A CASE OF MULTIPLE MYELOMA.

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Plates V and VI.

During recent years there have appeared several descriptions of a peculiar condition in which simultaneously several bones become the seat of a new growth which often erodes through the cortex and pushes aside neighboring tissues, but which never metastasizes into other organs. The results of the observations of such so-called multiple myelomata and related diseases have been well summarized and discussed by Hammer,[1] Winkler,[2] Wieland,[3] Paltauf,[4] and others, and it is not necessary to repeat this discussion. In brief, the conclusions are as follows: The tumors are distinguishable from other malignant tumors by their mode of growth and the absence of metastasis—from myelogenic sarcomata in particular by their multiplicity and the uniformity of their component cells, giant cells and spindle cells being practically absent. The resemblance of the myeloma cells to those of the bone-marrow and especially the great macroscopic resemblance of the tumors to the adjacent bone-marrow, from which they can scarcely be delimited, have given rise to the opinion that they spring from some of the bone-marrow cells, although Wieland attempts to disprove this. It has been suggested that the process is of an infectious nature. Comparisons with pseudoleukæmia and leukæmia seem to show that they may be readily distinguished.

Recently Wright[5] has described in the cells of such a tumor a

[1] Virchow's *Archiv*, 1894, cxxxvii, p. 280.

[2] Virchow's *Archiv*, 1900, clxi, p. 252.

[3] Primäre multiple Sarcome der Knochen. Inaug.-Diss., Basel, 1893.

[4] *Ergebnisse der allgemeinen Pathologie u. pathologischen Anatomie.* Herausgegeben von Lubarsch u. Ostertag, 1896, iii, 1, p. 676.

[5] Contributions to the Science of Medicine, dedicated by his pupils to William Henry Welch, p. 359. Baltimore, 1900.

resemblance to plasma cells and speaks of the new growth as a plasmoma.

The cases have been described under the most various titles, but there seems to be a well-defined condition easily distinguishable from the endotheliomata and sarcomata of bone for which the name myeloma is most fitting, a condition which Virchow prophesied,[6] although at that time no case had been published.

The description of the following case may be permitted as an addition to the still rather limited series reported. The clinical features, including the occurrence of albumosuria, have already been described by Dr. Hamburger in the *Bulletin of the Johns Hopkins Hospital*, 1901, xii, p. 38. They consisted in the spontaneous occurrence of fractures of several of the bones followed by the appearance of definite soft tumor masses over various bones. There was no marked anæmia—red corpuscles, 3,548,000; leucocytes, 4500; hæmoglobin, 52 per cent, with normal relations among the different varieties of white corpuscles. Albumosuria was definitely determined.

The autopsy record, copied in brief from the protocol, is as follows:

Anatomical diagnosis.—Multiple myeloma: tumor masses in femur, ilium, clavicle, sternum and scapula, with pathological fractures. Tumor mass protruding from skull. Chronic nephritis. Arteriosclerosis. Myomata uteri. Healed tuberculosis of lungs.

Body is that of an emaciated old woman. The right leg is shorter than the left by about 3 cm., and in the trochanteric region there is a tumor mass, at which point there is excessive mobility of the femur. Tumor nodules are to be felt over the left scapula, the left clavicle, and over the vertex of the skull, where the scalp is tensely stretched over the large, soft, almost fluctuant tumor.

The organs throughout showed evidences of senile atrophy, this being especially marked in the heart and liver. The lungs present old scarred tuberculous lesions at the apices. In the uterus there were several myomatous nodules. Nowhere in the organs was there any evidence of the formation of tumors such as those to be described in the bones.

On removal of the sternum it was found to contain at the point of insertion of the second and third costal cartilages a tumor mass which,

[6] Die krankhaften Geschwülste, Bd. ii, p. 7, Berlin, 1864.

being very soft, allowed free movement of the two parts of the sternum upon one another. The left clavicle was much enlarged at its sternal end, the bone being apparently distended by the tumor mass within, for the cortical portion was very thin and could be compressed by the fingers. On sawing through the bone lengthwise the cancellous bone was found to be much rarefied and the cortical portion very much thinned—the marrow was almost entirely replaced by the tumor mass, which extended quite to the acromial end.

