On the other hand, every practitioner is aware of the dangers of hyperpyrexia. This also finds its normal explanation in the terminal conclusion that:—

*8. Excess of fever (above 105° F.) is due to excessive excitation of the immunizing center and a corresponding overproduction of defensive bodies. This condition exposes the red corpuscles and the endothelial cells to proteolytic destruction (hæmolysis and autolysis) along with the pathogenic substances or bacteria.*[37]

Concluding Remarks.—Such are the facts which have led me to believe that the human organism is supplied with an autoprotective mechanism. Its functions, I may add, harmonize with the views of the modern biochemist who has found that increased metabolism is a characteristic of the febrile process; they also coincide with the observations of the bacteriologist that, while most pathogenic bacteria thrive at the normal temperature of the body, they promptly die when it is raised several degrees. They account for the teaching of clinical experience that a higher mortality occurs in apyretic cases than among those in which the febrile process had been active. They explain the harmful influence of hyperpyrexia, since excessive immunizing activity means proteolytic destructions of the blood-cells (hæmolysis) and even of tissue-cells (autolysis) besides the pathogenic agents themselves.

In the practical field, personal experience sustained by that of many colleagues who have carefully studied my doctrines has shown clearly that these embody the lever through which we can overcome infections. We need only analyze the beneficial action of vaccine therapy, of antitoxin, of drugs such as mercury, the iodides, and other so-called "alteratives," to recognize that their tendency, in therapeutic (non-toxic) doses, *is to raise the temperature*—proof that the immunizing process is active.

Yet, as is well known, the autoprotective resources of the body do not depend only upon the germicidal and autotoxic constituents of the blood-plasma. Indeed, they could not be

[37] The placing of animals in the heated chamber to determine the influence of high temperatures on the corpuscles is a useless and misleading experiment, since the proteolytic ferment, the active agent in the process, is not increased.—S.



carried out without the potent co-operation of the phagocytes, the importance of which in immunity has been revealed to us through the genius of Metchnikoff.

To obtain an idea of the relations of the internal secretions with these defensive cells, we should have at least an idea of their relations with the ductless glands, the manner in which the vital process is sustained in them, and the rôle each type of leucocyte fulfills in this connection. I know of no work in which these features are studied and must, therefore, build up the whole framework of the process, and thus try, at least, to ascertain the nature of the connection between the immunizing process as I have described it in the foregoing pages and the functions of the phagocytes.

## THE LEUCOCYTE IN ITS RELATIONS TO NUTRITION, ORGANIC FUNCTIONS, AND IMMUNITY.

Before inquiring into the physiological functions of each of the various varieties of white corpuscles, or leucocytes, it was deemed advisable to study the cell as a unit, and particularly the functional attributes of its main component structures: (1) the nuclear and cellular reticulum or mitoma; (2) the granules.

The Mitoma.—Alluding to basophile leucocytes, Howell[37a] states that the nucleus "is divided into lobes that are either entirely separated or are connected by fine protoplasmic threads." This is well illustrated in the annexed plate from a valuable study of the subject by G. L. Gulland,[38] by Fig. 1, a hyaline leucocyte from a newt's blood. These cells are undeveloped and their protoplasm does not as yet show "threads." But their nucleus is clearly supplied with them even at this early stage—a feature which suggests that the nucleus is an autonomous structure. This is further sustained by the presence, in the perinuclear portion of the cell, of a small body, the astrosphere, shown in Fig. 7, another undeveloped, or "hyaline," cell. This astrosphere is likewise present in fully developed leucocytes, as may be seen in Figs. 10, 12, and 16. Each cell

