NOON TEMPERATURES AT BLOCK ISLAND. (Fahrenheit Scale.)
(July and August, 1880, 1881, 1882, and 1883.)

		Average.	Maximum.	Minimum.	Monthly range.	Number of days on which temperature was at or above 80° F.	Number of days on which temperature was at or below 70° F.
1880	July ..	75.5°	81.0°	70.0°	11.0	3.0	4.0
	Aug ..	74.3	82.0	62.0	20.0	3.0	5.0
1881	July ..	73.4	80.0	66.0	14.0	2.0	9.0
	Aug ..	72.2	79.0	58.0	21.0	0.0	9.0
1882	July ..	74.2	82.0	60.0	22.0	6.0	6.0
	Aug ..	74.4	80.0	68.0	12.0	1.0	6.0
1883	July ..	73.8	80.0	65.0	15.0	2.0	6.0
	Aug ..	72.6	80.0	66.0	14.0	2.0	9.0
Average	July ..	74.22	80.75	65.22	15.5	3.2	6.2
	Aug ..	72.37	80.22	63.50	16.7	1.5	7.2

Huntington Richards.

[Below are added some more recent data in regard to the climatological conditions which exist at Block Island:

METEOROLOGICAL DATA OF BLOCK ISLAND FOR THE FOUR MONTHS, JUNE, JULY, AUGUST, SEPTEMBER, FROM 1890 TO 1897 INCLUSIVE, FROM THE UNITED STATES WEATHER BUREAU. (Fahrenheit Scale.)

	Mean average temperature for the four months.	Mean maximum temperature.	Mean minimum temperature.	Relative humidity.
1890	65.2°	73.0°	60.0°	87.3°
1891	65.2	81.0	52.7	89.0
1892	65.7	81.0	53.0	86.4
1893	64.4	79.7	51.5	85.0
1894	65.9	80.5	52.5	85.5
1895	65.8	81.5	50.0	86.6
1896	65.5	80.0	52.5	86.5
1897	65.4	79.9	51.7	85.7

The temperature of the summer proper is 67° F.; of autumn, 53° F.; winter, 32° F.; spring, 43° F.; and the annual mean, 56° F. The mean annual rainfall is 53 inches. Sunshine for summer, 63 per cent.; autumn, 43 per cent.; winter, 51 per cent.; and spring, 48 per cent. Annual mean, 53 per cent. (*Medical Record*, 1897).

The island is reached from New York, Providence, Newport, and New London. From the private letter of a gentleman who has passed many summers on the island, the following is extracted:

"There are more or less fogs on the island, but generally not enough to be uncomfortable; the bathing is good and perfectly safe. There is almost always a breeze, and of course no land breeze, so that the weather is cool and comfortable, and no one need fear any discomfort from the heat; there is practically absolute freedom from mosquitoes."

In another private letter of a gentleman who spent two months on the island it is stated that "the bathing is poor, dangerous on the seaward side, and stormy on the protected side." As he was unfortunate in meeting with an unfavorable season—"damp, foggy weather"—and was a sufferer from rheumatism, he may have been prejudiced in his opinion of the island and of its bathing facilities.

"There are probably twenty or thirty hotels on the island," says the former correspondent, "good, bad, and indifferent." There are also said to be cottages especially adapted for invalids and convalescents.

Block Island is a favorite place for excursionists, a condition which may be of annoyance to the summer resident.—*E. O. O.*]

BLODGETT'S SPRINGS.—Santa Clara County, California. Hotels and cottages. These excellent springs are picturesquely located in the coast range of mountains, about eight miles west of Gilroy. They are reached by the Southern Pacific Railroad to Gilroy, and from thence by a daily stage. The surroundings are beautiful. The atmosphere is pure, balmy, and invigorating, and the mineral water and baths are of considerable therapeutic value. One of the principal fountains is the Soda Spring. Anderson's analysis:

ONE UNITED STATES GALLON CONTAINS:

Solids.	Grains.
Sodium chloride	8.20
Sodium carbonate	9.92
Sodium sulphate	Trace.
Potassium chloride	Trace.
Potassium iodide	Trace.
Potassium carbonate	0.47
Magnesium carbonate	6.65
Magnesium sulphate	1.15
Calcium carbonate	7.31
Calcium sulphate	2.19
Ferrous carbonate	Trace.
Alumina	4.13
Borates	Trace.
Silica	4.11
Organic matter	Trace.
Total solids	44.13
Gases.	**Cubic inches.**
Carbonic acid	9.25
Sulphureted hydrogen	Trace.

The waters are antacid, diuretic, aperient, and tonic, and of value in acid dyspepsia and catarrh of the stomach, in constipation, and in kidney and bladder troubles.

The next spring in importance is the Sulphur Spring. It is very similar in chemical composition to the Soda Spring, but contains a much larger volume of sulphureted hydrogen (7.25 cubic inches per United States gallon). This water is also antacid, laxative, tonic, and diuretic, and is said to be useful in rheumatism and sciatica, chronic arthritis, and skin diseases. Excellent bathing facilities have been constructed. *James K. Crook.*

BLOOD, CIRCULATION OF THE. See *Circulation of the Blood.*

BLOOD, FORMATION OF THE.—A complete account of the formation of the blood ought naturally to contain a discussion of the origin and maintenance of the *liquor sanguinis* or plasma, in addition to a description of the formation, growth, and life history of the different corpuscular elements which are found suspended in that fluid and which constitute, together with it, the blood. But such an inclusive use of the term would open up to discussion under this heading all the phenomena of nutrition, metabolism, and excretion, for all these are concerned in the preservation of a normal blood plasma, and would lead to a repetition of much that has been treated of elsewhere. Accordingly, we shall confine ourselves in the present article to a description of the formation of the blood corpuscles, only incidentally mentioning the first origin of the *liquor sanguinis* in the fœtus, and omitting all description of its subsequent maintenance in normal condition. It will be convenient, in treating of the origin of the corpuscles, to divide the subject into two headings and describe separately their formation during intra-uterine and during extra-uterine life, since their mode of origin is somewhat different in the two conditions; and it will also add clearness to describe in each of these two sections the formation of the red corpuscles, or erythrocytes, including here what is known concerning the origin of the blood platelets, and then separately take up the account of the white corpuscles or leucocytes.

