

SOME OBSERVATIONS ON MEGACYTES IN LYMPHATIC TISSUES

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EIGHTEEN FIGURES

The observations here recorded were made especially on fetal nodes, on supernumerary spleens, and to a lesser extent on developing and mature lymph and hemal nodes. The material was obtained mainly in connection with other investigations, but covers a comparatively large series of nodes taken from bovines, sheep, cats, dogs, rabbits, guinea-pigs, rats, and several goats. The material from bovines, goats, and the sheep was gathered in the East, Middle West, and the far West.

One of the most striking features of many fetal hemal nodes is the occurrence of megacytes. I prefer the term megacyte to all other designations for giant cells, because it can include both poly- and mega-karyocytes in the sense of Howell ('90) as well as other large cells, such as megaloplasmocytes, macrophages, myeloplaxes, and osteoclasts. Moreover, it waives matters of function. Under low magnification it is not the single large nucleus nor the many nuclei which are so evident, but the large pink masses formed by the oxyphile cytoplasm. It is the cell then and not the nucleus that arrests attention. Indeed, the nucleus or nuclei of many giant cells form a relatively smaller portion of the volume of the whole cell than in case of the lymphocyte, and it is the relative and not the absolute size which is especially significant. Nor does it seem at all unlikely that one and the same cell may be a mega- or a poly-karyocyte at some time in its life history, but it always remains a megacyte. It is true that in fetal nodes one could quite as well speak of mega-

blasts, provided one does not thereby imply that they necessarily arise from or in the marrow, or that megacytes necessarily have only a megablastic origin.

Goodall ('08) held that the giant cells found in the blood of sheep embryos were derived from undifferentiated leucocytes and represented a final stage of the latter.' Goodall also stated that hemoglobin-containing cells are formed from megablasts found in the vessels and in the connective tissue. As will appear later, these observations tend to show that many megacytes are polycytic and undoubtedly also polygenetic in origin, although it is well to bear in mind in this connection the fact wisely emphasized by Prenant ('10) that

la production de cellules geantes dans des circonstances et des localites si diverses eveille tout de suite l'idee que ces elements naissent fortuitement aux depens de cellules quelconques des tissus sains ou malades, et qu'ils peuvent deriver aussi bien de celules epitheliales, endotheliales, conjunctives et lymphatiques. Mais l'hypothese d'une origine univoque n'est pas exclue par la diversite des circonstances et des lieux.

A fair idea of the size of the cells concerned in this report is afforded by the following table of measurements which, to be sure, can represent an approximation only. Nevertheless, the measurements in length and width were done carefully with a filar micrometer. The third dimension necessarily represents an estimate made by tracing the particular cell through a series of sections of known thickness. The greatest dimensions only are given and the measurements represent the nearest thousandths of a millimeter. The measurements in the first and second columns represent width and length, respectively. Those in the third column the estimated thickness.

1. 33	x 50	x 30	9. 33	x 40	x 25
2. 23	x 23	x 30	10. 20	x 33	x 50
3. 26.6	x 20	x 30	11. 15	x 56	x 25
4. 24	x 21	x 15	12. 13	x 24	x 10
5. 20	x 26	x 22	13. 14	x 26	x 23
6. 26	x 38	x 15	14. 24	x 21	x 15
7. 27	x 30	x 7	15. 23	x 23	x 30
8. 30	x 40	x 15	16. 30	x 50	x 30

Measurements 1 to 9, inclusive, were made on megacytes in supernumerary spleens mainly in the dog, and 10 to 16, inclusive, on those in fetal nodes of the sheep. Those found in fetal hemal nodes of bovines are about the same size. As the measurements show, the megacytes observed in hemal and lymph nodes and in supernumerary spleens, especially of dogs, are not extremely large when compared with osteoclasts which are commonly stated to reach a size of 100 micra. It must be borne in mind, however, that a single measurement really can convey little conception of the actual volume or the size of a cell unless it happens to be spherical or nearly so. Nor can two measurements convey much of an idea of the true volume, or three measurements of the form. The measurements of these megacytes coincide very well indeed with the size commonly given for megakaryocytes of the marrow, which are said to measure 25 to 30 micra.