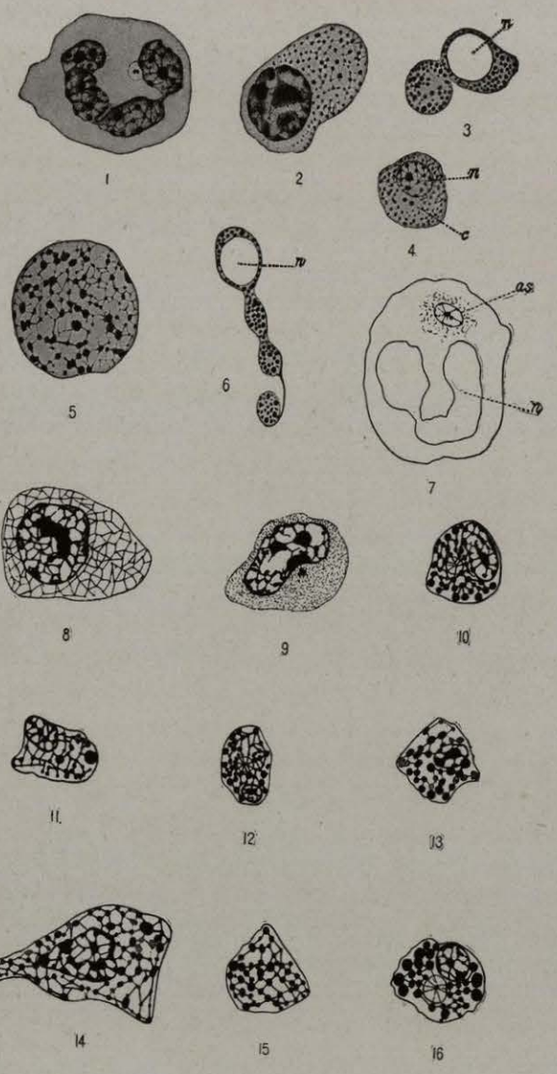
[37a] Howell: *Loc. cit.*
[38] G. L. Gulland: Journal of Physiology, vol. xix, 1896.

may, therefore, be said to contain two functional centers, each supplied with its net-work of fibers or threads.

Heidenhain is stated by Gulland to have found that "the granules are arranged radially to the astrosphere, with the smallest granules next the sphere, the largest at the periphery." This is exemplified with especial clearness in Figs. 10 and 16, and if the threads, or fibers, are traced from the center of the astrosphere, the gradual increase in size of granules as the periphery of the cell is approached is clearly indicated. Heidenhain also concluded, a feature fully confirmed by Gulland, that "there are never any granules within the astrosphere itself." It thus becomes evident that, while the nucleus is an autonomous structure, the same may be said of the astrosphere. In other words, a leucocyte seems to be supplied with two individual, though doubtless correlated, functional systems: (1) the nucleus *per se,* which contains a net-work of fibrils and granules; (2) the astrosphere, which represents the center of the cellular net-work of granule-laden fibrils.

As may be seen in the numerous cells represented in Gulland's plate, which cells have been drawn by him with the utmost care and fidelity to microscopic appearances, the fibers in the nucleus divide the latter into several irregular areas, while the radiating net-work of which the astrosphere is the center forms relatively regular spaces. The fibers in both structures run to their external boundaries, however, precisely as if they were attached to the external limiting membranes of each. And yet the nucleus alone seems to be supplied with such a membrane, while the surface of the cell is not. A prominent feature of these cells is the fact that their protoplasmic exterior is absolutely bare.

After a study of the characteristics of the granules, Gulland writes: "The granules of leucocytes are therefore *not* products of the metabolic activity of the cell imbedded in a structureless protoplasm, as was hitherto supposed, but represent an altered condition of the microsomes [the granules]. They always form part of the cytomitoma [the net-work of fibers] and are therefore *plasmatic,* and not paraplastic. They are probably concerned with amœboid movement, and they and the rest of the mitoma are more visible the more active the cell."




LEUCOCYTES; THEIR MITOMA AND MICROSOMES. *[Gulland.]*

[*Journal of Physiology.*]

Granules, as the plate distinctly shows, are plentiful within the nucleus, and in the cellular substance likewise; in fact, in the latter they are crowded around the centrosphere, the deepest portion of the cell.

If the granules are plasmatic, *i.e.*, formed by substances derived from the plasma, how does the latter reach the minute areas in which the granules are formed? Channels seem to me absolutely necessary for the passage of the blood-plasma, its alkaline phosphates, and other plasmatic salts from which the granules are formed.