The literature which has accumulated upon the subject of the origin, growth, and regeneration of the blood corpuscles is enormous, so that a mere recapitulation of the titles of papers written upon the subject would probably occupy more space than this entire article, which can accordingly not aim at completeness, but instead at giving a comprehensive bird's-eye view of the subject, and an outline only of the more important opinions held by various authors. At the end of the article are given a few references to *summarized* accounts of the subject

from various standpoints in which some hundreds of references to other original papers will be found, and the writer here acknowledges his indebtedness to the authors of these articles for the subject matter of the present sketch of the subject.

Intra-uterine Formation of Blood Corpuscles.—It is exceedingly interesting, from the evolutionist's point of view, to note that the first erythrocytes observed in the earlier embryonic stages in man and other mammals resemble those which persist throughout life in the lower vertebrates in being nucleated cells. In the human embryo at the fourth week all the red blood corpuscles are nucleated; at the third month, the nucleated cells form only one-sixth to one-eighth of the total number of blood corpuscles; at the fifth month, the nucleated cells are still quite numerous, although present in much diminished percentage; while at birth at full term nucleated red blood corpuscles are entirely absent, having been completely replaced in the circulating blood by the biconcave discs which characterize the blood of the mammalian adult.

It is generally agreed that the earliest red blood corpuscles which have been observed, arise outside the growing embryo in a portion of the mesoblastic tissue which is known as the *area vasculosa.* Here certain pigmented patches appear, caused by the development of hæmoglobin within the cells, which are known as "blood islands," and it is generally admitted that it is in these "blood islands" of the mesoblast *outside* the growing fœtus that the first blood-vessels and erythrocytes originate. At a later stage the blood-vessels within the embryo are formed by outgrowths from these, and from similar developments taking place within the body of the embryo.

There are, however, two principal theories extant as to the manner in which the initial blood-vessels and red corpuscles are formed in the mesoblastic cells.

The earlier of these two theories, which was originally supported by Reichert and Kölliker, states that the first blood corpuscles originate from solid cords of cells which later develop to form the heart and vessels, with the contained plasma and corpuscles. These solid cords appear in the vascular area and develop so as to form a communicating network. The peripheral cells in the cord alter later to form the walls of the future blood-vessel, while the central cells become pigmented by hæmoglobin, acquire a spheroidal shape, and remain attached to the peripheral part in tufts; meanwhile a fluid appears between the masses of cells within the developing vessel which forms the future plasma; this fluid, being set in motion by the contractions of the heart which has now developed in connection with the system, detaches by degrees the adherent cells, which then circulate and form the first red blood corpuscles. The number of circulating cells is increased afterward both by indirect division of those already circulating and by increase in a similar fashion of those still adherent to the wall of the embryonic blood-vessel and their subsequent detachment. This theory has lately been somewhat revived, as a result of direct observation during life on the transparent embryos of certain fishes. Here it is said that the first fluid driven round by the developing embryonic heart is a colorless plasma, in which nucleated red blood corpuscles appear later. It is further claimed that these corpuscles can be observed becoming detached at certain areas of the vascular system, and that from the frequency of karyokinetic figures occurring in the circulating corpuscles at this stage they undoubtedly undergo increase by indirect division while circulating.

The other view, which was introduced by Klein and is supported by Balfour, Schäfer, and most English histologists, holds that the first red blood corpuscles are formed by free endogenous subdivision of the nucleus within large mesoblastic cells of the vascular area.

The cells which are to form the future blood-vessels send out processes in various directions which anastomose with one another, and later communication is established by means of these processes, so that a continuous communicating network of vessels is thus formed. Meanwhile, within each of these large branching cells alterations take place resulting in a liquefaction of a portion of the cytoplasm to form the future plasma, while the remainder continues adherent around the nucleus. Extensive proliferation of the nucleus also takes place, and around each of the daughter nuclei a portion of protoplasm forms which finally becomes pigmented with hæmoglobin, so giving rise to red blood corpuscles. Still later the intercommuicating channels enlarge so as to allow of the passage of the corpuscles along them, and by the contractions of the heart which has now developed the corpuscles are driven along the system. The primary erythrocytes formed in this way closely resemble leucocytes in their appearance and properties, possessing like these the power of amœboid movement and of increase by cell division, and differ only in the almost complete absence of granules and in the faint yellow color of their cytoplasm.

According to Howell, two distinct types of nucleated red blood corpuscles are present side by side in the blood of the early embryo. One of these types is large and oval in shape, being two to four times as long in the long diameter as the corpuscle of the adult, and being in some cases biconcave, in others biconvex. The other variety is circular in outline and of about the size of the ordinary blood disc of the adult, from which it differs in being nucleated. Howell suggests that the large oval corpuscles may represent the form of the red corpuscle characteristic of the ancestors of the mammalia, and that they may hence be spoken of as ancestral corpuscles, while the smaller circular corpuscles of the usual size of the nucleated red corpuscles of the mammalia exhibit a modification of this ancestral form which has become characteristic of the blood of most of the mammalia. These latter corpuscles afterward lose their nuclei and are converted into the biconcave blood discs, the transition taking place in the young embryo in the circulating blood stream itself, but later being confined to certain specific organs.

The first blood-vessels within the body of the embryo are probably formed in a similar fashion from cells of the mesoblast, and communicate by a network with those already developed as above described in the vascular area outside the body. Through this whole system a current of blood is driven by the contractions of the fetal heart. In the later stages of embryonic life such a general formation as has been above described of red corpuscles throughout the vascular system probably entirely ceases except in regions where new vessels are being formed. The formation of new corpuscles, to replace those broken down, or to increase the number in the circulation as the embryo grows and the vascular system increases in volume, is confined in the later stages of embryonic life to certain organs exclusively; and it is further known that the organ most active in so supplying new corpuscles varies as the development advances. At first, the liver is the most important organ in the development of embryonic red blood corpuscles, but at a later stage this organ takes up other work, and the development of corpuscles in it gradually comes to a standstill. During this period the spleen has been increasing in size, and this organ next becomes the chief seat of formation of new red blood corpuscles. Still later, as the long bones develop and become capable of taking up the function of developing erythrocytes within their marrow, the hæmatopoietic function of the spleen also becomes depressed, and soon after birth it is probable that this function of the spleen, at least under normal conditions, becomes abortive, and the red marrow of the bones is finally left the sole source of supply of erythrocytes during the remainder of the life of the animal.