The right clavicle showed evidences of a healed fracture, the portions having united in a somewhat abnormal position, so that a slight angular deformity existed. The marrow of this bone also showed tumor masses, which did not, however, cause any extensive erosion of the bone.

From the spinous process of the left scapula there arose a soft tumor mass which on section was found to have eroded and replaced a considerable portion of the bony process. None of the cortex or cancellous bone tissue was to be discovered in this one. The ribs were not involved. Unfortunately the vertebral column was not sawn through, but there were no evident tumor masses visible from without. The right ilium was completely eroded through in its median portion by a large soft mass which had destroyed the whole thickness of the bone and which projected both ways—into the pelvis under the iliacus muscle, and outward under the muscles covering the outer surface of the ilium. The hip-joint on this side showed no abnormality, but in the intertrochanteric region a large tumor mass sprang from the marrow of the femur. At the upper end of the shaft of the femur there was a fracture, the shaft being displaced upward. On sawing through the bone at this point the intertrochanteric region was found to be extensively involved in the new growth, which extended into the adjacent tissues. The cancellous bone was almost entirely destroyed and the cortex much atrophied and roughened internally. For a distance of about 5 cm. the cavity of the shaft of the femur was invaded, the yellow marrow being pushed ahead and fairly sharply limited from the dark purple new growth. The bone marrow was atrophic and œdematous, greyish pink and moist in appearance, and sunken below the level of the cut surface of the invading tumor. The left femur showed no evidence of tumor formation.

Removal of the large mass at the vertex of the skull revealed a large aperture in the skull, the edges of which were very ragged, as if gnawed away, with here and there loose spicules of bone lying in the soft tumor mass which evidently sprang from the marrow cavity. This tumor mass spread itself between the cranium and the dura for a short dis-

tance, and, completely filling the aperture in the skull, projected outward to form the large soft mass felt under the scalp.

No other tumor nodules were to be found so far as it was possible to examine the bones.

These growths presented everywhere the same appearance. Everywhere they evidently sprang from the marrow of the bone from which they were not by any means sharply demarcated. Only where the tumor seemed to invade the yellow marrow of the shaft of the femur was the outline sharp, but even there the microscopical examination showed evidences of the presence of tumor elements far past this outline. Where the red marrow of the short bones formed the point of origin, the outline was not nearly so sharp. The well-defined tumor masses were perhaps somewhat firmer than such a mass of bone marrow would be. They varied somewhat in consistency however. In general they were soft; some of the larger were almost diffluent and flattened out when cut and laid out on a pan. Others were less soft, and in some parts the gelatinous pulpy consistency gave way to a fair degree of firmness. In color there was also considerable variation. The greater part of the masses was of a deep red color, perhaps even darker than that of the normal red bone marrow, but showing everywhere a greyish tint. Usually lines and streaks of grey were to be seen throughout this deep red, and in nearly all the masses definite nodules of firmer consistency and of greyish white color were found. At some points there was a slight yellow opacity.

Microscopically, the various authors have emphasized the regularity in form and size of the cells, and Wieland has adduced this as a distinction from the myelocytes. Nearly all writers have thought the tumor cells to be derived from some cell or other of the bone-marrow. Wright alone considers them to be plasma cells or closely related cells at least, to explain which he states that plasma cells are present in the bone-marrow. The results of attempts to determine the histogenesis of the cells in this case will appear from the following description of the microscopical appearances.

The tumor masses present in sections a remarkably homogeneous appearance (Plate V, Fig. 1). There is, as described in practically all of the other cases, a delicate stroma with rather wide meshes in which lie innumerable rather large round cells. These are not in intimate connection with one another, but lie singly and loose; some-

times where their number is very great they are somewhat compressed into a polygonal form, but in general they are fairly regularly rounded; they vary slightly and may be elongated or pear-shaped or even notched. The nucleus is large, round and vesicular, sometimes lying eccentrically. The protoplasm presents a rather ragged granular appearance. Blood-vessels exist throughout the tumor and are indeed rather numerous. The smaller ones lie in very intimate contact with the tumor cells, their walls being merely a single layer of endothelium. Connected with these and the coarser strands of the stroma are exceedingly fine filaments of connective tissue which run in between the cells. Everywhere scattered quite without order through the tumor mass and among the tumor cells are numerous red blood-corpuscles, which are quite well preserved. These evidently give the dark red color to the tumor masses, being absent or present in only very small quantity in the translucent greyish white nodules described above.