The prevailing view that the threads (mitoma) are concerned with the amœboid movements of leucocytes, as also inferred by Gulland, is by no means, it seems to me, incompatible with the possibility of their being plasma-channels, or efferent canaliculi. Indeed, their elasticity does not eliminate the possibility of their being tubular, while their extension and retraction may, as in the sweat-glands, afford the mechanical elements of an expulsive process. "It is certainly interesting to note that, the more active the cells of this series become," writes Gulland, referring to the acidophile (phagocytic) leucocytes, "the more visible become their mitoma and the microsomes which form part of it. The lymphocytes in which no mitoma can be seen are practically non-amœboid. The hyaline cells in which it is not very evident move but sluggishly. The oxyphile cells, with a well-marked mitoma and microsomes, move more rapidly, and the eosinophile cells, whose mitoma and microsomes are the most visible of all, move most rapidly." Again, he says: "It is certain that the length of thread lying between the microsomes varies immensely in different parts of the cell, and the short threads are usually the more deeply stained; so that it looks as though they were *contracted* and therefore *thickened*. On the other hand, the microsomes at the periphery are, generally speaking, the largest, and there can be no doubt that it is the circumference of the cell which moves most and moves farthest." As regards the basophile leucocytes, he states that, "as far as one can judge from fixed specimens, the larger basophile cells seem to have more power of movement than the smaller ones"—a feature easily accounted for, since they are not bactericidal, as are the acidophile leucocytes.

It seems probable, however, that in both acidophile and basophile cells the fibers take part in the mechanism through which they travel in the plasma, while contraction, thickening, etc., *i.e.*, the elements of a suction or expulsion process, are present to suggest the identity of the mechanism to which they owe their powers of locomotion.

Basophile leucocytes are not phagocytic; they do not, therefore, ingest foreign substances as do the latter, *i.e.*, by inglobing them. They must, therefore, be provided with a different mechanism for this purpose. If, in accord with my view, the mitoma represents a system of centrifugal canaliculi, it cannot serve for this purpose. Indeed, the external agencies penetrate the cell to the nucleus itself. Thus, W. R. Stokes and A. Wegefarth,[39] alluding to the researches of Bail,[40] say: "After injecting virulent staphylococci into the pleural cavity of rabbits he found that the leucocytes underwent a characteristic change. They formed round, empty bodies, containing several vacuoles in the *nucleus*."

How did the virulent staphylococci reach the nucleus's vacuoles? Metchnikoff's plate (opposite page 692 in this volume) will assist us in elucidating this question. It not only forcibly illustrates what this distinguished zoölogist sought to show, but likewise, it seems to me, a mechanism of ingestion, differing somewhat from the recognized "ingulfing" or "inglobing" process through which phagocytes take up germs, small particles, etc. An example of this mode of appropriating various plasmatic or foreign substances is illustrated in Fig. 5, which shows bacteria penetrating, from various directions, *into* the cell-wall, while Fig. 16 shows the bacteria *within* the perinuclear vacuole. As all the cells in Metchnikoff's plate are phagocyte , the mechanism of ingestion to which I refer is not only that of basophiles, but is obviously a feature of all leucocytes.

The fact must be emphasized that I say "perinuclear" vacuole, and not "nuclear" vacuole, for, if this and the other germ-laden cells just referred to are carefully examined, it will become evident that the bacteria lie in a pocket contiguous to,

[39] W. R. Stokes and A. Wegefarth: Bulletin of Johns Hopkins Hospital, Dec., 1897.
[40] Bail: Berliner klin. Wochenschrift, Oct. 11, 1897.



but not forming part of, the nucleus itself. I would not say, therefore, with Bail, "vacuoles *in* the nucleus," but vacuoles *around* the nucleus. Indeed, Gulland refers to Heidenhain as considering that "the nucleus lies free in the interfilar spaces, and is not organically connected with the cell-substance." This is quite in accord with my view, and it seems to me that it represents the cavity into which bodies ingested by leucocytes normally arrive, though smaller vacuoles are likewise present in the cytoplasm.

The actual presence of this perinuclear vacuole from which canaliculi would start appears to me indicated in several of the figures in the annexed Gulland's plate. Fig. 8, for instance, stained with iron-hæmatoxylin, shows that the nucleus is surrounded by an irregular limiting material of some kind; but if we compare the outline of this limiting substance with that of all the succeeding cells, an interesting feature asserts itself, viz.: its thickness is extremely variable. Although 12 may be said to be moderately regular, the others, in the following sequence: 11, 10, 13, 8, 9, and 14, are increasingly irregular. If, now, this irregularity itself is scrutinized, a significant fact is revealed: *i.e.*, the bulges, or projections, in the limiting structure are all at the expense of the nucleus. In Fig. 9, for instance, just above a clover-like figure near the center of the cell (probably the astrosphere), the marked bulging shows every evidence of having been formed by a substance which had compressed the nuclear substance inwardly. The stages of this compression are exemplified in Metchnikoff's plate, by Figs. 16 and 15, successively. In the former a single mass of liquid and germs is seen to have indented the center of the nucleus on one side, while in the second figure three cavities are shown which have distorted it. (The nucleus is indicated by an *n*.) In *both*, however, the compression has exceeded the normal boundaries of the limiting structure, and centrifugal bulging has occurred at the expense of the perinuclear protoplasm or cytoplasm. So marked has this become in Fig. 14 that the nucleus is not discernible.