Some of the above megacytes had an ill-defined border, while others were clearly delimited and looked as though they possessed a definite cell wall. As the measurements suggest, the variation in size is considerable, but nevertheless not nearly as great as that in form. The latter, it seems to me, is an especially significant fact, for it clearly indicates that giant cells of apparently the same type vary from flat rectangular, cylindrical to spherical cells. The irregularity in form, although marked in many specimens, is not revealed by the measurements. This irregularity may sometimes have been due to amoeboid activity, but in most of the cells in the illustrations it is probably a result of disintegration and degeneration.

That the measurements here given vary little and do not reveal cells of a uniform minimum measurement and of gradually increasing size is largely due to the fact that only undoubted specimens of giant cells were selected. What seemed like transition stages were not included.

Some of the smallest megacytes—that is clearly young cells of this type—were found in the nodes, vessels, and mesenchyme of sheep fetuses from 7 to 9.8 cm. V. B. length. These are represented in figures 1, 3, and 4. The cells in figures 1 and 2 were

taken from a node from the lumbar region of a sheep fetus of 7.3 cm., those in figures 3 and 4 from the same region of a fetus 9.8 cm. long. In figure 1 there are two fused cells, one of which contains two nuclei and the other only one but also an erythrocyte. These facts alone, it seems to me, show clearly that we have here a case of fusion of two cells or at least of attempted fusion. The fusion of a mass of cytoplasm with a degenerating nucleus such as lies near the large apparently fusing cells in figure 1 is also indicated. However, it seems highly probable to me that giant cells in hemal and lymph nodes also form by gradual enlargement of pre-lymphocytes. Van der Stricht ('91) also claimed to have found giant cells forming in this way from 'leucoblasts.' That certain large multinucleated, phagocytic cells found in some lymph nodes of the pig are formed in this way I am reporting elsewhere. Figure 2 shows merely a degenerating mass containing miscellaneous inclusions, and figure 3 a large intravascular polykaryocyte. The location of the latter itself attracts attention. Its relative size is indicated by the surrounding blood-cells and suggests that it could not have been carried very far in the circulating blood.

The masses represented in figures 5 to 7, inclusive, again represent necrotic masses such as the cell in figure 2. The mass in figure 6 shows two nuclei which look as though they were fusing, while the appearance of the nucleus in the specimen in figure 7 remotely suggests direct division. At least the form of the nucleus of this cell recalls the figures of amitoses in giant cells published by Duval and White ('07) in their studies of chronic glanders. I do not consider, however, that I have any special evidence for the occurrence of amitosis, or for mitoses for that matter, for I did not find, as Haidenhain ('07) did, that multiple mitoses are common in giant cells. Since Haidenhain regarded multiple mitoses without cell division, as a necessary complement of direct division of the nucleus it is evident of course that he believed that both processes occur in giant cells. Macklin ('16), on the other hand, found amitosis to be restricted to the nucleus of cells observed *in vitro*. I used no special stains, however, and do not deny the existence of nuclear division in

hemal and in lymph nodes and spleens described in detail as occurring in six phases by van der Stricht ('91) in pre-existing megacaryocytes.

The cells shown in figure 8 are similar to those in figure 1 except that more degenerating cells of various sizes, which seem about to fuse with the main mass, lie directly adjacent to the larger cells. Regarding the masses represented in figures 9 to 16, inclusive, nothing further need be said than that they belong in the same class. All of these cells and cell complexes were found in supernumerary spleens located in the great omentum of the dog. The two, three, or four cells in figure 17 again recall those in figures 1 and 8. Yet the latter are from sheep fetuses and the former from a supernumerary spleen of the dog. That represented in figure 18 is an extremely large cell from a node from an adult sheep drawn so as to indicate the amount of pericellular space. The surrounding parenchyma is only indicated in the sketch. Sometimes the pericellular space is much larger, however, and occasionally a perinuclear clear zone is also present. The rareness of occurrence of these zones as well as other matters, indicate that neither probably results wholly from shrinkage during fixation.

The borders of some of these megacytes are quite indistinct, others are notched, while still others seem to possess a series of vacuoles at the periphery. This particular cell measures 30 x 30 x 50 micra, the latter being the length. It also contains cell inclusions, is very well preserved, quite regular in outline, and as the measurements indicate is cylindrical in form.

