they meet the adrenal secretion and proceed with it to the right ventricle."

We can now understand how the granules of the neutrophiles are supplied to the muscle-fibers by quoting another of my statements (see page 434) concerning the distribution of fluids in the intimate structure of the heart: "Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. The canals—the lacunæ of Henle—are the intervals *between* the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the *lymphatic vessels*, the lacunæ have been considered as adjuncts, or *extensions*, of the latter." In this sense, therefore, the Thebesian channels are adjuncts of the lymphatic system, for it is through their intermediary that the lacunæ of Henle are supplied with myosinogen granules and —a feature I wish to emphasize—their nutritional peptones and their fibrinogen. All of these jointly supply the heart with its working energy, when acted upon by the adrenoxidase of the blood-stream, and, as is the case with all the organs previously reviewed, by the thyroiodase also contained in the red corpuscles.

The bulk of the venous blood which enters the heart is sent, we have seen, along with its adrenal secretion and its leucocytes—neutrophile and eosinophile—to the lungs, Virchow, Friedreich, Leyden, Cohnheim, Wagner, Lenhartz, and other investigators having found them in the sputum, and histology having demonstrated their presence in the alveoli. Again, the path for these leucocytes from the intestine to the true respiratory areas of the lungs is comparatively direct: features which distinctly suggest that the protective functions in the respiratory tract resemble those in the intestinal canal, as regards the eosinophilic granules and the phagocytic functions of the neutrophiles, both kinds of cells being present, as we have seen. Of course, the intestinal lymph-follicles being the source of these cells, another arrangement prevails in the pulmonary lobules: *i.e.*, that to which we referred on page 713, to the effect

that the lobular epithelium *per se* is an aggregate of neutrophiles and eosinophiles.

We can readily understand, now, why the eosinophiles deplete themselves of their granules in the alveoli: *i.e.*, to dissolve them in the plasma prior to their absorption by the red corpuscles. Indeed, the reticular structure of red corpuscles, "the same as that of colorless blood-corpuscles,"[82] observed by Louis Elsberg in 1879, seems to me to present all the features that have led me to consider as canaliculi the threads that constitute this reticulum in the latter cells. That the red-corpuscle "granulations," "platelets," or "hæmatoblasts" derived from them are mere droplets of adrenoxidase poured out through these canaliculi is shown by the fact that the characteristic affinity (requiring oxygen and alkaline salts, according to Ehrlich) for methylene-blue again appears: *i.e.*, as manifested by the deep-blue stain which we found in other structures, the axis-cylinder, neuroglia, etc., and in the leucocytes themselves. This fact was also noted by Litten.[83] That the droplets pass out through centrifugal channels in the cell, and that the latter presents the general mechanical characteristics of leucocytes, is also suggested by the researches of Hirschfeld,[84] who observed that the "blood-plates" are first seen as circular disks occupying the center of the cell, then move very slowly toward the periphery, and finally drop out of the cell through a minute aperture, which closes up again. As the "plate" leaves the cell the external portion gradually increases in size and is connected with the rest by a thread. Several of these may leave the cell together from different parts of the periphery. He also found them to stain with methylene-blue and hæmatoxylin. It is evident that we have in the red corpuscle a diminutive nucleated sponge capable of absorbing hæmoglobin from the serum of the pulmonary alveoli and of dealing it out in the blood-stream as needed by the tissues.

This feature and the functions of the leucocytes just described introduce complemental factors in the respiratory process as I interpreted it in the second chapter. It now seems

[82] M. L. Holbrook: "Proceedings of the American Microscopical Society," vol. 1894.
[83] Litten: Deutsche med. Wochenschrift, Nov. 2, 1899.
[84] Hirschfeld: Virchow's Archiv, vol. clxvi, 1901.

to me that the whole process is summarized in the following conclusions:—

1. The true respiratory areas in the pulmonary lobules are composed of the alveolar endothelial plates (the non-nucleated epithelium) and groups of eosinophile leucocytes (the nucleated epithelium) interposed between the former.

2. The eosinophile cells are the bodies in which hæmoglobin is formed from the proteids, bilirubin, and iron absorbed by their parent-cells, the neutrophiles, in the intestinal canal.

3. When the eosinophile leucocytes reach the alveoli from the liver via the heart they assume an orderly arrangement and alter their shape, so as to form the alveolar epithelium.

4. The eosinophile leucocytes supply the adjacent plasma with their hæmatin, and the latter is absorbed by the underlying red corpuscles along with the oxygenized secretion (adrenoxidase) to form hæmoglobin.