More careful examination of the characteristic cells of the tumor was made by the aid of various methods.

The cells are distinctly of one type, although variations in size and general appearance occur (Plate V, Fig. 1). The well-preserved cells vary in diameter from 13-21 μ. Perhaps their size is best shown by the camera drawing of a number of them where they can be compared with red corpuscles. Fig. 2 (Plate V) shows their relation in size to other well-known cells, B being tumor cells, A plasma cells, and C myelocytes. Their outline is in general smooth and sharp, and there are no processes or evidences of intimate union with adjacent cells. Ordinarily they lie quite free side by side in the spaces in the stroma, generally separated from one another by interspaces in which red corpuscles may be found.

The nucleus is quite large and rounded, and of a definitely vesicular type. It may be situated at any part of the cell, often near one extremity, when, as so frequently occurs, the cell has an elongated pear shape, this perhaps suggesting the appearance of a plasma cell. It is not at all uncommon to find two or three nuclei in one cell, and indeed four round and quite separate nuclei have been observed in a single well-preserved rounded cell. Each of these nuclei has the vesicular type and other characteristics to be described for the single ones (Plate VI, Figs. 3 and 5). In almost every intact nucleus a sharply outlined shining round nucleolus can be made out; its size is best seen in the drawings, all of which are made accurately to the same scale with the camera lucida. This nucleolus can be best seen in sections stained with carbolic fuchsin or safranin, where it stands out as

a glistening red refractive body, or with carbolthionin, where it stains bright blue and is very conspicuous. It is also to be seen in hæmatoxylin specimens, although somewhat masked by the adjacent tingible substances in the nucleus; stained with polychrome methylene blue it appears rather paler and greyer than the remaining nuclear structure.

Beside the nucleolus the nucleus contains points and strands of chromatin arranged sometimes in a somewhat radial way, sometimes more irregularly. In dried smears from the tumor mass fixed with heat and stained with Ehrlich's triple stain, the nuclei present a peculiar appearance. They look large and flattened out and stain in general a homogeneous pale blue. The nucleolus is not especially evident; it takes here a rather paler color than the remaining nuclear substance. The pale blue color does not, however, appear throughout the nucleus, for there are irregular spaces which show no blue but a reddish stain. One gets the impression that the nucleus is composed of ramifying bands of blue staining substance in the meshes of which the nuclear substance does not stain or stains only like the general protoplasm of the cell (Plate VI, Fig. 7). In this way a certain similarity exists between the staining properties of these cells and of the myelocytes. The nuclei of megaloblasts are also sometimes seen to show the same curious appearance. In the myelocytes this lacunar condition of the nucleus is quite visible, although it is somewhat masked by the presence of the granules. When the smear is stained in hæmatoxylin and eosin, however, it is very plainly to be seen. A smear from normal red bone-marrow shows many cells in addition to the granulated myelocyte, which, except in the fact that neutrophile granules are absent, resemble the myelocytes exactly, and the nuclei of these show very definitely this arrangement of fields of blue and pink.

The protoplasm appears in sections rather ragged and granular. The granules are not very sharply outlined; they are not so minute as the neutrophile granulations of polynuclear leucocytes or of myelocytes, nor so large and definite as the eosinophile granulations. Indeed one can scarcely speak of definite sharp granules, but rather of a somewhat granular appearance of the protoplasm. The raggedness is added to by the frequent occurrence of minute vacuole-like spaces, which sometimes become quite prominent. Winkler found in his case a fatty degeneration of the tumor cells and the tiny spaces in the protoplasm of these cells do suggest the presence of fat. Formaline specimens treated by Marchi's method, however, show no evidence of it.