The greater frequency in the occurrence of giant cells in fetal nodes was very striking. Groups of two to four large acidophile cells with prominent vesicular nuclei sometimes containing distinct chromatin granules are frequently seen in fetal nodes from the sheep. Not infrequently very distinct oxyphile masses with three to five isolated distinct vesicular nuclei with degenerate-looking chromatin granules and nuclear network and a nucleolus are also found, but mitotic figures were never seen. Some of the individual cells look as though they were ameboid. Maccabrani ('11) also emphasized that the free megakaryocytes

which occur in various organs always show indications of amoeboid activity, and Schridde ('07) stated that Askanazy had directly observed amoeboid movements on a warm stage. Weidenreich ('07), on the other hand, did not think that giant cells are amoeboid and accounted for their presence in the parenchyma by assuming that they were enmeshed by the encroachment of the parenchyma on the sinus from the endothelium of which they arose. Weidenreich also divided giant cells into 'direct and indirect' hemophages and regarded the former which were erythro-phagocytic as endothelial in origin, and the latter which were eosinophilic-phagocytic as reticular in origin. Although Arey ('17) emphasized the degenerate character of osteoclasts, he stated that they must of course have gained admission to the vessels, thus apparently assuming an amoeboid activity.

In other cases heaps of distinct, well-preserved nuclei with barely enough cytoplasm to surround them are also seen. These and the large oxyphile cells with vesicular nuclei found in fetal nodes certainly seem to be of mesenchymal origin, and their irregular form suggests amoeboid activity. Some of these cells are well-preserved and spherical; others are oval or oblong and look degenerate. The cells seen in fetal nodes were more regular in outline and less frequently polynuclear, but I cannot subscribe to Haidenhain's ('07) statement that megakaryocytes occur only in hematopoietic organs for I have found them in a real early fat lobule (Meyer, '17). However my conception of the word megakaryocyte does not limit it to large cells with a hollow, spherical nucleus having a discontinuous wall.

Cells with a single, large, regular, spherical nucleus, others with an irregular highly lobulated nucleus, and still others with many small isolated nuclei are also found. Some of the latter naturally remind one of myeloplaxes, and it is probable that they are responsible for Drummond's ('00) assertion that the giant cells of 'haemolymph glands' are exactly like those in bone marrow. The location of the nucleus or nuclei of these giant cells is usually eccentric. The nuclei are decidedly polymorphous, vesicular, and in the better-preserved cells, always contain numerous chromatin granules. In the less well-preserved cells the

nuclei were more pycnotic and showed other signs of degeneration. Evidences of karyorrhexis were rare and nothing was seen which could be definitely identified as centrioles, although some of the nuclei in well-preserved cells showed a definite nuclear network and a well-preserved cytoplasm.

My conclusion regarding the greater frequency of megacytes in fetal nodes harmonizes well with the earlier opinion that megakaryocytes occur in the spleens of young animals only and with the observations of de Kervily ('12) who, however, found them present in the spleens of adults also. This investigator found as many as forty giant cells in one square millimeter of the spleen of the hedgehog, 30 in the rat, only 1 to 5 in the mouse, but only 3 in 25 *square millimeters* of the spleen of the guinea-pig, and still less in the spleen of the rabbit. Weidenreich, on the contrary, found the lymph nodes of the rabbit the seats of giant cells par excellence. Haidenhain ('97) also described peculiar giant cells (polykaryocytes) under pathological conditions, in the lymph nodes of a rabbit. De Kervily found them very numerous in the spleen of the new-born cat. From 40 to 50 per square centimeter were present in a pup one month old, 30 to 100 in a pup two months old, and occasionally 4 to 100 per square centimeter in adult dogs. In bovine subcutaneous hemal nodes I found some sections which averaged two megacytes per square millimeter, but I never saw any sections in which practically one-sixteenth of the entire area was occupied by them as de Kervily found for the spleen of the hedgehog.

Sometimes the megacytes of fetal nodes lay isolated, but not infrequently several lay close together or even in contact. In some supernumerary spleens from the mesentery of a dog almost each section contained several cells. Groups of two to six cells were occasionally found in both supernumerary spleens and fetal hemal nodes. In nodes taken from adult animals they always lay in the lymphatic parenchyma, but in bovine fetal subcutaneous nodes they rarely also lay under the capsule and in purely hemal areas. They were usually surrounded by a small space which, I presume, could be regarded as resulting from shrinkage. This pericellular space was less evident in fetal nodes in which isolated

megakaryocytes were rarely found in blood-vessels and in the surrounding mesenchyme as well. An intravascular location was never observed in nodes from adult animals. Those found in the mesenchyme about fetal nodes and the much larger often degenerating cells found in adult nodes were very irregular in form and often possessed processes extending out in various directions.