That the liver becomes a seat of formation of new red blood corpuscles in the embryo almost as soon as it begins to form, was first clearly shown by Kölliker, who believed that the nucleated erythrocytes developed from certain nucleated white corpuscles contained in the developing blood-vessels, that they became pigmented from a formation of hæmoglobin, and then subsequently lost their nuclei, so becoming transformed into non-nucleated red blood corpuscles. Neumann states that the red blood corpuscles are formed within certain large cells of the embryonic liver by an endogenous division of the original nucleus and a portion of the cell protoplasm, whereby a number of nucleated corpuscles appear within the original large cell.

Howell describes the blood-forming cells in the embryonic liver as occurring, not indiscriminately, but grouped into cords or strings lying between the columns of true liver cells which are just commencing to show a definite structural arrangement. (See Fig. 509.) These

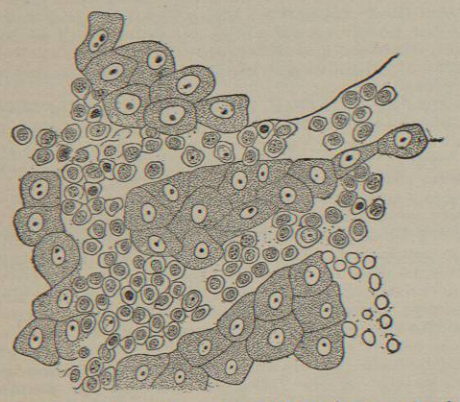

FIG. 509.—Section of the Liver of a Fetal Cat, 2.7 cm., Showing the Development of the Liver Vessels and the Nucleated Red Corpuscles. To the right of the figure the newly formed vessel contains a number of non-nucleated red corpuscles. (After Howell.)

cords of cells develop into the blood-vessels, and it is probable that the peripheral cells, by flattening and otherwise altering, form the endothelial wall of the vessel, while the central cells are set free as red blood corpuscles. Also at places the solid mass of cells is interrupted by vacant spaces filled with plasma which contains only a few fully developed red corpuscles either with or without nuclei. The masses of cells above described are at first colorless, but afterward they develop hæmoglobin, thus becoming pigmented.

The formation of red blood corpuscles in the spleen is demonstrated by the presence in that organ of nucleated erythrocytes in considerable number from the fifth month of intra-uterine life until a few months after birth.

The share taken by the spleen in the formation of red blood corpuscles in the embryo is in any case an important one only during the latter half of intra-uterine life, after the process of formation in the liver begins to abate and before the long bones are fully formed. The process of multiplication of erythrocytes in the spleen is probably identical with that above described in the case of the liver; it persists, though in much lessened degree, up to the end of fetal life, and even for a period thereafter which is variously stated by different observers as from two or three weeks up to as many months. Eventually the formation of red blood corpuscles in the spleen entirely ceases, according to most modern observers, and this process is afterward confined to the red marrow. It has been clearly shown that the nucleated erythrocytes in all stages of intra-uterine development increase in number by mitotic division, and the relative activity of different organs as seats of formation has been rated from the relative number of erythrocytes showing karyokinetic figures in any given part. At first the cells undergoing division are seen in the circulating blood; later they may be observed only in the liver, and do not occur, or only occasionally, in the blood in other parts of the body; still later they are found in great numbers in the spleen; but at the close of intra-uterine life and thereafter they are found but rarely in the spleen *save after extensive bleeding*, and are almost solely confined to the red marrow. This is an interesting confirmation of the order, stated above, in which the hæmatopoietic organs of intra-uterine life take up their functions.

The manner in which these nucleated erythrocytes are converted gradually into non-nucleated cells as embryonic life advances, is probably the same as that by which a similar change occurs in extra-uterine life, and hence the reader is referred to that section of the article for a discussion of the subject.

A mode of development of red blood corpuscles which is distinctly different from all those above described in that non-nucleated corpuscles are formed therein, was first observed independently by Schäfer and Ranvier as taking place in large cells of the connective tissue just before birth, or just after birth in the case of mammals born in an immature condition, such as the white rat.

The large connective-tissue cells in which this peculiar intracellular formation of blood discs has been observed were named angioblasts by Schäfer and vaso-formative cells by Ranvier. Schäfer describes this method of formation of blood discs somewhat as follows:

A portion of the protoplasm of the angioblastic cell acquires a reddish hue from the development of hæmoglobin, and after a time this pigmented substance separates in the form of globules within the cells, which at first vary in size from a minute speck up to globules of the diameter of a mature red blood disc or even larger; but later the globules become more uniform in size. At a later stage, the angioblastic cells become elongated and pointed at their ends, and processes grow out from them to join similar processes of neighboring cells. Vacuoles now form within the cells, and by enlarging coalesce to form a cavity filled with fluid in which the reddish globules, which are by this time becoming disc-shaped, float. Finally the cavity extends through the cell processes into those of adjoining cells, thus constituting a hollow network of communicating vessels which becomes united with blood-vessels already formed so as be a part of the vascular system. In this manner the blood discs formed as above described pass into the circulating blood.

This type of formation of blood discs in the mammalia is confined to the portion of intra-uterine life immediately preceding birth, but in a few mammals which are born in an immature condition it may be observed for a short period after birth. At a later stage, although new vessels are similarly formed in growing connective tissue, no blood discs are observed in the process of genesis within them. Quite recently Hayem claims to have observed blood platelets as well as blood discs within these vaso-formative cells of young connective tissue.

Little is known as to the formation or mode of growth of either blood platelets or leucocytes during embryonic life, but it is certain that both are present in the blood during the later stages of intra-uterine existence, and also that both appear at a much later period than the red corpuscles. In a human embryo of five months Howell found both white blood corpuscles and blood platelets, but both were present only in small numbers. The white corpuscles were of two kinds, as in the adult, one variety being of small size with a single vesicular nucleus resembling the lymphocytes, while the other kind was of larger size, faintly granular, and apparently with several nuclei or a fragmented nucleus.

According to Schäfer, the earliest white blood corpuscles of embryonic life are in all probability amœboid cells of mesoblastic origin which have wandered into the blood-vessels or lymphatics, where they either may be increased in number by similar additions or may multiply by division.

Löwit states that white blood corpuscles are also formed in the liver during a portion of embryonic life, but at a later stage than the red corpuscles. It will subsequently be pointed out that during extra-uterine life white corpuscles are chiefly formed in lymphatic tissue. The lymphatic glands commence to develop somewhat late in

fetal life, and after this there is no doubt that they, like the somewhat more diffuse lymphatic tissue formed elsewhere before them, take up the function of supplying leucocytes by mitotic division of the amœboid cells which they contain. It has also been stated that leucocytes are formed in intra-uterine life in the intestinal epithelium or the tissue underlying it.