In the sections stained with the triacid Biondi-Heidenhain mixture the protoplasmic granules appear, but they take no definite coloration

different from that of the adjacent protoplasm. In smears stained with the Ehrlich triple stain the whole protoplasm has a pale pink coloration. *No specific granulations are to be seen.*

In sections as well as in smears stained with the polychrome methylene blue of Unna or the alkaline methylene blue the protoplasm takes on only the palest greenish grey coloration; there is nothing of the specific staining described by Unna and others for the plasma cells. With polychrome methylene blue and eosin the protoplasm stains with eosin.

The relation of these cells to the other normal cells from which they might possibly arise is therefore about as follows: In size they greatly exceed the plasma cells, but agree fairly well with the myelocytes and non-granular cells resembling myelocytes found in the bone-marrow. With polychrome methylene blue, etc., they do not show the reaction typical of the plasma cells; on the other hand, their protoplasm, although in its raggedness it does resemble the "granoplasma" described by Unna for the plasma cells, shows none of the specific granulations characteristic of the myelocytes. The presence of a nucleolus must be admitted for all these various types of cells, so that it is of no help in determining such relations. The cells of the myeloma and the myelocytes and non-granular cells of the bone-marrow have in common, however, the peculiar lacunar structure of the nucleus, as seen in dried smears, which H. F. Müller[7] describes as follows: "With adequate magnification one sees in the myelocytes a remarkable nuclear structure; one finds often nuclei in which definite clear fields are visible. These may be in part nuclear substance, but in many such nuclei these fields seem to represent the cell substance which stretches itself into pre-existent holes or pores in the nucleus." And then again, "there is a large round or oval nucleus limited by a thin chromatin wall which shows frequently more or less numerous larger and smaller clear areas, which are often plainly seen to be definite apertures in the nucleus through which the cell substance extends into the interior of the nuclear body."

This structure seems so peculiar that its occurrence in these various cells at least indicates their close relation to one another. The descrip-

[7] *Deutsches Archiv f. klin. Med.* 1891, xlviii, p. 57.

tions and figures of plasma cells in the papers of Unna,[8] Jadassohn,[9] Marschalko,[10] Justi,[11] Krompecher,[12] and Councilman [13] give no hint of such a structure in the nuclei of these cells.

The myeloma cells are apparently separated from the myelocytes by the absence of the characteristic neutrophile granulations. An examination of a bone-marrow smear, and more especially of a smear from actively proliferating bone-marrow, will convince one of the great variations in the abundance of the granules which occur in these cells. In a recent paper on the relation of the myelocytes to leucocytosis, Rubinstein [14] describes the transitions which take place in the development of myelocytes from smaller cells whose protoplasm is quite free from granules. These young myelocytes reach quite the size of the adult myelocytes before the granules appear, which they do gradually a few at a time. The resemblance then between these non-granular myelocytes, as they may perhaps be called, and the myeloma cells is most striking, and suggests most strongly the origin of the myeloma from these characteristic cells of the bone-marrow in one or other stage of their development.

Further evidence of this close relation is given in the abundant presence of the tumor cells in the marrow adjacent to the tumor masses, where they take on exactly the arrangement of the myelocytes among the fat cells and are intermingled with the occasional eosinophile cells. Indeed if, in a large section, we pass gradually from the relatively normal marrow toward the tumor, we find a gradual and insensible transition, the myelocytes being replaced entirely in time by the tumor cells, which become more and more densely arranged, forming finally definite nodules. Among the trabeculæ of the cancellous bone this consolidation of the cells which have the position and form of myelocytes into solid strands in direct continuity with the tumor mass is very convincing evidence of the direct relation between the tumor and bone-marrow cells.

[8] *Monatshefte f. prakt. Dermatologie*, 1891, xii, p. 296.
[9] *Berliner klin. Wochenschrift*, 1893, xxx, p. 222.
[10] *Archiv f. Dermatologie u. Syphilis*, 1895, xxx, p. 3.
[11] Virchow's *Archiv*, 1897, cl, p. 197.
[12] Ziegler's *Beiträge z. path. Anat.*, 1898, xxiv, p. 163.
[13] *Journal of Experimental Medicine*, 1898, iii, p. 401.
[14] *Zeitsch. f. klin. Med.*, 1901, xlii, p. 161.