The megacytes in fetal nodes were not only more numerous, more regular in form and smaller, but also better preserved. They also contained a smaller number of nuclei or were uninucleated. These facts, to be sure, may be regarded as pointing to the conclusion of Jackson ('04) and Renaut ('93) that the megakaryocyte is only a younger form of the polykaryocyte and also agree with the observation of Dickson ('08) on bone marrow, that megakaryocytes rapidly degenerate. Not infrequently a large block or mass of cytoplasm which looked as though it had been detached and containing no nuclei was found adjacent to the main cell. Weidenreich ('02) also speaks of masses which stain with acid fuchsin lying near the nuclei of the reticulum cells. These masses are, according to Weidenreich, formed by the fusion of degenerating eosinophiles which have been phagocytosed by reticulum cells which have thus become giant cells. Lewis ('04) also spoke of giant cells which destroyed the coarsely granular eosinophiles, but added that evidences of such activity are not common. Robertson ('90) described large leucocytes with seven to eight nuclei which stain poorly with haematoxylin as the nuclei increase in size, but increasingly well with eosin. Robertson thought that the nuclei of these cells become erythrocytes. Although the presence of inclusions, due probably to phagocytic activity, was noticed, pigmentation was never observed. Among the inclusions erythrocytes and leucocytes were frequently found in bovine, fetal, hemal nodes.

In all the many cells examined not a single undoubted case of either direct or indirect division was observed, although the chromatin network and chromatin granules were plainly visible, as a rule, in the vesicular nuclei of well-preserved cells. Macca-bruni, who stated that the megakaryocytes found in the bone

marrow, spleen, liver and hemolymph nodes and the lung of many species are always uninuclear, reported the absence of amitoses but the presence of mitoses which, however, proceeded only as far as the anaphase. This, it seems to me, is a very interesting observation, for it would also seem to suggest necrobiotic phenomena, universally observed by Maccabruni. I did not notice any circumscribed difference in the staining characters of the protoplasm, however. With the routine stains used no division into zones as described by Kostanecki '91, van der Stricht '91c and Haidenhain was recognizable. Although not completely homogeneous, the whole cytoplasm seemed quite uniform in structure. In some cells it looked quite amorphous, but in others especially in the apparently younger and better-preserved cells, it had a more granular appearance.

Some of the cells in fetal tissue contained only a single nucleus, others two, and still others six or more distinct nuclei or a single lobulated nucleus. But lobulation was much more common in the cells from adult tissue, the nucleus of which had a more complex form. This fact might suggest that the lobulation is only apparent and may result from fusion of the separate nuclei of fused cells as well as from budding.

From the study of these megacytes as found in developing and mature nodes one is prompted to assume a multiple origin. Some of those found in the mesenchyme of fetal nodes and others in hemorrhagic lymph nodes in which very active phagocytosis is evident, are apparently of connective-tissue origin. Those found in the fetal vessels I am inclined to regard as of endothelial origin, while most of those found in mature nodes from adult animals do not seem to have either of these origins, but arise mainly through the fusion of leucocytes which seem to correspond to the polyblasts of Maximow. However, I have no evidence supporting his conclusion that these transformed lymphocytes or polyblasts which Maximow found forming foreign body giant cells may later become fixed connective-tissue cells. Moreover, I should prefer to use the term leucocyte, although not in the sense of polymorphonuclear, instead of lymphocyte for the young cells within the node.

Were it not for the fact that some of the well-preserved, moderately-sized, specimens in fetal nodes, and rarely also some in adult nodes, contain several distinct nuclei which, to be sure, may have arisen by nuclear division, one would seem to be justified in assuming that most if not all of the giant cells here concerned are so-called plasmodia which have resulted from fusion of degenerating cells. There are many things which would seem to bear no other interpretation. Indeed, the whole impression gained by this study confirms this conception held by Borel ('93), Faber ('93), Duenschmann ('94), and also by others. It is interesting to recall in this connection that Pren-tiss ('15) and Arey ('17) never observed nuclear division of any kind and concluded that osteoclasts arise from osteoblasts,¹ although Geddes ('12, '13) declared that "It may at once be stated that an osteoclast is a composite mass consisting of the fused bodies of two, three, or more cartilage cells containing any number of osteoblasts—in short, it is a meso-ectodermal syncytium."

