from the author

ON THE

DEVELOPMENT AND RETROGRESSION

OF

THE FAT-CELL.

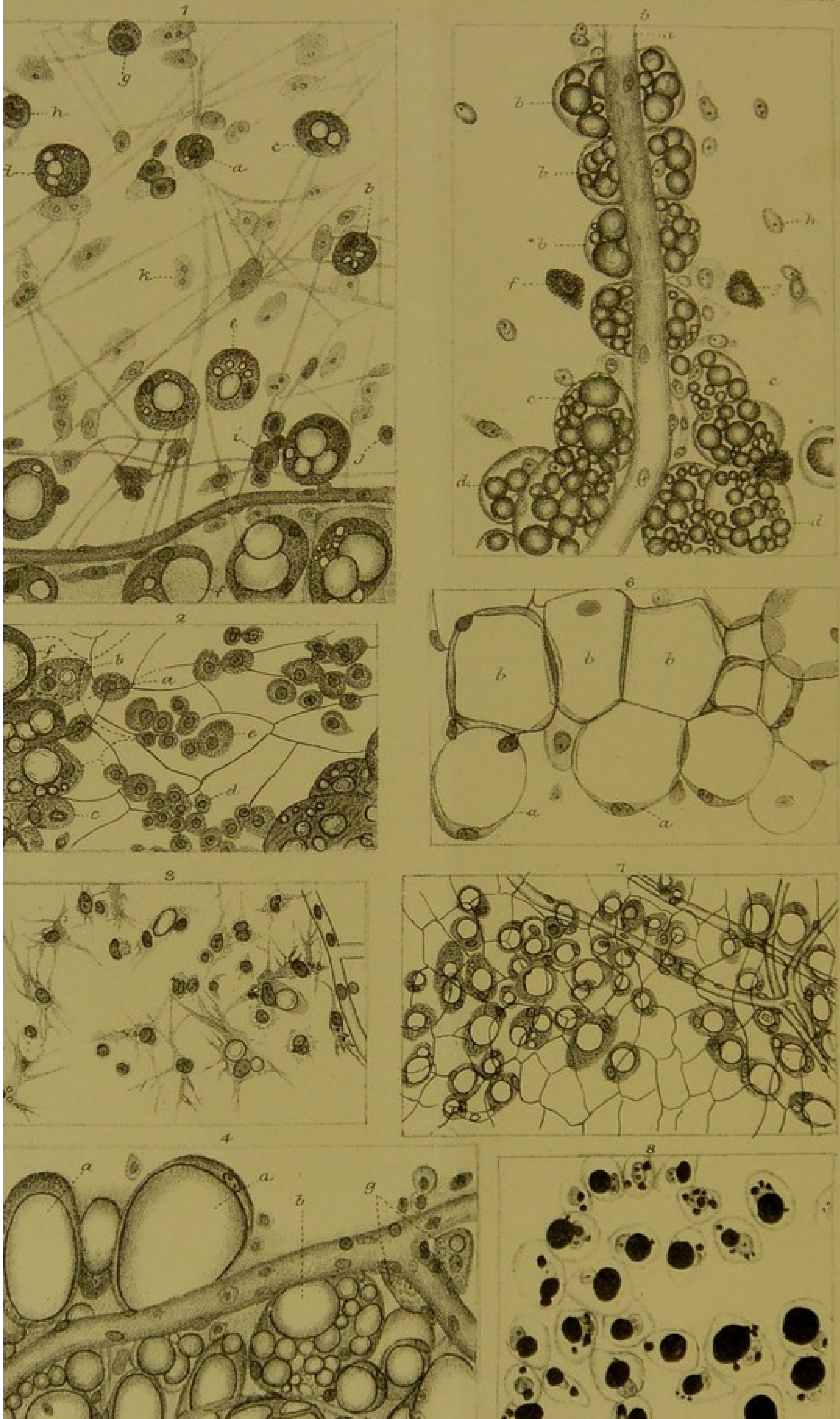
BY

GEORGE HOGGAN, M.B.,

AND

FRANCES ELIZABETH HOGGAN, M.D.