Various alterations in the appearance of the tumor cells, which may perhaps best be interpreted as degenerative changes, frequently occur. Division of the cells by karyokinesis has not been once observed in this case, although such nuclear figures were carefully sought after. As described above, however, many of the cells contain more than one nucleus—sometimes as many as four—and in such cases the cell is generally larger than the average, in some instances reaching a great size (Plate VI, Figs. 3 and 5). These multiple nuclei are generally rich in chromatin and stain very deeply. They are often quite irregular in outline and occasionally they are seen to be in connection with one another by a band which may be so thin as to appear as a mere filament of nuclear substance. This is very probably to be considered as evidence of amitotic division—a process demonstrated by Nedjelsky[15] in Marchand's laboratory to be not uncommon in various tumors (Plate VI, Figs. 4 and 6).

Often the nucleus of a tumor cell of average size and with the general appearance of being well preserved shows a dense clumping of its chromatin into several rounded deeply staining solid masses which lie then against the limiting membrane of the nucleus (Plate V, Fig. 1). Again, other cells show a tendency toward disintegration of the protoplasm which breaks up into fine granular masses. The nuclei of such cells often appear very pale. Finally, certain cells, sometimes of nearly the average size but generally much larger, show the presence of vacuoles of greater or less size in their somewhat swollen looking and disintegrated protoplasm. The nuclei are pale and crowded to one side, and in the vacuoles are rounded bodies showing transitions in size and appearance from very small highly refractive round bodies to rounded masses of the size of a red corpuscle or slightly larger. These are denser and more solid and refractive than the red corpuscles (Plate VI, Fig. 8). With the Biondi-Heidenhain stain, with which they show best, they stain a bright orange-yellow or brown; with polychrome methylene blue they take little or no stain, except for a rounded denser fleck in the centre, which, visible by its slight variation in color in the Biondi-Heidenhain

[15] Ziegler's *Beiträge zur path. Anat.*, 1900, xxvii, p. 431.

preparation, stains pale blue here. Such cells are often much disintegrated and the inclusions are sometimes found free. These bodies are apparently very similar to the cell inclusions so commonly found in carcinomata and other tumors, as to which there is at present such active discussion.

The tumor mass as described above contains in the interstices between the cells very numerous red blood-corpuscles in a very well-preserved condition. There is very little evidence of any breaking down of the red corpuscles—hardly any deposit of hæmatoidin in the tissues, which would certainly be present if the presence of the blood were due to actual hæmorrhage. Red corpuscles are found scattered in considerable numbers among the myelocytes and other cells in the normal bone-marrow, however, and it seems probable that the condition here is analogous. The walls of the blood-vessels in the tumor are nevertheless of extreme thinness and extravasations might readily occur.

So also tumor cells are quite frequently found inside these blood-vessels lying among the red corpuscles (Plate V, Fig. 1), although an examination of the circulating blood a few days before the death of the woman showed only one or two doubtful myelocyte-like cells among a great number of leucocytes, the varieties of which were those of the blood in practically normal relations.

In conclusion, then, we have in this case multiple new growths from the bone-marrow, not very sharply delimited from the marrow and showing very gradual transitions into it. The cells have the form and general characters of the bone-marrow cells, lacking the specific granules of the myelocytes but possessing the peculiar nuclear structure found in the myelocytes and their formative antecedents. They differ in essential particulars from the plasma cells, and in view of these facts and the fact that they largely replace the myelocytes in the marrow in the neighborhood of the tumor, there being no sharp boundary between the myeloma-like marrow and the myelocyte marrow, we may consider them directly related to these cells and probably derived from the large non-granular forerunners of the myelocytes.

Degenerative changes, the presence of numerous cell inclusions, and the abundance of red blood-cells scattered in the tumor mass have been noted. The etiology of the affection remains obscure.

DESCRIPTION OF PLATES V AND VI.

PLATE V.