According to Ziegler, the white corpuscles may be regarded as separated cells of the mesoderm, and the lymphatic glands as portions of the mesoderm which retain in this respect their embryonic character, and accordingly throughout life give rise to fresh mesodermic cells (the white blood corpuscles) which are carried off in the lymph.

The fact that the leucocytes are not found in the circulating blood in the earlier stages of fetal life shows that these are not formed in those organs which generate the erythrocytes, and hence that they are not, properly speaking, intrinsic constituents of the blood, but rather have been added from without probably by the agency of the lymph-forming organs. At this stage amœboid cells are also to be found in the tissues outside the blood-vessels as well as in the circulating blood stream, and accordingly they may be looked upon as normal constituents of all tissues which are carried into the blood by the agency of the lymph stream, and then afterward circulate in the blood for a variable time.

Extra-uterine Formation of Blood Corpuscles.—The earliest view entertained with regard to the origin of the red blood corpuscles in extra-uterine life was that they developed from the white corpuscles. This view was first enunciated by Wharton Jones in 1846, who supposed that the red corpuscles were the modified nuclei of the white corpuscles. The formation of a red corpuscle from a white one, according to this observer, consisted in a disappearance of the protoplasm surrounding the nucleus and a development of hæmoglobin in the latter which took on the peculiar shape of the blood disc. Kölliker also supported the view that the red were formed from the white blood corpuscles, but gave an entirely different account of the mode of development. He thought, from a comparison in size, that the blood discs arose from the small uni-nucleated white corpuscles derived from the lymphatic glands, and claimed that these have frequently a yellowish tinge, probably due to the presence of hæmoglobin, and hence that they may develop into erythrocytes just as in the embryo, where, he states, the first nucleated cells found in the blood-vessels are originally colorless. Kölliker admitted that no transition stages could be satisfactorily demonstrated in the blood, and in part attempted to explain this as possibly due to the rapidity of the change in certain stages. He supposed that the chief acts in the change were the disappearance of the nucleus and the modification in shape of the protoplasm. He further admitted that the large multinuclear leucocytes probably did not undergo any such metamorphosis into red blood corpuscles. This theory was supported by many observers, and some described the appearance in the blood of transitional forms between the white and red corpuscles, especially under exceptional conditions, in which the rate of formation of red corpuscles might be expected to be increased, as, for example, after excessive hemorrhage or in leukæmia; while under opposed conditions, such as inanition, these transitional forms were said entirely to disappear. Thus Erb claimed to have observed certain red corpuscles which contained a fragmented nucleus or granules apparently of nuclear origin. He supposed that white corpuscles arose in the lymphatic glands and spleen and passed into the blood stream as small uni-nucleated cells with a scanty cytoplasm. The cell increased in size and then underwent two modifications, one of which consisted in the partial disappearance of the nucleus by fragmentation, and the other in the development of hæmoglobin in the cytoplasm, so giving rise to his observed transitional forms. Finally, the cell became somewhat smaller and took on the characteristic shape of the blood disc.

A later theory located the origin of the blood discs in the spleen, where they were supposed to be formed endogenously within certain large cells of the splenic pulp. This theory rested on the experimental observation that within these splenic cells blood discs could be observed in various stages of formation; but while this experimental observation is generally admitted to-day, it is taught by many observers that this indicates a destruction of effete red blood corpuscles within the organ, and not a building up of new ones. The stages of alteration within these erythroclastic cells present all the appearances of degradation in the irregular and broken outline of the corpuscles, and not those of new formation.

The chemistry of the spleen proteids also supports the view that there is such a breaking down of hæmoglobin within this organ accompanied by a conservation of the iron-containing portion of the hæmoglobin molecule, for the spleen is the richest organ of the body in iron-containing proteids other than hæmoglobin. A similar presence of proteids containing iron in the liver, as well as the formation of the bile pigments which are so closely related to hæmoglobin, indicates that chemical processes connected with the metabolism of hæmoglobin also occur in the liver cells. The fact first demonstrated by Schäfer, that the plasma of the splenic vein contains no free hæmoglobin, shows clearly that the chemical alteration undergone by the red corpuscles disintegrated in the spleen is a deep-seated one, and not merely a physical breaking up of the blood disc as a physiological organization.

The next important advance in our knowledge of the extra-uterine formation of red blood corpuscles was made independently and practically simultaneously by Neumann and Bizzozero in 1868, by the discovery of nucleated red blood corpuscles in great number in the red marrow of bone, which closely resemble those found in embryonic life, but differ in being present at all stages of the animal's subsequent life. This important discovery may be said to have completely revolutionized our knowledge of the subject, and it is now very generally believed that except under very abnormal conditions no red blood corpuscles are formed elsewhere than in the red marrow of bone, although there are still differences of opinion as to the origin of these nucleated erythrocytes of the red marrow, as to the way in which they increase, and as to the manner and place in which they alter so as to give rise to the perfected blood discs. The erythrocytes of red marrow are nucleated cells of very variable size which are capable of very active amœboid movement, but differ from ordinary leucocytes of blood or lymph, and also from the other leucocytic elements of the marrow itself, in that they are tinged a light yellow color in the fresh condition by the presence of hæmoglobin. These cells undergo division, as was first shown by Bizzozero, by karyokinesis, and in this way undoubtedly are largely if not entirely regenerated in the marrow. In most sections of red marrow karyokinetic figures are easily observed, of which the diaster is the most frequently occurring form. It is also stated that the number of cells undergoing such indirect division is enormously increased after severe hemorrhage, so illustrating the much-increased rapidity of formation of blood discs.

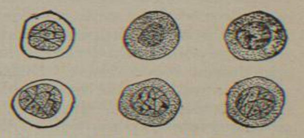

FIG. 510.—Nucleated Red Corpuscles, Showing the Mature and the Immature Forms, the Intermediate Stages, and the Colorless Erythroblasts. (Adapted from Howell.)

Howell divides the nucleated red blood corpuscles into immature cells and mature cells, according to the behavior of the nucleus toward chromatin-staining reagents. As extreme types he describes those containing in their nuclei a network of chromatin showing conspicuous, highly staining granules at its nodal points, and those in which the nucleus shows no reticular structure whatever, but takes a uniform stain as though the chromatin were evenly distributed throughout it (see Fig. 510). The latter is the more mature type; in it the nucleus is smaller than in the immature type, and, according to Howell, is being prepared for extrusion by being situated eccentrically, or indeed partially extruded. All shades of transition are to be found between the typically mature and immature types.

