2nd or initial red colored blood circulation of erythroblast.

In 1922, page 41, Physiological Reviews, Dr. Florence Sabin writes, in "Origin of the Cells of the Blood," that, "Maximow, 1909-1910, finds that the first blood cells of mammals develop within the vessels of the embryonic membrane, as do those of the chick; that the primary cells are first lymphocytes then erythroblasts."

Again, page 53: "M. thinks origin of red cells from the endothelia is only transitory, that the secondary permanent red cells are extra vascular in origin."

These happy predictions were anticipated and verified in the human, in 1902 and 1906, both articles with illustrations being presented in the Amer. Jour. Obstet. In these articles, "Origin of blood corpuscles" in the human, was shown to lie in the chorion of the ovum. The Interpretations promised in 1906: "Further details will be presented in a future article, entitled, 'Origin of the Red-Blood Plastid' in which article it will be shown that the origin of the blood plastid lies not 'in the proliferation of endothelia; or in the intracellular connective tissue cell; or in the medulla of the bone;' the three popular theories for the origin of the non-nucleated red blood corpuscle," (Stahl). Blood Islands and Yolk Sac theories will not be touched upon here, except to inquire, are not both subsequent to primal blood corpuscle?

DESCRIPTIVE.

FIG 1.—The normal nucleated pure crescent form of erythrocyte found in the blood vessel of a 7-8th week human ovum. This crescent occurs nucleated and non-nucleated. This is the first of the crescents found in the blood vessels of the chorion.

The similiarity in form and outline of this normal type crescent shaped erythrocyte, to the pathologic type shown by Minot and Lee, in Fig. 7, is readily seen.

FIG. 2.—Enlargement of the nucleated crescent erythrocyte seen in Fig. 1. The thought had occurred that possibly a section of a large erythroblast cell slightly curved upon itself, might have resulted in this picture; but the large nucleus, just before and resting against the arch of the crescent, interposes between sectioning knife and crescent, leaving a clear interval between knife and crescent, preventing and ruling out such a probable result;

EXPLANATIONS OF FIGURES 5 AND 6.

FIG. 5.—Illustration not text taken from Emmel, Plate 1, Fig. 4. Cup-shaped crescent forms of erythrocytes; from experiments with membranes of pig embryo.

Blood corpuscle differentiation from erythroblast to erythrocyte.

Similarity to Fig. 4, above, human cup-shaped crescent, 7-8th week, easily seen.

FIG. 6.—Illustrations not text from Plate 5, Figs. 42-43-44, Emmel. Experiments pig embryo.

A—The dumbbell-shaped erythrocyte; a case of amitosis. The same form exists in a blood vessel of the chorion in the human, 7-8th week.

B—43-44—Crescent-shaped erythrocytes; pig embryo. The same forms are seen in the Area Vasculosa of the human at 7-8th week; see Fig. 4 above.

Fig. 5

A B

Fig. 6

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in consequence, therefore, here the normal uninjured pure nucleated crescent form of differentiating erythrocyte.

Fig. 3.—The normal non-nucleated crescent form of erythrocyte, found in another blood vessel of the chorion of a 7-8th week ovum; another type of intra-blood-vessel-differentiation. Note the delicate nucleus, apparently just extruded into the hollow of the crescent.

Fig. 4.—The normal cup-shaped crescent erythrocyte, found in the Area Vasculosa of a 7-8th week human ovum. The meshes of a delicate arachnoidal tissue is shown here, in which, are seen this cup-shaped crescent; a large cell with several nuclei to the left, as though amitosis in intention and ready for division, multiplication, and differentiation; into several offspring, one offspring for every nucleolus. Many neonate young erythrocytes are also seen throughout this area, extending in large numbers and in many columns of pure unmixed erythrocytes, throughout this area and into contiguous areas. This area, in toto, seems a finishing area in blood corpuscle differentiation. For only here in this area and at this time, are the young pure non-nucleated erythrocytes seen in large numbers and in long columns; on the contrary, in the blood vessels of its chorion and villi, the erythrocytes appear only occasionally; the pure erythroblast still predominating in those vessels.