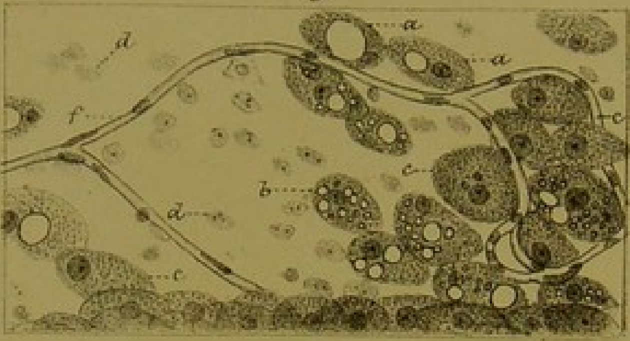
Reprinted from the 'Journal of the Royal Microscopical Society,' Vol. II., No. 4, June, 1879.



F. E. Higgan del. West, Newman & Co. lith.

Development & Retrogression of the Fat Cell.

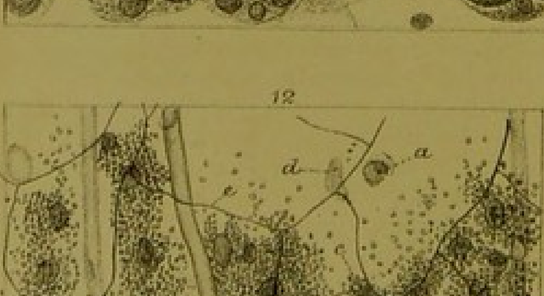
9



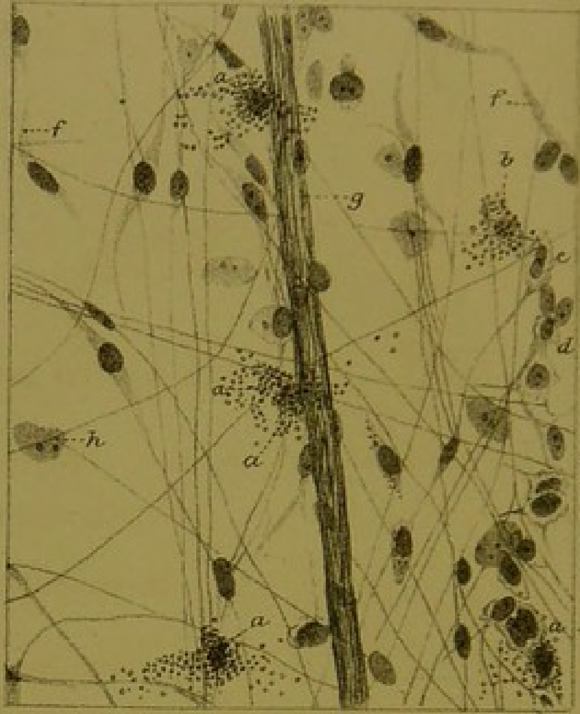
10

11

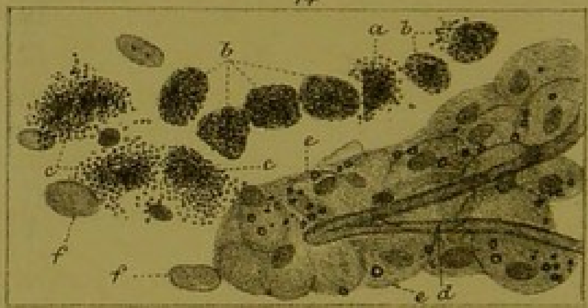
12



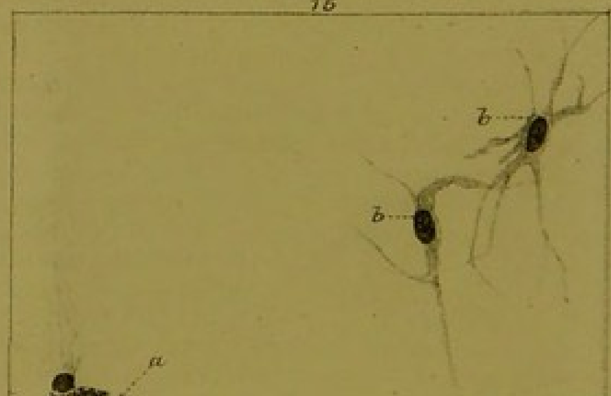
13



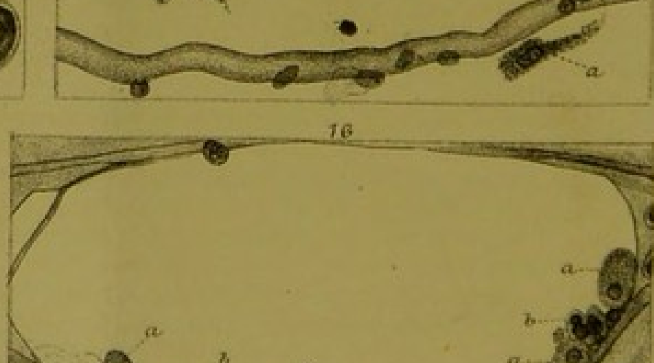
14



15



16



G.&F.E. Hoggan del. West, Newman & Co. lith.