5. Leucocytogenesis being governed by the adrenal system, the main factors of the above respiratory process, the production of eosinophile cells and of adrenal secretion, are thus dependent upon the functional integrity of this system.

6. The neutrophile leucocytes which accompany the eosinophiles migrate from the capillaries of the pulmonary artery to the perialveolar lymphatics, and supply the interlobular structures with their nutritional and functional elements: i.e., *peptones, myosinogen, and fibrinogen.*

7. During certain diseases neutrophile and basophile leucocytes may also penetrate into the alveoli and be found in the sputum.

The Basophile Leucocytes.—These cells show the division into two groups, "finely granular" and "coarsely granular," which characterizes those just reviewed. They seem to differ from the latter in every other way, however, for, while these are amœboid, basophiles are not considered so by most histologists. Gulland—rightly, in my opinion—contends that they are, the variations of shape that they show and the manner in which they are scattered throughout the body being adduced as main reasons. The nucleus is round, oval, or kidney-like; is less clearly differentiated from the cell-substance,

and stains with much greater difficulty than that of the neutrophile.

As regards their distribution, Ehrlich and Ranvier found them in the peritoneal, pleural, and pericardial cavities, and also in the connective tissue, but, as emphasized by Kanthack and Hardy, the cells in the connective tissue differ somewhat in shape and size from those in the three cavities mentioned. The latter investigators also found the coarsely granular basophiles "exceedingly numerous in connective-tissue spaces, where they form sometimes an almost complete sheath for the *lymph-capillaries.*" Their distribution furthermore resembles that of the eosinophiles in the fact that they are relatively very scarce in the blood.

The chemical characteristics of the basophile granules is suggested by a curious phenomenon which is especially noticeable in animals, and to which Kanthack and Hardy refer in the following words: "The unstable, or *explosive, nature* of the coarsely granular basophile cells in certain animals is one of their most remarkable characters. In the rat and mouse perfect preparations of these cells may be very easily made, but in the guinea-pig and rabbit they can be preserved only with the most rapid fixation by heat or absolute alcohol. In these animals the mere exposure of the cœlomic fluid to the air, or to contact with a cover-slip for a few seconds, is sufficient to cause their complete disappearance. Cells characterized by great instability have been described elsewhere in astacus[85] as the 'explosive' cell of that animal, and the basophile cells of the guinea-pig and rabbit might, with equal justice, be designated the explosive cells of those animals." A familiar histological fact will suggest the relationship between such a cell and adrenoxidase. Berdal,[86] quoting Ranvier, says: "The action of oxygen or of the air may be observed in an extremely simple way: A lymph preparation which has served for the examination of amœboid movements is carefully surrounded with paraffin and set aside for thirty-six hours. If, at the end of that time, the lymphatic cells are examined, all will be seen to have reassumed the spherical form and to no longer project

[85] Hardy: Journal of Physiology, Nos. 1 and 2, vol. xiii.
[86] Berdal: *Loc. cit.*, p. 275.

pseudopodia. Removal of the paraffin and raising of the disk so as to admit a small quantity of air will suffice to cause the amœboid motion to recur." The explosive nature of the coarsely granular basophile cell can only be due to the one cause: the presence of large proportion of phosphorus, both in its nuclein and granules.

In their paper upon the free granules derived from leucocytes Stokes and Wegefarth review the investigations of H. F. Müller, of Nothnagel's clinic.[87] This observer found them both in diseased and normal blood, and describes them as "highly refractive, round, or dumb-bell shaped bodies which show a dancing, molecular movement, but no independent motion." When mounted in 1 per cent. osmic acid "the reaction for fat does not occur," nor can they be dissolved by acetic acid or ether. An important feature in connection with our inquiry is that Müller is recorded as stating that "he does not consider them as Ehrlich's neutrophilic granules escaped from leucocytes," and that "the neutrophilic granules are dissolved by dilute acetic acid, while the bodies which he has studied are not dissolved by this acid." This is in perfect accord with the chemical analyses of Milroy and Malcolm, who found that acids dissolved eosinophile granules, and with the observations of Lenhartz in respect to those found in sputum. Stokes and Wegefarth further emphasize the dissimilarity of basophiles from acidophiles in general, as viewed from my standpoint, when they say, doubtless referring to Ranvier's interpretation of the purpose of the granules of white globules: "They are not concerned in the formation of fibrin, since they remain outside of the fibrinous net-work or are only accidentally attached to it." We thus have evidence to the effect that basophiles are different from neutrophiles, both chemically and functionally.