In a most interesting blood corpuscle study by Victor E. Emmel in his article on "Erythroblasts, in the membranes of pig embryo"; Amer. Jour. Anat., Vol. 16, 1914, he presented a series of blood corpuscle illustrations, picturing changes from the erythroblast to the erythrocyte in the membranes of pig embryo. These findings are all the more remarkable and interesting as they are the results from experimental effort in artificial induction of blood corpuscle differentiations from the erythroblast to the erythrocyte, in the pig embryo. He was very successful, for he produced exact changes in forms in differentiations that occur from the erythroblast to the erythrocyte in the human ovum, from the 5-8th week; intra and extra uterine.

Emmel's plates and figures are presented herewith in part, with a personal discussion not Prof. Emmel's text.

Fig. 5.—Plate 1, Fig. 4, shows an example of what Emmel calls a cup-shaped erythrocyte; another one above it. These seem but another form of the true crescent type of the erythroblast division, the form of crescent without the base of the cup; as shown

in Figs. 1-2-3, as seen above, the normal crescent form. Take Emmel's cup-shaped erythroblast, minus the base, and a true normal crescent form is left, as above. Now stretch this crescent between its horns and there is left an attentuated figure very much like Emmel's figures seen in his beautiful study of the Sickle-cell Erythrocyte in Prof. Herrick's, new find, Sickle-cell Anæmia, 1910. Thus may be explained, Sickle-cell origin as a form corresponding to the normal crescent type of blood erythrocyte, as changed by the lowered tone of blood corpuscle differentiation in the anæmias.

Such changes are readily seen in illustrations of the sickle-cell erythrocyte of Sickle-cell Anæmia; see Fig. 9 and explanations; both the nucleated and non-nucleated forms of sickle-cell erythrocytes are there shown.

Fig. 6.—Plate 5, Figs. 42-43-44; the results from experiments with membranes of pig embryo. The same forms of blood corpuscles occur in the vessels of the chorion and in the area vasculosa in the human ovum at 7-8th week. Emmel speaks of this type, 43-44, as cup-shaped erythrocytes; yet their relationship to the pure crescent forms seem very close. They are strikingly similiar in form to that of the human type seen above in Fig. 4.

THE PATHOLOGIC CRESCENT-SHAPED ERYTHROCYTE.

The deformity of cell changes in the poikylocytosis of the anæmias is well known since the time of Neumann, 1860.

Fig. 7.—Minot and Lee of Harvard present in Nelson's System on Medicine, a remarkable example of pure nucleated crescent form of erythrocyte in a case of Acquired Hæmolytic Jaundice; Plate 7 (x 1300). It will be noticed that this crescent type is a duplicate of the normal pure nucleated crescent in Fig. 1, above.

Fig. 8.—Buchanan, R. J. M., in Oxford Medical Publication, Liverpool, 1909, affords another such an example of pure nucleated crescent form occurring in a case of Mixed Leukæmia.

Fig. 9.—Not text but "Illustration 2—Blood in active phase; stained smear," taken from Dr. V. P. Sydenstricker, Augusta, Georgia, Sickle-cell Anæmia, Jour. Amer. Med. Ass., July 15, 1924. Aside from the sickle-cell erythrocytes in this illustration, it shows also a number of other interesting phenomena correspond-

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Explanations of Figures 7 and 8.

Fig. 7.—The pure nucleated crescent form of erythrocyte, pathologic. Minot and Lee, Harvard. From a case of Acquired Hæmolytic Jaundice.

Fig. 8.—The pure nucleated crescent form of erythrocyte, pathologic; from a case of Mixed Leukæmia. Buchanan, R. J. M., Oxford Med. Pub.