Development & Retrogression of the Fat Cell

XIX.—*On the Development and Retrogression of the Fat-cell.*

By George Hoggan, M.B., and Frances Elizabeth Hoggan, M.D.

(*Read* 12*th March*, 1879.)

Plates XIII. and XIV.

Part I.—*Development of the Fat cell.*

If in the animal body there be one element whose simple structure and generally accessible position would lead us to expect that its life-history could easily be traced, and that consequently a general unanimity of opinion regarding it must necessarily exist

---

DESCRIPTION OF THE PLATES.

Plate XIII.—Development of Fat-cells.

Fig. 1.—First deposition of fat in wandering cells retracted into a globular form, from broad ligament of pregnant mouse. *a*. First appearance of fat in a cell as two minute oil-globules. *b*, *c*, *d*, *e*, *f*. Cells in which gradual increase of contained fat can be traced towards the capillary. *g*. Cells similar to *a* in which no fat has as yet been deposited. All the above cells lie beneath the endothelium and in the matrix of the membrane. *h*. A wandering cell with constricted nucleus lying in one of the holes in the membrane, and therefore on the free surface; it is evidently only a younger form of *g* and *h*. *i*, *j*. Still younger specimens of wandering cells lying on the free surface of the membrane; *i* has two nuclei. *k*. Nuclei of the endothelium covering both surfaces of the membrane.

Fig. 2.—Relation of fat-tracts to wandering cells, from mesentery of rat. *d*, *e*. Members of a shoal of wandering cells lying on free surface of endothelium. *a*. A member of the same kind of cells, but lying beneath the surface of the endothelium. *b*, *c*. Cells similar to the above, but further advanced, lying also underneath the endothelium and becoming fat-cells; *b* has already two fat-globules within it, and has attached itself to the group of fat-cells of which *f* is a fully developed specimen. Only the cell-markings of the upper surface endothelium are drawn, except at *a*, where the dotted line marks the lower surface cell-markings.

Fig. 3.—First deposition of fat in wandering cells fixed in their branched condition, from the broad ligament of a pregnant mouse. All these cells lie in the matrix of the membrane. Nuclei of endothelium not inserted.

Fig. 4.—Fat-cells developing centrally as regards the blood-vessel, from the broad ligament of a pregnant rat. *g*, *g*. Fat beginning to be deposited in cells close to the blood-vessel. *a*, *a*. Cells fully distended with fat, lying farther away from blood-vessel; in these cells the fat has been slowly and steadily accumulating. *b*, *b*. Cells containing many fat-globules, the result of rapid deposition.

Fig. 5.—From the mesentery of a rat found starving, to which plenty of rich

amongst observers, we might certainly suppose that the fat-cell was that element.

Instead of this unanimity, however, we find the most opposite opinions held at the present day as to its origin alone, while about its disappearance, so far as we can discover, nothing really definite is known. We therefore propose in this paper to trace the life-history of the fat-cell from its origin in the wandering cell, its development, its decline, and its final disappearance from the stage under the same form in which it made its first appearance there.

---

food was given, and the animal killed twenty hours afterwards. Tissue treated with silver, osmic acid, and logwood solutions. *b, c, d*. Cells in which many globules of fat have been deposited rapidly. These cells were probably previously fat-cells from which the fat had been absorbed, as seen in Figs. 9 and 10. *f, g*. Cells from which fat had not only been absorbed, but whose protoplasm had been disintegrating by granular exodus, as seen in Figs. 10, 12, and 13. The return of nutriment sent the granules back to the cell, where they now stain so intensely as in most cases to hide the nucleus. In *g* the nucleus is visible, and although stained as deeply as the nuclei of the neighbouring cells, it appears almost colourless as compared with the intense blue of the clustering granules round it. *a*. Vein. *h, h*. Nuclei of the endothelium.