Fig. 1. Portion of a section of the tumor from ilium. In the centre a thin walled blood vessel in which a tumor cell lies among the blood corpuscles. Several of the cells show the condensation of the chromatin into solid masses. Among the tumor cells are many red corpuscles.

Fig. 2. *A* Plasma cells, *B* cells from the tumor, *C* myelocytes from normal bone marrow. The drawing is intended to show merely the relative size of the cells and of their nuclei.

PLATE VI.

Figs. 3 and 5. Large tumor cells with multiple nuclei.

Figs. 4 and 6. Similar large cells in which the peculiar form of the nucleus is suggestive of amitotic division.

Fig. 7. Cell from myeloma as it appears in a heated smear stained with Ehrlich's triple stain. The lacunar appearance of the nucleus is exactly that seen in the myelocyte and its related cells.

Fig. 8. Several large somewhat degenerated cells with rounded inclusions lying in vacuoles in the protoplasm—one cell of the average size and appearance found in the tumor is introduced here for comparison.

All the figures except Fig. 7 are drawn with camera lucida to the same scale.

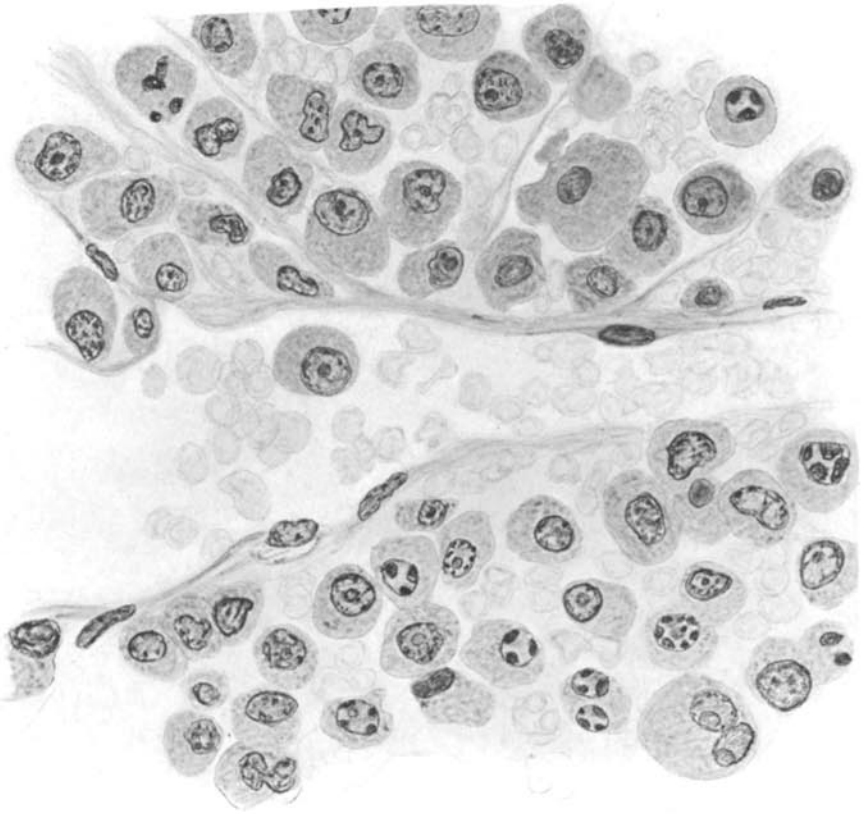

FIG. 1.