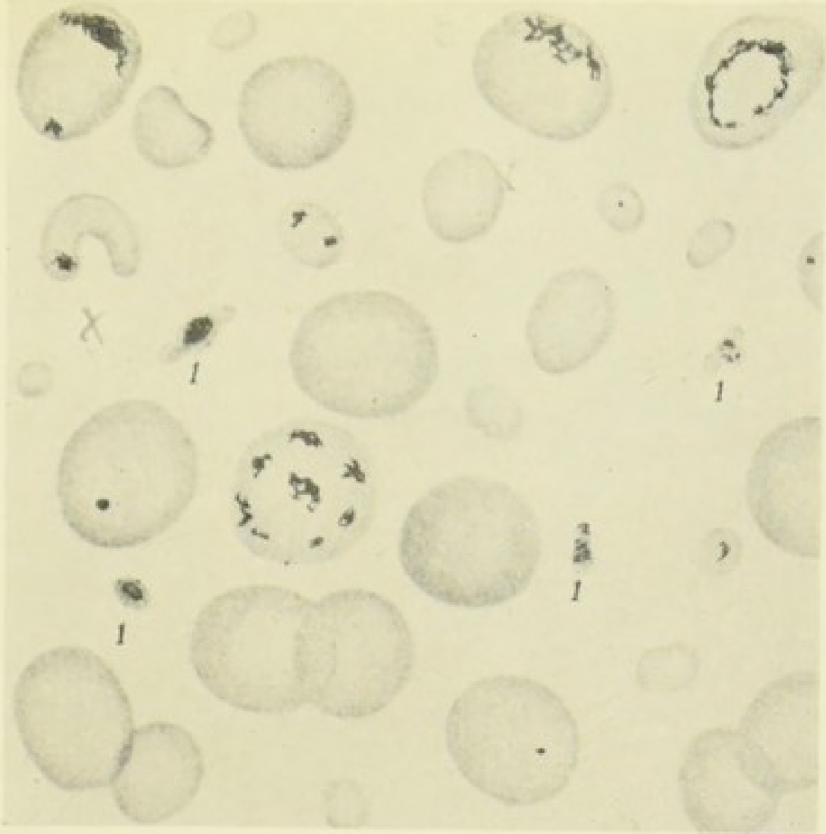

FIG. 7

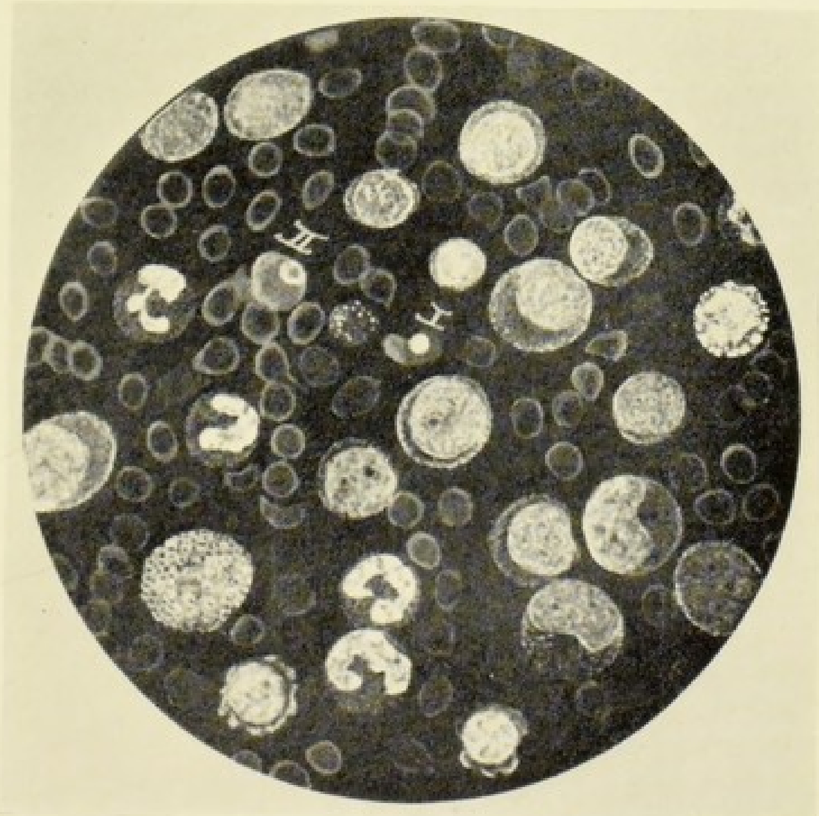

FIG. 8

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ing to those occurring in normal blood corpuscle differentiation.