What is the nature of these granules? Müller is stated to disbelieve "that they are true particles of fat, since they do not give a reaction with osmic acid," while he is credited with the opinion "that they may be bodies resembling fat, but which fail to show the osmic acid stain." Indeed, the persistence with which this characteristic appearance is noted by investi-

[87] H. F. Müller: Centralbl. für allg. Path. u. path. Anat., vol. viii, 1896.

gators is noteworthy. Thus, Kölliker,[88] Ranvier,[89] Bizzorero,[90] von Lünbeck,[91] and Hayem[92] are referred to by Stokes and Wegefarth as having also observed bodies resembling fat-granules in the blood of normal human beings, those of the last-named investigator and others described by Schiefferdecker and Kossel[93] also as fat-granules being thought by Müller to be identical to those observed by him. That they are fat-*like*, as thought by Müller, but not fat, seems clear.

Müller, we have seen, refers (as do other investigators) to the fact that these granules are "highly refractive." As this sign also attends eosinophilic granules, it would appear to have but little differential value; such is not the case, however, when this property is jointly considered with the osmic acid reaction, for we have here the *two main distinctive signs of myelin.* "It is extremely refringent," writes Berdal, referring to the latter; and he also alludes to the familiar fact that "myelin treated with osmic acid" stains black.

Still, if the granules are composed of myelin, the active constituent of the latter, lecithin, should be present, since we found this body not only in the myelin of nerves, but also in that of the neuron and the interior of the dendrites. That some granules do contain this body is evident, inasmuch as Foster, in his review of the physiological chemistry of white corpuscles, writes: "Next in importance to the proteids as constant constituents of the white cells come certain fats. Among these the most conspicuous is the complex fatty body, *lecithin.*" As we now know that the nuclei of all leucocytes are similar in composition, this can only apply to their granules.

This involves the necessity of differentiating between the two kinds of granules present, the acidophiles (neutrophiles and eosinophiles) and basophiles. Foster points to this distinction, it seems to me, when he says: "next in importance to the proteids," etc. The basophilic granules are evidently not composed of nucleo-proteids; a fact which eliminates the acidophile cells and their granules. Indeed, we have confirmatory

[88] Kölliker: "Handbuch der Gewebelehre des Menschen," 1867.
[89] Ranvier: "Traité Technique d'Histologie," 1875.
[90] Bizzorero: "Handbuch der klin. Med.," 1887.
[91] Von Lünbeck: "Grundriss einer klinischen Pathologie des Blutes," 1896.
[92] Hayem: "Du sang et de ses altérations anatomiques," 1889.
[93] Schiefferdecker and Kossel: Gewebelehre, Bd. xi, 1891.

evidence that it is not the latter which contain lecithin in the following allusion to both kinds of acidophile granules by Milroy and Malcolm: "The fact that neither alcohol nor ether dissolves the granules excludes the possibility that they consist of fat or lecithin."

How do basophile cells acquire their lecithin-building constituents? As is well known, emulsified fats also penetrate the intestinal villi, but, instead of entering as do nucleo-proteids into the venules, they enter the lymphatic circulation directly, by way of the lacteals. Are they absorbed by the villi, and then by the lacteals, or are they also taken up by leucocytes and carried into the latter? Inasmuch as the lymph contained in the lymphatic vessels is itself crowded with leucocytes similar to some of those found in the blood-stream, we must first ascertain whether these leucocytes in any way leave the lymphatic circulation in the intestine as they evidently do when the lymph-ducts open into the general venous system at the junction of the internal jugular and the subclavian veins on both sides.

It may prove useful, however, to recall from the start that the so-called "chyme" and "chyle" represent the same liquid, *i.e.*, the lymph, and that these terms were suggested by a temporary *quantitative* difference in the constituents of the lymph in the mesenteric lymphatics, which are greatly increased during the process of absorption. Again, it may also be well to refer to the fact that lymph is merely blood-plasma practically devoid of red corpuscles, but containing lymphocytes and coarsely granular basophile leucocytes, and, besides, minute fat-globules which show an active Brownian movement, though covered with a thin layer of protoplasm to prevent their running together as fat-drops are wont to do.

"Lymph also contains fibrin," writes Mathias Duval, "but a fibrin which is slow to coagulate spontaneously; indeed, lymph removed from the vessel begins, after a quarter of an hour or so, to harden into a colorless jelly, from which a reticulated mass soon becomes separated, as does blood-fibrin undergoing coagulation." The cause of this delay seems to me but a natural result of the absence of both varieties of acidophile leucocytes, while the slow coagulation is but a normal consequence of the

fact that the lymph is plasma which, though derived from the blood, and deprived of neutrophile leucocytes, nevertheless contains more or less fibrinogen. "More or less" is applicable in a double sense here, for lymph taken from the lymphatics of the extremities, for instance, coagulates more rapidly than that taken from some vessels of the trunk. Lymph also contains serum-albumin and serum-globulin in reduced quantity, and relatively very small proportions of urea, neutral fats, and sugar, as compared to the blood. Such is not the case, however, as regards inorganic salts, which are present in the lymph and blood in similar proportions.