The identity of the mitoma as a system of canaliculi suggests itself in another way. I have shown that the axis-cylinders of nerves, neuroglia fibrils, etc., contained blood-

plasma. Such being the case, if the fibers or "threads" in leucocytes are likewise plasma channels, they must stain, as do the former, when treated to various dyes. We have seen (pages 541 to 543) that methylene-blue dissolved in salt solution and injected into the vessels of a living animal colored the axis-cylinders blue, according to Ehrlich, and that this investigator defined the conditions of nerve-structure essential to the methylene-blue reaction as "oxygen saturation and alkalinity" —the very attributes of blood-plasma. Referring to the various stains used by him, Gulland says: "In examining the basophile cells I used almost entirely various methylene-blue solutions," and, later on: "The basophile cells of the dog's intestinal villi, when fixed with absolute alcohol and stained with alcoholic methylene-blue, give exactly the same results, as to mitoma and granules, as other basophiles." Evidently, as regards the methylene-blue stain, nerve-fibrils and mitoma (my canaliculi) are similar. Again, besides the plate reproduced here, Gulland presents two colored plates, in which the characteristic affinity of each cell for stains appears; the six basophile leucocytes stained with methylene-blue (normal) distinctly show that structures which stain most deeply are the chromatic, *i.e.*, the nuclear mitoma; then, more faintly, the cellular mitoma. It seems clear that, as regards methylene-blue stain at least, the conditions are similar to those of nerves as far as the mitoma—or canaliculi—are concerned.

The same correspondence exists between nerve-fibrils and the mitoma when hæmatoxylin is used. We have seen (page 536) that, according to McCarthy, the rods that project radially from the axis-cylinder "stain with carmine and hæmatoxylin, which do not stain the myelin." The fact that the axis-cylinder takes hæmatoxylin hardly needs to be emphasized, its use in histological laboratories when nervous structures are studied being second only to picrocarmine for general staining. A beautiful example of hæmatoxylin-stained human cerebro-spinal and sciatic nerves is to be found in Clarkson's "Histology," page 204, for instance. All the eosinophile leucocytes shown in the annexed plate, in which the nuclear and the peri-nuclear granules and mitoma are so clearly defined, were stained with Heidenhain's iron-hæmatoxylin, which only differs from



the usual solution in that it colors the cellular elements that take it a dark gray or black. This also shows that it is not only with the mitoma of basophile leucocytes that the staining characteristics of nerve-fibrils—*i.e.*, plasma-containing channels—coincide, but also with that of eosinophile cells. Even Apáthy's fibrils are recalled by the effects of corresponding stains, for Senn writes,[41] referring to the minute anatomy of the leucocyte: "The reticulated structure is well shown by staining with chloride of gold, which stains the protoplasmic *strings*, but not the interstitial substance." It seems quite evident, therefore, that *the mitoma*, i.e., *the intracellular and intranuclear networks of fibers in mature leucocytes, are canaliculi for blood-plasma.*

Functional Mechanism of the Leucocyte.—I have expressed the view that the nuclear canaliculi open into a vacuole which surrounds the nucleus (see Fig. 14 in Gulland's plate) and that the outer wall of this vacuole acts as terminal for some of the canaliculi of the cell-substance. Although, as suggested by Fig. 11, the canalicular orifices that open into the vacuole from both directions may correspond (the nuclear orifices being in that case opposite the cellular openings), such is by no means always the case. Indeed, in Fig. 16, for example, but two or three of the external canaliculi seem to be connected with the vacuole, while this cavity serves as terminal for all the *intra*nuclear channels—if such they are.