6—The nucleated sickle-cell erythrocyte, malformed through dyscrasia of anæmia; analogue to the normal nucleated crescent erythrocyte, Fig. 1, above.

7—The non-nucleated sickle-cell erythrocyte, malformed, analogue to the normal non-nucleated erythrocyte seen in Fig. 3, above.

Another of the valued features of this illustration is the picturing of changes in detail of the differentiations; in the disappearance of the nucleus from the blood cell in the differentiations, from the nucleated to the non-nucleated erythrocyte; differentiation being the same in the normal as in the pathologic.

1—Nucleus of erythrocyte wandered to edge of its cell.

2—Just ready for extrusion of nucleus into general blood stream.

3—Nucleus rests loosely in cell cavity as though moment just before casting off.

4—Peripheral cell cavity as though just emptied of a nucleus.

5—Many nuclei-whole-extruded into general blood stream.

Finally, the many perfect non-nucleated erythrocytes disseminated throughout the general field.

Discussion: In disappearance of nucleus from erythrocyte: Migration and Extrusion versus Fragmentation and Absorption.

In this illustration can also be seen crucial decisions in the now far more mild controversy of Migration and Extrusion of nucleus of erythrocyte versus Fragmentation and Absorption.

Here is seen plainly Migration of blood cell nucleus to the edge of its cell; then Extrusion of nucleus as a whole into the general blood stream, where undoubtedly Fragmentation occurs; finally Absorption. In the normal, see Fig. 2 above.

May it not be that in the Fragmentation of the nucleus in the stream of the general circulation, into such minute particles as to be until now, unrecognizable to stain and microscope; that in this minute Fragmentation, as invisible nucleoli, that therein may lie the secret and seed of Continuation of Erythrocyte in Mature Life and even in that of Fetal Existence.

Fig. 10.—Cross section of blood space-vessel from villus 7-8th week; content mono-nucleated erythroblasts; erythroblasts in stroma of villus; observe nuclei wandering from second row towards the blood vessel, several empty spaces in second row; several coarse multi-nucleated nuclei in rim of blood vessel; the flat-

tened elongated ones have often been interpreted as endothelial inclined; but not so, they are nuclei from the second row undergoing differentiation now into the spindle or elongated form from the large round nucleus with several nucleoli; where the nucleus has developed into now two small offspring still clinging together in elongated form, soon to break apart on their way towards hematinization and erythroblast formation in the blood stream. Such elongated or spindle-shaped nuclei are seen in the villus stroma between the edge of the blood vessel and the second row of the villus. Illustration of intra-connective tissue differentiation.

EXPLANATIONS OF FIGURES 9 AND 10.

FIG. 9.—Sickle-cell erythrocytes in sickle-cell anæmia; nucleated and non-nucleated forms.

Illustration not text from Dr. V. P. Sydenstricker. Jour. Amer. Med. Ass. 1924.

6—Nucleated sickle-cell.

7—Non-nucleated sickle-cells.

Disappearance of nucleus in blood corpuscle differentiation, from nucleated to non-nucleated erythrocyte; here each step is clearly and plainly shown, an exceptional illustration for this purpose. Differentiations are alike in the normal and pathologic.

1—Nucleus of erythrocyte wanders to edge of its cell.

2—Just ready to extrude nucleus into general blood stream.

3—Nucleus rests loosely in the cell cavity as though moment just before casting off.

4—Peripheral cell cavity as though just emptied of a nucleus.

5—Many nuclei-whole-extruded into the general blood stream.

Finally, the many perfect non-nucleated erythrocytes disseminated throughout the general field. Use handglass.