In addition to the nucleated erythrocytes, the red marrow contains other varieties of cells which are interesting here because they have been assigned by many observers a function as precursors of the nucleated erythrocyte stage of development.

That one of these to which much importance is generally attached as a forerunner of the erythrocyte is a leucocytic cell which cannot be said to differ in appearance in any respect from the immature nucleated red cell above described, save in that it contains no hæmoglobin. This type of cell has been described by Osler, Löwit, and others, and has been designated, from this supposed function, an erythroblast by Löwit. These cells must not be confused with ordinary leucocytes of the blood, also found in the marrow, and may be distinguished by the homogeneous appearance of their cell protoplasm, and, according to Löwit, by the fact that they never make amœboid movements nor ingest foreign particles.

The third type of cell seen in red marrow is what is termed the ordinary or proper marrow cell. This is somewhat larger than the other cells described above, and contains a prominent vesicular nucleus of oval shape showing one or two clearly marked nucleoli. In some varieties of this cell, according to Howell, the nucleus becomes elongated in shape and may be bent horseshoe-shape, or may even be coiled upon itself one or more times. Other cells, according to the same observer, may be detected in which the cell protoplasm is loaded with coarse granules.

In addition to these three types of cell of ordinary size the marrow contains a large number of cells peculiar to this tissue called giant cells; these are huge cells with only a single nucleus, which may be either notched or elongated and coiled upon itself so as to simulate the appearance of a number of nuclei. These cells are said by most authors to be different from the myeloplaques found near the developing bone, as well as in pathological formations under many conditions. The latter are multinucleated, and when found in bone marrow occur in such positions as to make the observer surmise that they are connected with bone absorption and accordingly are not intrinsic constituents of red marrow.

Many views are still maintained as to the origin of the nucleated erythrocytes of the marrow. One of the most important of these is that enunciated by Bizzozero, who, as above stated, first drew attention to the frequent occurrence of indirect division in these cells. This observer holds the view that the cells in question are direct descendants of the similar embryonic cells described above as occurring in embryonic life, which are carried to the red marrow as soon as this begins to develop, and take on the hæmatopoietic functions which were up till then taken care of by the embryonic spleen and liver. In the red marrow these cells increase by karyokinetic division, and in this way replace that fraction of their number which is continuously being modified to pass into the circulation as blood discs. Bizzozero is of the opinion that no other mode of origin of nucleated erythrocytes has been demonstrated, and that such a mode of origin forms an adequate explanation. Accordingly he regards the smallest faintly pigmented erythrocyte as the first stage toward the formation of the blood disc in the red marrow, and considers that the other types of cells present take no part in the formation of the red blood corpuscles. This view, that the nucleated erythrocytes of the marrow form a type which is *sui generis*, is supported by Schäfer and other observers; but probably the majority of writers, while not denying that these cells when once formed can increase by indirect division, hold with Neumann that they originate from non-pigmented cells of the marrow. Most of those holding the latter view consider that the second type of marrow cell described above is the colorless predecessor of the erythrocyte of the marrow, and have described these cells independently under different names. Löwit terms them erythroblasts, and deprecates the common use of this term to describe their colored descendants, which, according to him, should be called nucleated erythrocytes. Neumann also objects to the term of erythroblasts for the nucleated hæmoglobin-containing cells of the marrow, contending that such a term is applicable only to the colorless forms which precede them.

Malassez states that the nucleated red blood corpuscles are derived from the proper marrow cells by these giving rise first to spherical cells of large size which do not readily stain, contain little or no hæmoglobin, and possess a very diffuse nucleus. These cells are termed protohæmatoblasts by Malassez, and give rise to the nucleated erythrocytes by passing through two or three stages of alteration in which the cell protoplasm becomes granulated, and the nucleus at first enlarges, becomes prominent and uniformly granular, but later decreases in size and shows a reticular structure. At the same time that these changes are progressing the cell becomes more and more deeply tinted with hæmoglobin and takes on the appearance of the nucleated erythrocyte.

Foà and Salvioli express the view that the first stage in the formation of the erythrocyte is one type of the giant cell, namely, that described by Bizzozero as the type with budding nucleus, in which the nucleus is not multiple but apparently made up of a convoluted string of nuclei still in connection with one another. This giant cell, which is termed an hæmatoblast by these authors, breaks up into a number of small hyaline cells by the separation of the compound nucleus into its constituent buds, each of which has a fragment of the original cell protoplasm attached to it. The hyaline cells later change to nucleated red corpuscles by the development of hæmoglobin. Osler derives the nucleated red blood corpuscles from colorless hyaline cells of 9 to 12 μ in diameter containing a finely granular nucleus, which in turn arise from small lymphoid elements (2.5 to 5 μ) resembling free nuclei but often showing a narrow border of cell protoplasm. A very similar view has been proposed by Obrastzow, who, however, believes that the free nuclei give rise both to erythrocytes and proper marrow cells. According to this author, the erythrocyte contains no nucleus in the living state, the apparent nucleus being a post-mortem effect.

Howell combines most of these theories of origin of the mature nucleated erythrocyte by describing them as different consecutive stages in a rather lengthened course of development. We may, following this author, probably trace the stages in development backward as follows: The nucleated red blood corpuscles differ in structure with their age, and two extreme types may be distinguished—one mature and ready to be converted into a non-nucleated corpuscle, and one immature, as shown by the character of the nucleus and the amount of hæmoglobin. The immature corpuscle multiplies by karyokinesis, and the daughter cells sooner or later appear as mature nucleated corpuscles. The immature or young nucleated corpuscles are in turn derived from spherical colorless erythroblasts, having a definite histological structure and found in the marrow. These erythroblasts multiply by karyokinesis. The erythroblasts again are derived from larger embryonic cells, usually described in the adult as ordinary marrow cells.

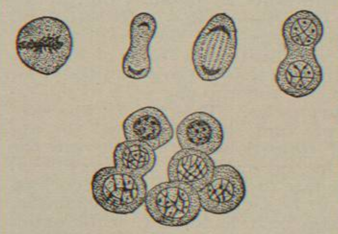

FIG. 511.—Multiplication of the Nucleated Red Corpuscles. Marrow of young kitten after bleeding. Showing above karyokinetic division of erythroblast, and below the formation of mature from immature erythrocytes. (Adapted from Howell.)