Fig. 6.—Margin of a group of fully developed fat-cells, as they are generally seen, from the mesentery of a guinea-pig, treated with silver and logwood solutions and mounted in varnish, showing the effect of compression in making them assume a polyhedral shape. *a, a*. Fat-cells whose free borders still retain the circular form. *b, b*. Fat-cells assuming the polyhedral form through pressure of neighbouring fat-cells. This is the form in which they are found in nine cases out of ten.

Fig. 7.—Fat becoming absorbed from fat-cells. From the omentum of a young man who died of cancer and much emaciated. More than one-half of the contained fat has been absorbed from the cells.

Fig. 8.—Fat-absorption in a further advanced stage than Fig. 7, from the subcutaneous tissue of a young man who died of Eastern leprosy, much emaciated. Tissue treated with osmic acid and picro-carmine. Some of these cells still retain the angular form they possessed when fully distended with fat and compressed by neighbouring fat-cells.

Plate XIV.

Fig. 9.—Still further advanced stage of fat-absorption, from the broad ligament of a pregnant mouse, found almost dead from starvation. In this specimen the first stage of retrogression—that of fat-absorption—is seen completed. *a, a*. Monoglobular fat-cells, once fully distended, by fat now undergoing absorption. *b, b*. Multiglobular fat-cells undergoing fat-absorption in the multiglobular condition. *c, c*. Fat-cells from which all the fat has been absorbed. *d, d*. Nuclei of the surface endothelium. *e, e*. Edge of dense tract of exhausted fat-cells lying along lines of great blood-vessels. *f*. Capillary blood-vessel. No difference is traceable between the fat-cells in man and those of the smaller mammals.

Fig. 10.—From the same preparation as Fig. 9, showing the commencement of the second stage in retrogression of the fat-cell, when the cell-substance breaks up and moves off in the form of granules. *h*. Group of exhausted fat-cells from which all the fat has become absorbed. *a*. General break up of one of the cells of the group; the granules are seen passing away from it in every possible direction. *b, c*. Similar cells, in which the break-up is even further advanced. *f*. Spindle-shaped cell belonging to a capillary now broken up. *k*. Nuclei of surface endothelium.

Fig. 11.—From the same animal as Fig. 5, where fat has been deposited in cells similar to those seen in group *h*, Fig. 10. These cells had undergone granular change but not exodus, so that the newly formed fat-globules appear

This task proves much simpler than might have been expected, considering the opposite opinions held on the subject, partly owing to the modifications we have introduced into methods of preparation of tissues for examination, and partly because we find that the opposite opinions referred to are due principally to the fact that observers have regarded the same cell element from different points of view, in different shapes, and under different aliases; so that, while those who have examined it from the front have insisted that the fat was first developed in a flat or round cell, those who have

---

imbedded in a granular matrix, unlike that in Fig. 5, which is transparent and had not retrograded so far as in this figure. *a*, *a*. Exhausted and granular fat-cells in which fat has been re-deposited. *b*. Similar cell, from which some of the fat has been extruded, but its protoplasm, having been previously fixed by silver and osmic acid, has not contracted. *c*. Granular cells which had undergone exodus, but to which the granules have returned. *d*. Wandering cell. Preparation stained with logwood.

FIG. 12.—Preparation from a rat which died of old age, showing a mass of fat-cells undergoing granular exodus and moving off *en masse* from the bed where they had been formed. *a*. Wandering cell. *b*. Exhausted fat-cells which have not undergone granular exodus. *c*, *c*. Fat-cells undergoing granular exodus and moving off *en masse*. Preparation treated with silver, osmic acid, and picro-carmine.

FIG. 13.—From the same preparation as Figs. 9 and 10; shows the end of the second stage of retrogression of the fat-cell. *a*, *a*. Fat-cells in a further advanced stage of exodus than those in Figs. 10 and 12. *b*. Cell in the last stage of granular exodus, nucleus and cell-outline again becoming distinct. *d*, *d*. Group of cells in a branched condition, and still containing a few granules. They appear to be the wandering cells, resulting from original fat-cells, lying in the same position as the group *e*. *f*. Spindle-shaped cells, resulting from the break-up of capillaries that were distributed to the now absorbed fat-tract. *g*. Large blood-vessel, now contracted and about to break up into spindle-cells. *h*. Nuclei of surface endothelium.