FIG. 10.—Cross section of blood vessel from villus near attached one to decidua described in Figure 2, 1906; Vessel margin, no endothelium; content, mono-nucleated erythroblasts; erythroblasts in stroma of villus; observe nuclei wandering from second row, several empty space effects there; several coarse multinucleated nuclei in rim of blood vessel.

1. Large second row nucleus wandering into blood space-vessel; with large handglass, this nucleus appears to have several nucleoli as though ready to break up into several offspring, future erythroblasts; others around edge; no endothelium; this picture probably affords another explanation of former theory, that proliferation of endothelium gave origin to red blood corpuscles. This no endothelium feature of this blood space-vessel is seen throughout early blood-vessel expression, even in the important umbilical arteries and vein of the umbilical cord of the 5-6th week; where no endothelium is again the picture and the rule. The two flattened cells in lower edge of lumen are elongated spindle-shaped nuclei, dividing into several offspring; but not endothelial inclined.

2. Note second row nuclei seem directed inwards toward stroma of villus, especially at 2; showing principle of direction and activity.

3. Empty spaces suggesting departed nuclei.

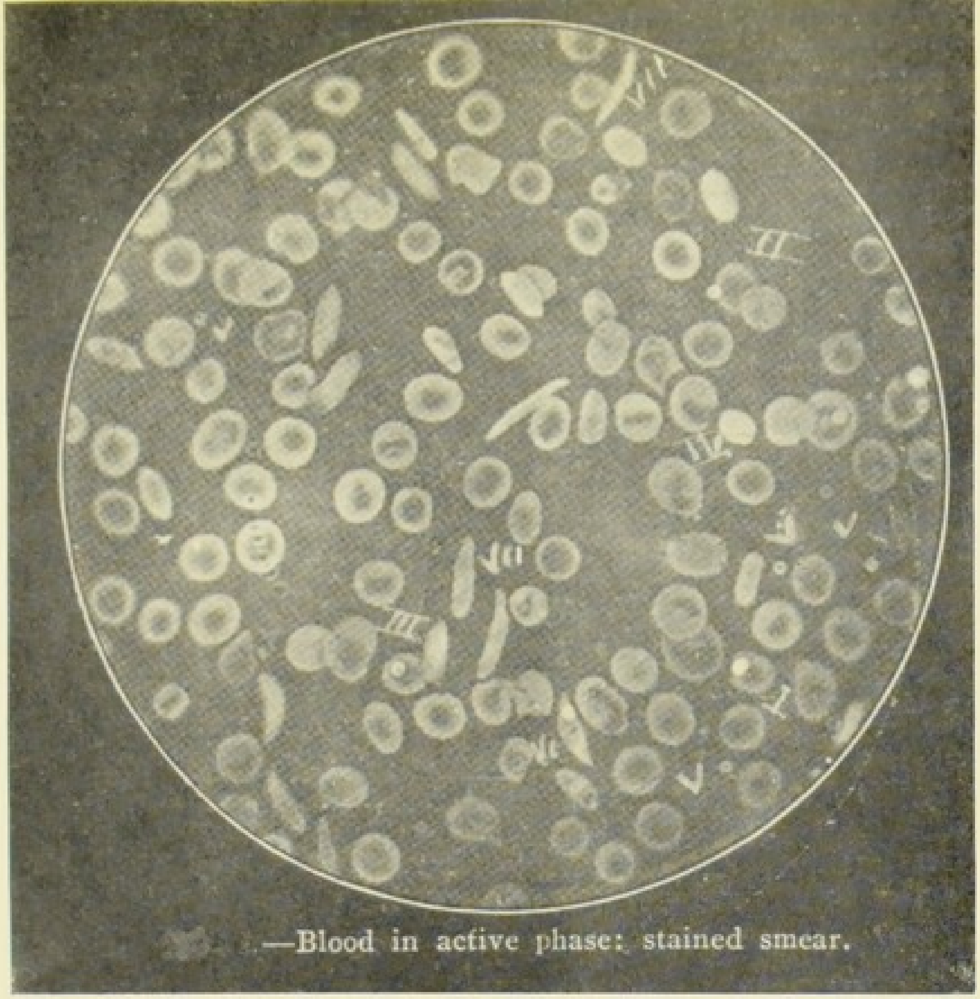
4. Empty space with nucleus just below; nucleus appears dividing into two offspring.