In these cells the structure of the nucleus differs from that of the erythroblast. The erythroblasts do not arise from these larger marrow cells in the same generation by a diminution in size, but the marrow cells multiply by karyokinesis, and the daughter cells of the first or following generations acquire the structure of erythroblasts.

There is also much diversity of opinion as to the manner in which the nucleated erythrocyte of red marrow becomes converted into the characteristic non-nucleated biconcave disc of mammalian blood. In fact all possible opinions have been presented by the ingenuity of various authors between the extremes that the red corpuscles are still nucleated, and that they are the nuclei of the nucleated corpuscles of which the cell protoplasm has disappeared. There is little doubt, however, that the non-nucleated corpuscle arises by the disappearance of the nucleus in some manner, and we need discuss here only a few of the chief ways in which it has been claimed that this disappearance of the nucleus is accomplished.

The earliest view and at the same time that which at the present day claims most adherents was originally expressed by Kölliker with regard to the nucleated embryonic erythrocytes, and was later extended by Neumann to include those cells discovered by him in the red marrow. According to this view the nucleus is gradually absorbed by the cell protoplasm after a previous partial fragmentation. "The cells gradually become more and more flattened, and even present slight excavations, whilst their nuclei manifestly diminish, and, on the application of acetic acid, exhibit a great tendency to disintegration. Ultimately, the *nuclei* disappear altogether and the blood cells become *non-nucleated*, like those of the adult, of which they all soon assume the form, being at first somewhat irregular" (Kölliker).

Neumann describes the nucleus as becoming smaller, more homogeneous, and later notched or indented, in the process of disappearing. He also describes certain cells containing only one or two granules of nuclear matter which he regards as the final stage in the disintegration and absorption of the nucleus. Another view which is supported by Rindfleisch, Howell, and others is that the nucleated cells become non-nucleated by a process of extrusion of the nucleus. The various authors who hold this view differ somewhat as to the manner in which the nucleus is expelled. Rindfleisch describes the nucleus as escaping from the cell surrounded by a small amount of colorless protoplasm, and leaving behind a residue of a reddish-yellow color, which is at first somewhat bell-shaped from the escape of the nucleus and afterward takes on the biconcave shape of the adult red blood corpuscle. For every red blood disc so formed there is in this manner set free in the circulation a colorless element, the further fate of which the author leaves unsettled. It is possible that it may once more form hæmoglobin in its cell protoplasm, which may increase in bulk and later give birth in similar fashion to a second non-nucleated red blood corpuscle.

Howell, on the other hand, states that the nucleus is extruded from the cell in a free condition and he has never been able to observe an envelope of protoplasm surrounding it as it escapes. Also free nuclei which have presumably been extruded from corpuscles are frequently seen in sections and teased specimens of red marrow. Howell admits that the homogeneous nucleus of ripe erythrocytes of the marrow may often be seen segmented or notched as described by Neumann, but as he has also seen similarly altered nuclei in the process of extrusion he holds that this segmentation does not prove that the nucleus disappears by absorption.

The extrusion of the nucleus can best be seen in teased specimens from the red marrow of animals which have recently been bled previous to killing and in which, therefore, the rate of formation of blood discs would naturally be much increased. All stages can be detected from that in which the nucleus has merely an eccentric position up to the period when it lies completely outside the cell.

It is well known that the nuclei are readily pressed out from the red blood corpuscles of amphibia after death by simple pressure of the cover glass or the action of chemical reagents, and Howell points out that the extrusion of the nucleus in the erythrocytes of the marrow cannot be any similar *artefact* for the following reasons: 1. The number of extruding nuclei is increased in animals which have previously been bled frequently. 2. The process of extrusion can be observed with the corpuscles in a perfectly fresh condition as soon as the specimen has been teased out in the animal's own serum. 3. Extrusion is seen when the cells have been fixed as rapidly as possible either by corrosive sublimate or by methyl green solution. 4. All the cells showing extrusion belong to Howell's mature variety (*vide supra*), for none of the extruding nuclei show any traces of a nuclear network. Still it is stated by Fellner, Osler, and other observers that the extrusion of the nucleus is to be regarded as a post-mortem change and that such extrusion does not occur under normal conditions in the living cell. Malassez denies that the nucleated red blood corpuscles lose their nuclei at all, maintaining that these retain their individuality throughout their life, but give rise to the red blood discs by a process of gemmation or budding. At some portion of the cell the cell protoplasm sends out a bud which enlarges, becomes constricted off from the rest of the cell, and is finally detached as a globule of hæmoglobinated protoplasm which afterward takes on the biconcave shape of the blood disc.

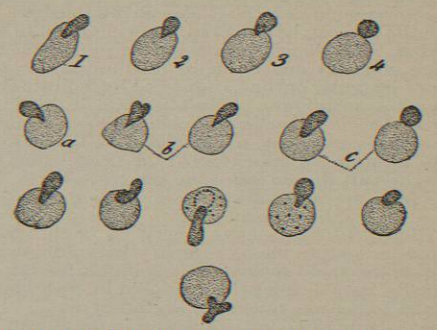

FIG. 512.—Shows the Way in Which the Nucleus Escapes from the Nucleated Red Corpuscles. 1, 2, 3, 4, represent different stages of the extrusion noticed upon the living corpuscles; *a*, specimen from the circulating blood of an adult cat, bled four times; *b*, specimens from the circulating blood of a kitten forty days old, bled twice; *c*, specimens from the blood of a fetal cat, 9 cm. long. Others from the marrow of an adult cat, two of the figures showing the granules present in the corpuscle which have been interpreted erroneously as a sign of the disintegration of the nucleus. (After Howell.)

With regard to the place of formation of the blood discs, it is almost universally admitted that the red marrow of bone is the tissue in which they are produced most abundantly. Neumann even maintains that this tissue is the only one which yields them, even under most exceptional circumstances, for their increased production, such as after excessive or oft-repeated blood-letting. Other observers, such as Bizzozero, hold that while the red marrow is the only seat of production under normal physiological conditions, yet other organs may take on the function of forming red blood corpuscles under abnormal conditions of increased production. Thus, nucleated red blood corpuscles have been found in the spleen of the dog and guinea-pig if the animals have previously been subjected to excessive bleeding (Bizzozero and Salvioli). Clinical observations also are on record in which it is stated that nucleated red corpuscles are found in the blood in severe cases of leukæmia or pernicious anæmia (Osler and Gardner). Howell has also observed a recurrence of the hæmatopoietic function of the spleen with regard to red blood corpuscles after excessive bleeding, although normally no nucleated red blood corpuscles are present in that organ.