The greater number of megacytes found in fetal nodes recalls the observation of Prenant ('10) regarding 'cellules geantes irritative' to the effect that newly-formed blood-vessels were always present where these cells were formed. Nevertheless, most of the giant cells of these nodes impress one not by their vitality, but by the lack of it. They do not, as a rule, seem actively phagocytic, and many of them show marked vacuolation and possess areas of cytoplasmic degeneration. Many of the nuclei, too, show necrobiotic changes. They are often pycnotic. Others are mere shadows.

That practically all the megacytes in hemal nodes are in process of disintegration and that many of the cellular and nuclear constituents are more or less accidental inclusions in the disintegrating cytoplasm is quite evident. The overwhelming number of these giant cells look like disintegrating complexes with which other disintegrating or degenerating cells may fuse even

¹ Since this was written Arey 17b has regarded the osteoclast as a phagocyte, apparently implying that fusion products never observed to undergo mitosis, nevertheless may be physiologically active and continue a progressive evolution.

in a very late stage in their life history. The bizarre shape and blurred character of the nuclei, the disintegrating and poorly delimited cytoplasm and the entire absence of phagocytic activity in all but a few cells from the nodes of adults, as well as the small, irregular, deeper-staining, degenerating areas or masses of cytoplasm some of which have a remote resemblance to Negri bodies, are all indications to this effect.

Although much smaller cells with multiple and also with relatively large cells with individual regular nuclei are found, the only cells which can be regarded as precursors of the larger cells which apparently act as fusion centers are large uninucleated leucocytes with oxyphile cytoplasm and a vesicular nucleus oval or circular in outline. These cells which do not seem to be very actively phagocytic also can be seen in relations which suggest fusion with each other. Instances which suggest various stages in the fusion of nuclei can also be seen, and I am much impressed with the idea that these giant cells are not very active or essential constituents. Prentiss and Arey also emphasized the degenerate character of the osteoclast, although Arey nevertheless says that indications of their transformation into marrow reticulum are not lacking. Neither Prentiss nor Arey makes any reference to the elaborate system of canals in osteoclasts which Retzius suggested might be related to a secretory activity. Weidenreich ('02) also spoke of canals in giant cells, but I was never able to recognize any.

Upon contrasting these giant cells with those in tuberculosis which Evans ('15), from evidence obtained by vital stains, regards as fusion products of endothelial cells, the absence of the necrotic center of the latter is evident at once. That such a necrotic center is absent follows from the different location of the nucleus alone. The protoplasmic extensions from the periphery so common in the tubercular giant cell are frequently present, however, in the megacytes observed. In myeloplaxes or so-called osteoclasts the nuclei, too, are distributed throughout the body of the cell and are quite uniform in size. The fact that Prentiss and Arey from an examination of developing bone and teeth in the pig, also came to the conclusion that osteoclasts re-

sult from fusion of osteoblasts I regard of special interest in connection with what I have myself observed in hemal nodes in which this mode of origin of these large masses seems much more prevalent.

Whatever opinion one may hold of the presence of megacytes in adult nodes, it is evident that disease cannot be responsible for their presence in fetal nodes. Yet they are most numerous here. This fact perhaps may be correlated with the greater rate of proliferation and destruction of cells during fetal life. Moreover, since the circulatory conditions are somewhat different in developing nodes, stagnation is likely to be greater in them, thus not only tending to effect an accumulation of wornout cells in the node itself, but also making phagocytosis by circulating polymorphonuclear leucocytes more difficult. There would be a tendency to accumulation of cell waste in fetal nodes not only for this reason, but also because there is not much evidence of phagocytosis in them.

In reporting these largely incidental observations I am not implying that the conception of the giant cell as a fusion product is a new one. As Marchand '83, who held a contrary opinion, pointed out, it is not new to pathology even, for Lang, Thoma, Gaule, Arnold, Waldstein and Kierner all considered the giant cell of tuberculosis as resulting from fusion. Later Arnold '87 changed his opinion however. Very recently I have also found undoubted instances of giant cells in the decidua which were not of chorionic origin that resulted from fusion of typical decidual cells. I have also seen giant cells in the stroma of the chorionic villi, which undoubtedly arose from the fusion of Hofbauer cells, and although I do not regard fusion as the only mode of origin I am inclined to regard it as a very common one.