5. Large nucleus about to divide.

6. Position of nucleus in the erythroblast suggests ease of nucleus extrusion from cell in differentiation to the offspring, the erythrocyte; extrude the nucleus, there is left the cup-shaped crescent form for further differentiation.

In the normal casting off, see Fig. 2 above.

In the pathologic casting off, see Fig. 9 above.



—Blood in active phase: stained smear.

Fig. 9

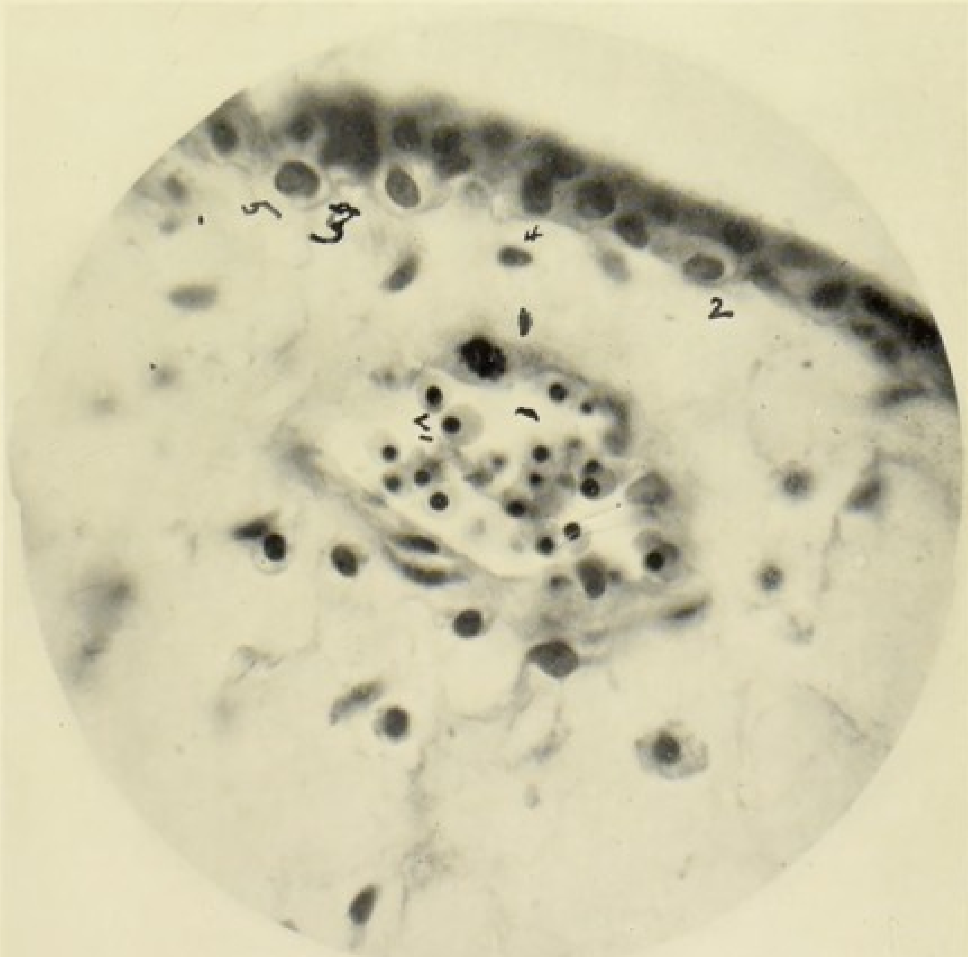


Fig. 10

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Note particularly the No Endothelium feature of this blood space-vessel—for there is much assertion to the contrary.

Figs. 1-2-3-4 and 10 from a Research, soon to appear, on "Origin of Blood and Plasm: blood corpuscle differentiation, from primal blood corpuscle to the final mature erythrocyte."

Pittsfield Building

Chicago, Illinois
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