Löwit and one or two other observers claim that both spleen and lymphatic glands are to be looked upon as blood-forming organs in addition to the red marrow. In all of these organs, according to Löwit, two kinds of colorless cells may be recognized which he terms "leucoblasts" and "erythroblasts" respectively, because the former give rise to the white and the latter to the red blood corpuscles. These two types of cell are distinguished by differences both in the action of their nuclei toward staining reagents, and in the mode of their division in reproducing new cells; also no intermediate forms between the two can be observed, showing them to be distinct types. The leucoblasts possess a prominent nucleus which contains one or more nodules of chromatin, usually of irregular outline, connected by delicate threads to the nuclear membrane. The after-fate of these is considered under development of white blood corpuscles. Division takes place by a movement of the chromatin granules from the equator toward the poles which Löwit proposes to call *divisio indirecta per granula*, to distinguish it from the true karyokinetic division which takes place in the erythrocyte and which he terms *divisio per fila*. The erythroblasts have a network of chromatin in their nucleus, and divide by ordinary karyokinesis; they never show amœboid movement nor ingest foreign particles; finally they develop hæmoglobin in their cell substance and so become nucleated erythrocytes.

In the marrow of bone always, and in the spleen under certain conditions above alluded to, transition stages may be observed, but in the lymphatic glands no intermediate forms between erythroblast and nucleated erythrocyte are ever to be seen, and hence Löwit supposes either that the transition in this latter case takes place in the lymph or blood stream or in both, or that the erythroblasts formed in the lymphatic glands are carried to the marrow and there undergo the final change into nucleated erythrocytes. Löwit further holds that a great number of the erythroblasts enter the blood stream from the spleen and lymphatic glands in a colorless condition, and are in the blood stream itself rapidly converted first into nucleated and later into non-nucleated erythrocytes. The two types of cells above described have also been observed subsequently by Denys and by Gibson, and the latter writer claims to have observed nucleated red blood corpuscles in the mesenteric lymphatic glands after ligature of the thoracic duct. Denys states that in the marrow of birds which has been double stained with fuchsin and methyl green, the nuclei of the erythroblasts stain green while those of the leucoblasts stain red. As a result of this distinctive staining the important fact is brought out that the two types of cell are not indiscriminately mixed, but that the erythroblasts occur in cords or strings forming the capillary portion of the vascular system of the marrow. A delicate endothelial wall marks off the cord of erythroblasts from the surrounding mass of leucoblasts.

Some observers state that red blood corpuscles develop in bone and cartilage, and particularly in the line of ossification between the growing bone and its hyaline cartilage, but this has again been denied by Neumann and others. Winogradow states that nucleated red corpuscles form in the lymphatic glands of the dog after spleen extirpation, but this result also has failed to obtain confirmation at the hands of other workers. Quite a different theory to all these is that supported by Hayem, in that it ascribes the origin of red blood corpuscles to the blood platelets or "elementary particles" of Zimmermann instead of the nucleated erythrocytes. This view was originally suggested by Zimmermann, but has been worked out in detail by Hayem, who has given more attention to the blood platelets than any other worker on the subject. Hayem describes the blood platelets as young red blood corpuscles and terms them hæmatoblasts. Certain of them, according to his description, are similar in shape to the biconcave discs, and possess a greenish tint from the presence of hæmoglobin. He claims to have observed intermediate forms between the typical blood platelet and the typical red blood corpuscle, and states that these transitional forms are greatly increased in number after severe hemorrhage when a more rapid regeneration of corpuscles is presumably taking place. Under such circumstances the blood platelets may increase so greatly in amount as to outnumber the red corpuscles.

There is also much difference of opinion as to the manner in which the blood platelets are formed. Pouchet, who supports Hayem's view that the red blood corpuscles are formed from the platelets, supposes that the platelets are either extruded from the white blood corpuscles as "polar bodies" or that they arise as concretions in the plasma. Gibson describes two varieties of platelet under the names of colorless and colored "microcytes." The former he supposes to be derived from the extruded nuclei of both nucleated red corpuscles and white corpuscles, and the latter (which he regards as identical with Hayem's hæmatoblasts) he supposes arise from fragmentation of mature blood discs in some manner in the circulation. Howell denies that the extruded nuclei of the erythrocytes give origin to blood platelets, showing that during the period that they persist in the blood as morphological elements, they stain quite differently from the blood platelets. It is probable, according to this author, that the extruded nuclei of the red blood corpuscles dissolve in the plasma, and possibly increase the percentage of fibrinogen therein. With regard to the origin of the blood platelets, Howell supports the view that they are the final products of disintegration of the multinucleated leucocytes, by drawing attention to the close resemblance between well-preserved blood platelets and the fragmented nuclei of the multinuclear leucocytes as far as size, shape, and general appearance are concerned. The resemblance is increased by the appearances noticed in the blood of an animal after frequent bleeding. Here blood platelets may be observed containing one or more deeply staining granules which closely resemble the chromatin granules of the nuclei, and are probably the result of too rapid expulsion of the nucleus on account of the increased activity in the blood connected with regeneration. The blood platelets further stain similarly to the nuclei when subjected to the action of multiple staining. Howell suggests that such disintegration of corpuscles within the plasma may have an important function in the regeneration of the proteids of that fluid.

It is almost universally agreed that the lymphocyte is the youngest form of leucocyte found in the blood. The lymphocyte is so termed because it is believed that it originates in lymphoid tissue and is added to the blood in the lymph stream.

The fact that the number of lymphocytes in the lymph is largely increased after its passage through a lymphatic gland, as well as the presence of immense numbers of similar cells in the lymphoid tissue, demonstrates that lymphocytes are formed in the lymphatic glands and are continuously carried away by the lymph and added to the circulating blood. Also in the blood white corpuscles are to be found which differ in no respect from these lymphocytes of the lymphoid tissues, and between these and the other varieties of leucocyte transitional cells are to be observed, so that there can be little doubt that all the other forms are stages in the further development of the lymphocyte.