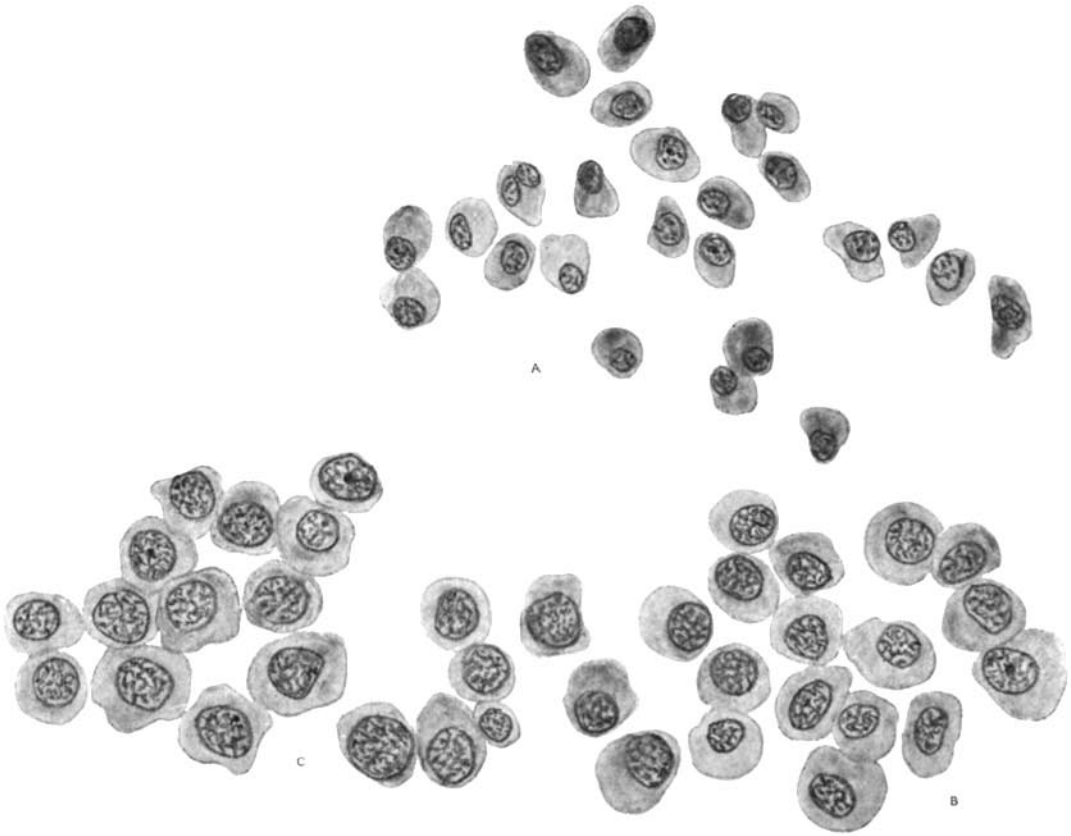

FIG. 2.

FIG. 3.

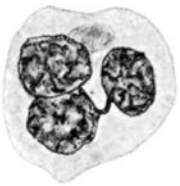

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

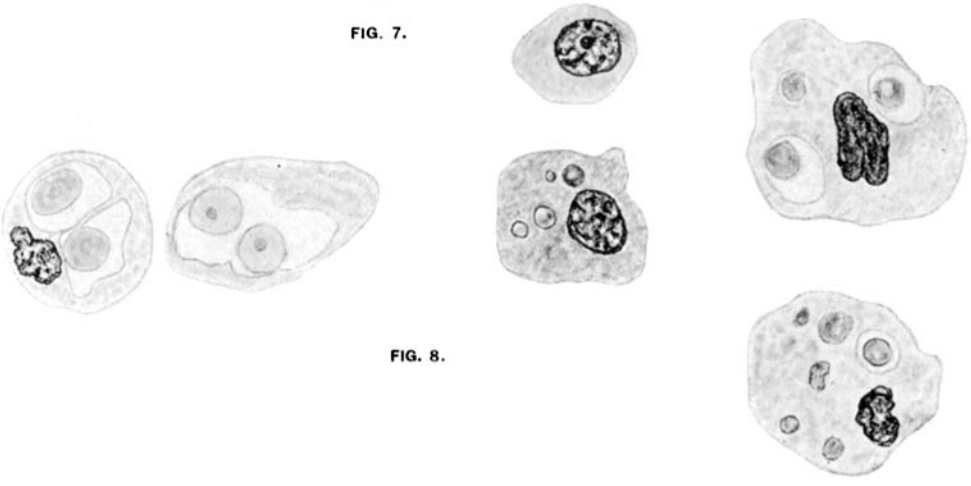

FIG. 8.