What is the nature of the process through which fats are taken up from the intestine and their itinerary in the blood-stream until they are used for the elaboration of basophile granules?

Stewart,[94] referring to the nature of this process, says: "The common view has long been that the greater part of the fat escapes decomposition, and, after emulsification by the soaps formed from the liberated fatty acids, is absorbed as neutral fat by the epithelial cells covering the villi. If an animal is killed during digestion of a fatty meal, these cells are found to contain globules of different sizes, which stain black with osmic acid, and dissolved out by ether, leaving vacuoles in the cell-substance, and are therefore fat. It has always been difficult to explain how droplets of emulsified fat could get into the interior of the epithelial cells, and yet it certainly passes into them, and not between them." Foster also refers to this feature in the following quotations: "It has, it is true, been maintained by some that they [the neutral fats] pass *between*[95] the cells, and not into them, but the evidence is distinctly against this view." Alluding to the rods of the striated border, he says: "We may imagine that the globules pass into the cell-substance by help, in some way, of these rods through amœboid movements comparable with the ingestive movements of the body of an amœba; but we have no positive evidence to support this view." . . . "Within the columnar cell, the fat may be seen, both in osmic acid preparations and in fresh living

[94] Stewart: *Loc. cit.*, p. 370.
[95] All italics below this word are my own.

cells, to be disposed in globules of various sizes, some large and some small, each globule placed in a space of the protoplasmic cell-substance. It does not follow that the fat actually entered the cell exactly in the form of these *globules;* it may be that the fat passes the striated border in *very* minute spherules, which, reaching the body of the cell, run together into larger globules; but whether this is so or not we do not know."

All this seems pointedly to suggest that the epithelial cells take up minute fat-particles to submit them to some local process. Böhm and von Davidoff[96] emphasize the feature of the process when they say, referring to the fat-globules in the epithelial cells: "It seemed most probable that protoplasmic threads (pseudopodia) were thrown out from each through its *cuticular* zone, which, after taking up the fat, withdrew with it again into the cell. But when it was shown that, after feeding with fatty acids or soaps, globules of fats still appeared in the epithelial cells as before, and that the chyle also contained fat, the hypothesis was suggested that the fat is split up by the pancreatic juice into glycerin and fatty acids, and that the fatty acids are then dissolved by the bile and the alkalies of the intestinal juice, only again to combine with the glycerin to form fat *within* the epithelial cells." Stewart further states that "when an animal is fed with fatty acids they are not only absorbed, but appear as neutral fats in the chyle of the thoracic duct, having combined with glycerin in the intestinal wall, and the epithelial cells contain globules of fat, just as they do when the animal is fed with neutral fat." It seems clear, from these and other available data, that *the epithelial cells of the villi capture fat-globules from the intestinal contents and if need be convert this fat into neutral fats.*

We have seen, however, that the villi also take up the leucocytes which ingest proteids. It is important, in this connection, to clearly distinguish the two mechanisms involved one from the other. Böhm and von Davidoff testify to the passage of such cells into the villi by stating: "Leucocytes are sometimes found within the epithelial cells, but more usually between them, and, according to Stöhr, when seen in these positions are in *the act* of migrating into the lumen of the in-

[96] Böhm and von Davidoff: *Loc. cit.*, p. 256.

testine." Stewart, however, remarks, in this connection: "Leucocytes have been asserted to be the active agents in the absorption of fats. They have been described as pushing their way *between* the epithelial cells, fishing, as it were, for fatty particles in the juices of the intestine, and then traveling back to discharge their cargo into the lymph. This view, however, is erroneous." It is erroneous, but only in one respect, in my opinion, *i.e.,* their direct connection with the absorption of fats, for, as stated, the functions of these wandering cells is to carry proteids to the intravillous venules. These do not, therefore, enter the intravillous lacteals. But *other* leucocytes penetrate the latter with the neutral fat-globules. "Although the leucocytes do not aid in the absorption of fat from the *intestine,*" says Stewart, "they appear to take it up from the epithelial cells, conveying it through the spaces of the net-work of adenoid tissue that occupies the interior of the villus, to discharge it into the central lacteal, where it mingles with the lymph." The distinction I suggest in this connection appears to me to remove the confusion that exists in the literature of the subject. Briefly, my conception of the process is as follows: *While the leucocytes which ingest proteids from the intestinal foodstuffs pass between the epithelial cells and enter the venules, the leucocytes which ingest fats only carry the latter from the inner limits of the epithelial cells to the interior of the lacteal, and deposit them therein.*