Most observers also hold that leucocytes are formed in the spleen and red marrow in addition to the lymphoid tissues. Löwit describes the leucocytes as arising from certain cells in these tissues which he terms leucoblasts. The general characteristics which distinguish these from erythroblasts have already been stated; it may be added that Löwit describes the leucoblasts as entering the lymph stream and eventually reaching the blood as uninuclear leucocytes which are rather small and are devoid of the power of making amœboid movements. In the blood stream they increase in size while the nuclei take on the form seen in the polymorphonuclear cells; ultimately multinuclear leucocytes arise from these as a final stage which is followed by the disintegration and solution of the corpuscle. Löwit believes, from estimations of the relative number of the different forms of leucocyte in the blood coming from the blood-forming organs, in the

right and left heart, and in the peripheral arteries, that the transition from the lymphocyte to the other forms takes place rapidly in the venous blood before reaching the left heart. Flemming and a great many other workers hold, in contradistinction to Löwit, that multiplication of the leucocytes takes place by a true mitotic division. It is certain also that the eosinophile cells of Ehrlich exhibit karyokinetic figures while undergoing division. Bannworth has described cells possessing all the properties of Löwit's leucoblasts, as undergoing karyokinetic division in the spleen pulp.

The life history of the leucocyte may then probably be described as follows: It arises from leucoblastic cells in lymphoid tissue and probably also in the splenic pulp and red bone marrow, and reaches the blood as a small cell, with a prominent vesicular nucleus surrounded by a trace of cell protoplasm. This variety of leucocyte is incapable of amœboid movement, but gives rise in process of growth to a large cell which is amœboid, and is further characterized by possessing a large envelope of finely granular protoplasm around its nucleus. In some varieties of this stage the granules in the cell protoplasm are more conspicuous than in others. The next development takes place by an alteration in the nucleus, which is no longer spherical or oval but drawn out into a strap or horseshoe shape, or indeed coiled or folded upon itself so as in some cases closely to resemble a multiple nucleus. This gives rise to the polymorphonuclear cell, which is still capable of amœboid movement, and which by fragmentation of the complex nucleus gives rise to the multinuclear leucocyte.

The earlier view was that the polymorphonuclear and multinuclear leucocytes were those in process of cell division, but it is now more commonly believed that the nucleus in these cells is undergoing fragmentation previous to the disintegration of the cell. *Benjamin Moore.*

The following references will be found to furnish a key to the source of most of the statements given in this article:

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BLOOD, NORMAL.—The blood would seem to conform to the general definition of a tissue, in that it is composed of a cellular and an intercellular substance. It differs, however, from any other tissue of the animal body in the fact that the intercellular substance is a fluid, and that it is a *moving* substance propelled by the beat of the heart throughout a system of closed tubes; it also, perhaps, contains a greater variety of morphologically and physiologically dissimilar elements than any other tissue; the blood, or its congener the lymph, is found in all structures, affording nourishment to them and taking in their waste products in return. There is no passage of morphological constituents from the general tissues into the blood as may sometimes occur from the blood to the tissues, as during diapedesis.

According to the same standard, the lymph would seem to come within the limits of the definition, although it is poorer in cellular elements. Whether certain of the semi-fluid secretions, such as the orchitic and mammary during the colostrum period, might come within the range of this definition, we may perhaps regard as unsettled, although it is a question if the fundamental procedure is not analogous when we consider the relationship of the leucocytes to the lymph glands and that of the red corpuscles to the bone marrow and certain other organs.

The total number of cells in the body has been estimated by C. Francke* to be 26,500,000,000,000, of which 4,000,000,000,000 are fixed cells, while the cells in the blood are not fixed, and according to the best calculations these amount to 22,500,000,000,000. So that the cells in the blood, which are small, outnumber those of the other tissues (some of which, for example the muscle cells, are relatively immense) about five and one-half times.

Blood in general has for its functions (*a*) the conveyance of nutritious material to all parts of the body, (*b*) to remove waste products from the tissues, (*c*) to carry oxygen for tissue (or internal) respiration, and (*d*) to equalize the temperature of the body.

Color and Constituents.—Blood has the appearance of a red, slightly viscous fluid, this effect being due to the suspension of innumerable microscopic bodies, the red corpuscles or erythrocytes, in a clear yellowish fluid, the plasma or liquor sanguinis. In addition to the red corpuscles, but much less numerous, are the white corpuscles or leucocytes. A third element is the blood platelet, a small discoid colorless particle, demonstrable microscopically in freshly drawn blood. There may also be blood granules of different kinds, considered as transformation products of the formed elements.

The color of arterial blood is a bright red, that of the veins is darker or of a bluish-purple tint. This difference is due to the relative amount of oxygen or carbon dioxide present. Arterial blood furthermore differs from venous in that it possesses more O, less CO_2, more extractives, more salts, more sugar, less urea, and is usually warmer.

Arterial blood becomes dark when respiration is imperfect, for example, in the fœtus, during anæsthesia by chloroform, when the trachea is compressed, and in individuals when submitted to a high temperature (which reduces the excretion of CO_2). Venous blood is rendered brighter in animals which have been made to breathe pure oxygen, or when poisoned by carbon monoxide gas, in blood leaving glands in a state of secretory activity or muscles in a state of rest (Bernard), and in hibernating animals.

In the pulmonic circulation the arteries normally contain dark, and the veins bright red blood.

Odor.—Blood has an odor which differs in man and animals. This is thought to be due to the presence of certain volatile acids. If concentrated sulphuric acid be added to blood it liberates these acids from their combinations with alkalies, and the characteristic odor is more perceptible.

Taste.—Blood has a saline taste, due to the various salts dissolved in the plasma.

Temperature.—Blood varies normally in its temperature from 36.5° to 37.8° C. (97.7° to 100° F.). It varies also in different parts of the body. The warmest blood in the body is in the hepatic vein. The blood of the left is cooler than that of the right ventricle, because as it passes through the lungs it is cooled by the inspired air. The blood of the skin is also slightly cooler than that of the viscera. In the arteries, however, it is, as a rule, slightly warmer than in the corresponding veins.

Amount.—The amount of blood in the body has usually been determined by drawing a measured amount, defibrinating it, and diluting portions of it in differing degrees for later comparison. The rest of the blood is then collected and defibrinated, and the vessels washed out with salt solution until the solution comes out colorless. The washings are added to the collected blood, and this is further diluted until it corresponds in tint to one of the previous samples of known dilution. The total quantity of blood in the vessels can then be calculated. In addition to this the whole body can be minced into fine pieces, extracted with water to get any blood that

* "Die menschliche Zelle," 1891.