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PLATE 1

EXPLANATION OF FIGURES

- Figs. 1 and 2, inclusive, from nodes of a sheep fetus 7.3 cm. V. B. \times 850.
- Figs. 3 and 4, inclusive, from nodes of a sheep fetus 9.8 cm. V. B. \times 1050.
- Figs. 5 to 8, inclusive, from a sheep fetus 37.5 cm. V. B. \times 750.

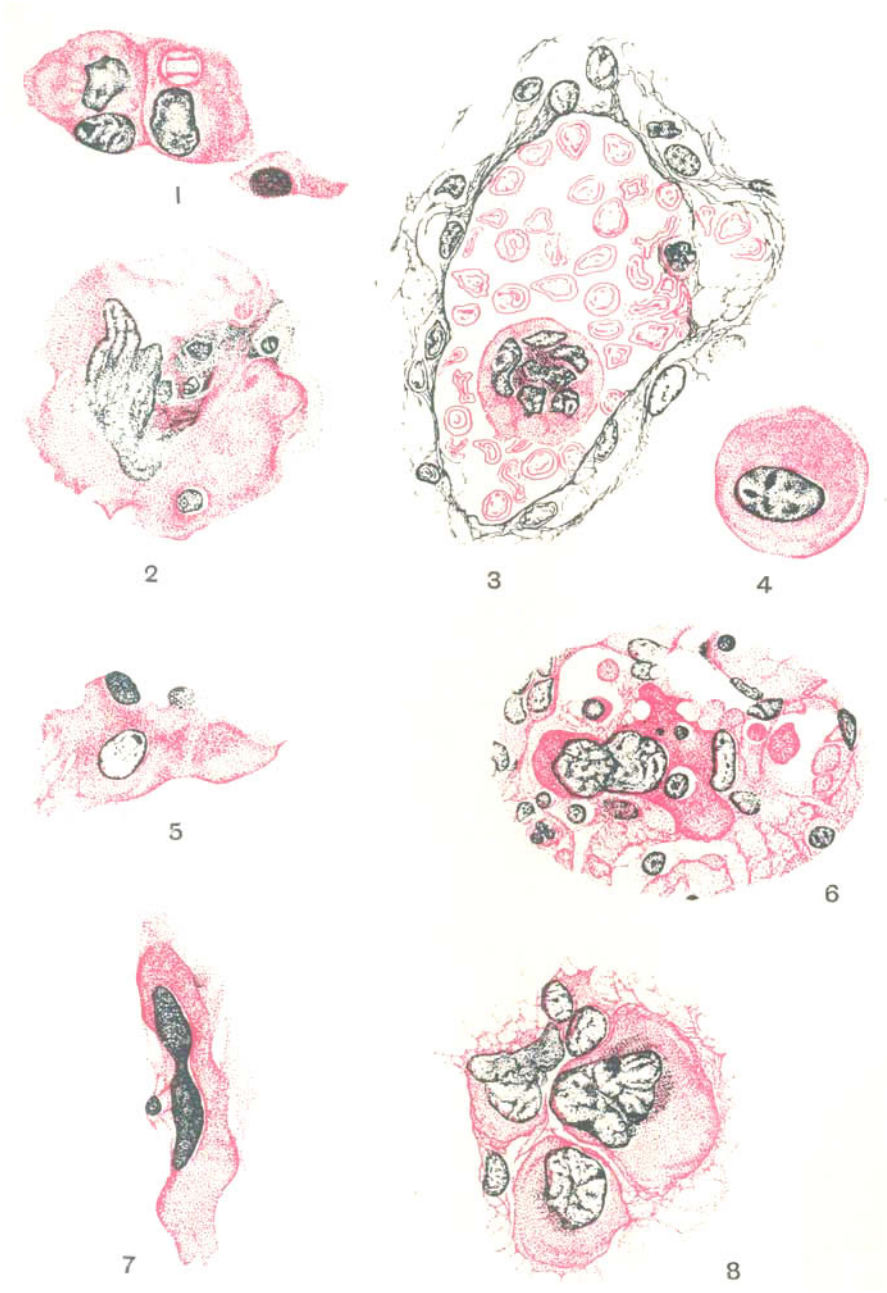


PLATE 2

EXPLANATION OF FIGURES

Figs. 9 to 12, inclusive, from a supernumerary spleen of the adult pig. 9 and 10, $\times 920$; 11 and 12, $\times 1050$.

Figs. 13 to 17, inclusive, from the same as 9 to 12. $\times 850$.

Fig. 18 from a hemal node of an adult sheep. $\times 630$.