Sir Michael Foster expresses the opinion that the number of leucocytes found to contain any appreciable degree of fat is too small to account for the amount of fat absorbed. But it seems to me that, if these only transfer the fat from the epithelial cells to the lacteals, the to-and-fro excursions of each cell and the enormous number of villi over which the food of a single meal has to pass amply compensate for the apparent paucity of cells. An additional reason adduced by Foster is the fact that the administration of a saline such as magnesium sulphate "produces effects the very reverse of absorption," these cells being present in unusual numbers. As interpreted from my standpoint, and as will be shown when the action of purgatives is studied, these agents greatly increase the flow of serum into the intestinal canal by reflex action and crowd its walls with defensive agencies, including leucocytes. We are dealing here not with a normal process, such as is the fat-absorbing function, but with an engorgement by protective elements.

The axial contraction and relaxation which occur in the villus to cause its various contents to gravitate into their respective channels may, however, be instrumental in causing fat-particles that have already passed the epithelium to enter not only the lacteal, but the venules also, fat-globules, or what purported to be such, having been found in the blood. This feature and the manner in which fat-globules reach the general lymphatic circulation are exemplified in the following lines by Stewart: "The contraction of the smooth muscular fibers of the villus and the peristaltic movements of the intestinal walls alter the capacity of the lacteal chamber, and so alternately fill it from the lymph of the adenoid reticulum and empty it into the lymphatic vessel with which it is connected. By this kind of pumping action the passage of fat and other substances into the lymphatics is aided. In the dog no fat is absorbed by the blood-vessels, except perhaps a small quantity in the form of soaps; it nearly all goes into the lacteals, and thence by the general lymph-stream through the thoracic duct into the blood."

An interesting feature now asserts itself. Again are all the basophiles poured into a channel, the left subclavian vein, which empties into a large venous trunk, the superior vena cava, which in turn carries them to the right heart. We have practically a repetition of the process witnessed in the case of the neutrophiles with the exception of the passage through the liver, the basophiles being directly transmitted to the heart, and therefore likewise to the pulmonary lobules.

Indeed, my view that the granules of these cells *are* myelin seems confirmed in this connection, for, while Lenhartz alludes to the neutrophilic granules found in colorless sputum, and to the fact that the sputum of asthmatics contains "numerous eosinophile and quite numerous *basophile* leucocytes," he also refers, when reviewing the characteristics of the cells observed microscopically in this connection, to cells that "present considerable coarse granulation," and remarks: "Here, however, the spherules show a decidedly dull appearance, resembling that seen in *crushed nerve-substances*. For this reason they were designated by Virchow as *myelin droplets*." Moreover, Lenhartz[97] publishes a colored plate, one of the figures of which represents what he terms with E. Wagner "heart-lesion cells" found in the lungs. The granules of these, he says, "are similar to myelin, and, occasionally, *more refringent than fat*."

Evidently the nervous system is supplied with its myelin precisely as the muscles are supplied with their myosinogen. Kanthack and Hardy state that the coarsely granular cells are not only rare, but completely absent from the blood, while the finely granular are relatively rare in the latter except some hours after a meal. "To say that these cells are found in the body only in very small numbers, being confined to the blood and scanty even there," remark these investigators, referring to the finely granular basophiles, "is probably only equivalent to saying that we are at present very ignorant as to their history, distribution, and significance. However, since we find this cell in the blood, but do not find it either in the cœlomic fluid or in the interstitial spaces of the tissues (except, perhaps, in those of the mucous coat of the *alimentary canal*), we must, until further facts are forthcoming, regard it as the basophile cell of the blood." Still, they refer to the coarsely granular cells as "occurring only in the extravascular spaces" and in the "interstices of the connective tissue."

It is probable that we have in the finely granular cell the freshly laden cell on its way, when in the blood, to its normal habitat, the connective-tissue spaces, where their granules develop into their normal size. Indeed, Gulland alludes to a basophile cell, represented in one of his plates, of which he says: "The leucocyte was seen to have been fixed in the act of *passing through a narrow hole* between two bundles of connective tissue." This cell is furthermore accompanied by a large number of granules held in a net-work of fibers, which the cell appears to drag along in its travels. It is of this variety of leucocyte that Gulland says: "It has often been remarked that these cells show a great tendency to leave their granules behind them," etc., and the one which, in the portion of this

[97] Lenhartz: "Mikroskopie und Chemie am Krankenbett," 1900.