Is the connection between this vacuole and the exterior of the cell direct or indirect: *i.e.*, through separate channels leading directly to the exterior or to those connected with the astrosphere's system? That the communication is independent of the latter is emphasized by the presence of granules in the path of all canaliculi, as shown in Gulland's plate. A continuous function depending upon an inflow of plasma would obviously be in constant danger of arrest were the granular channels centripetal pathways. Again, in all leucocytes, acidophiles as well as basophiles, the nucleus stains in the same manner, the granules alone, as we have seen, showing variations in this particular. The same may be said of the reticulum, for we have seen, by the staining reactions, that the compounds com-

[41] Senn: "Principles of Surgery," 3d ed., 1901.

posing the granules are bathed in oxidizing substance, *i.e.*, adrenoxidase. This uniformity of nuclear and cellular fluids in the canaliculi suggests the presence of a very common mechanism—one, indeed, which must serve to *eliminate* its contents, judging from the fact already mentioned, that the intracellular granules increase in size outwardly, the largest granules being at or near the surface. A common centrifugal canalicular system again suggests the presence of a system common to all leucocytes, whether phagocytic or not, for the introduction (not necessarily of particles or other discernible agencies) of more or less liquid or viscid bodies required by the cell for its own nutrition, or connected with its own physiological functions: *i.e.*, the elaboration of granules. The canaliculi serving only for the centrifugal elimination of the latter, the centripetal paths must penetrate to the vacuoles *between* the canaliculi, or "threads," as already explained, and as shown in Metchnikoff's plate, Fig. 5. We are evidently not dealing here with mere inclusion or pseudopodial flowing around the germs, for the latter may be seen to penetrate the cell between the granules, and, judging from Figs. 13, 14, 15, and 16, directly into the perinuclear vacuole itself.

Is the cell supplied with *centripetal* canaliculi *in addition* to the centrifugal system which I believe to be represented by the reticulum? The fact that micro-organisms can penetrate directly *into* the vacuole between the external layer of granules is not alone to suggest that such is the case, but the manner in which the leucocyte takes up stains likewise does so. As can readily be seen, the absorption of the dye by the cell occurs without involving any alteration of its shape which can at all be associated with the process. That the absorption cannot occur through the visible canaliculi: *i.e.*, those that take stain because they constantly contain fluid, is rendered very probable by the presence of the granules, which must entirely close their external orifices. It must occur, therefore, through paths presenting some analogy to the pores of certain sponges, which allow the surrounding water to pass into the interior of the sponge, so long as it does not carry any harmful products along with it (Metchnikoff). And yet the fact that such a system of channels does not exist is shown by the promiscuous



directions taken by bacteria in penetrating into the cell. Indeed, their bodies are not directed axially toward the perinuclear vacuole; they seem, once within the external layer of granules, to point in almost any direction. We are brought back, therefore, to the soft, yielding, protoplasmic cell-substance of the amœba, which will allow liquids to transude easily through it, and the more dense materials to cleave their path into it and down to the vacuole, without leaving a wound behind them. "On introducing pigeon leucocytes filled with anthrax bacilli (to which the pigeon is very refractory) into bouillon," says Metchnikoff, "bacilli grow, *pierce* the protoplasm of the cells, and form well-developed filaments, showing definitely that the bacilli were inglobed in a living condition." We might say "ingest," however, for the perinuclear vacuole asserts its identity as a digestive organ—the familiar digestive vacuole—in several ways: *i.e.*, as a cavity in which all the materials that supply the cell with functional energy—*i.e.*, with life—are drawn.

Metchnikoff,[42] referring to the intracellular digestion to which amœbæ submit the materials they ingulf, writes as follows: "A closer observation of the group of protozoa compels us to the conviction that this digestive function must play an important rôle in the mutual relations of these lowly organisms. Many rhizopoda and infusoria live in media swarming with other unicellular organisms, including bacteria. The latter, which multiply very rapidly, serve as food to many of the protozoa. Thus, various amœbæ devour bacilli, which undergo certain definite changes in the interior of the protoplasm. Without altering their shape, the bacilli acquire the power of taking up solutions of vesuvin, which does not stain these microbes when living in their natural conditions. Since precisely similar changes are also observed in the interior of vorticellæ and infusoria, which live on bacteria, it is evident that they are due to a digestive influence exerted by the contents of the protozoa." This conclusion is in harmony with the observation of B. Hofer[43] on digestion in amœbæ. This investigator has shown that "the more the food is altered in the in-

[42] Metchnikoff: "Lectures on the Comparative Pathology of Inflammation," translated by F. A. and E. H. Starling, pp. 18 *et seq.*, 1891.
[43] B. Hofer: Jenaische Zeitschrift, vol. xxiv, 1889.