FIG. 14.—From the same animal as Fig. 12; shows different stages in retrogression of fat-cells, where the granules have returned, consequently upon some short return of nutrition. *e*, *e*. Cells in a fat-tract which have not yet undergone granular break-up. *c*, *c*. Cells undergoing granular exodus. *b*, *b*. Cells which have undergone granular exodus, but to which the granules have returned. *a*. A cell midway in condition between *b* and *c*, and which is assuming the branched or wandering condition. *f*. Nuclei of surface endothelium. *d*. Capillary of fat-tract. Preparation treated with silver, osmic acid, and logwood.

FIG. 15.—From mesentery of young rat weaned naturally by its mother about a week previously, consequently upon which, although well supplied with food, it had become very lean, and showed granular cells in the branched or wandering condition. *a*, *a*. Branched granular cells lying alongside a blood-vessel, to be compared with the ordinary branched cells, *b*, *b*, commonly called connective-tissue cells, but virtually wandering cells.

FIG. 16.—From the same animal as Fig. 15, showing granular cells *a*, *a*, lying amidst a group of ordinary wandering cells *b*, *b*, in a natural hole of the broad ligament of the liver, and, therefore, on its free surface, which they have probably reached as seen in Fig. 15. These cells are now in the condition of cell *h*, Fig. 1, with which we commenced, and in the same preparation different stages of the granular cells may be traced, until they end in the ordinary wandering cell.

All these drawings have been made by the camera lucida, under the same power of 800 diameters, reduced afterwards one-half except Figs. 9 and 11 reduced to one-third. When not otherwise stated, the tissues have been fixed by silver, stained by pyrogallate of iron, and mounted in glycerine.

seen it edgeways have as stoutly maintained that it was developed from a branched or spindle cell.

Thus it is that Flemming, whose researches, published nine years ago, are probably the most extensive on this subject, not only insists that fat-cells are developed from the branched fixed cells of the connective tissue alone, but he emphasizes this opinion by declaring that he commenced his investigations in the full belief that fat-cells were developed from wandering cells, and that his investigations forced him to give up this his original idea. Klein also, whose opinions on this question are probably the latest that have appeared in English, does not seem to have worked out the question for himself, but accepts and teaches Flemming's conclusions, with the exception of the one where Flemming holds that the fat-cells are developed from the adventitia of blood-vessels.

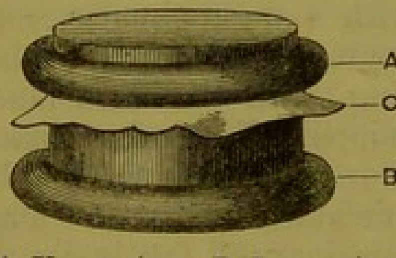
He also specially refers his readers to the branched cells of the fossa infraorbitalis of rabbits as the most suitable in which to study the development of fat-cells, and states "that he thinks it unnecessary to warn his readers against the possible assumption that the lymph-corpuscles are the elements which become converted into fat-cells."

Ranvier, in his 'Traité d'Histologie,' now being published, states distinctly that fat-cells are developed from round cells (corps globuleux), and gives drawings which are characteristically clear and trustworthy. He states that he is entirely opposed to Flemming's ideas, and holds that the round cells from which fat-cells are developed are special in their character even from their origin. Of other observers we may briefly note that Rollett holds the opinion that fat-cells are developed from small round granular cells. Virchow and Frey say that in the embryo they are developed from round cells, but they agree with Von Wittich and Foerster that in the intermuscular connective tissue and in pathological formations they are developed from spindle and branched cells. Czajewicz holds that they are developed from small, delicate, flattened cells, which look like spindle-cells when seen edgeways, but he does not even mention the wandering cells, although they were well known when he wrote. Toldt, again, believes that fat-tracts are glandular in their nature; and Ranvier agrees with him so far as to call a fat-cell a unicellular gland. According to Toldt, these glands (fat-tracts) develop from special centres in the embryo, whereas in the adult fat-cells are only developed from pre-existing fat-cells.

Turning now to our own researches, we wish first to state that we can see no reason for specially studying the growth of fat-cells in the embryo. They are not embryonic structures in the ordinary sense of the term, but are merely adjuncts to the processes of nutrition, whether found in adult or embryo, the process of development being similar in both; and in studying their life-history under the

Microscope we are studying physiological changes rather than special anatomical elements, changes which, in the space of a few days, may pass from the first appearance of fat in a cell to its full development, and subsequent decline and disappearance.

While the conclusions of many of the observers we have enumerated have been arrived at on the bodies of fishes, frogs, porpoises, &c., we have specially drawn our conclusions from investigations carried out on the smaller mammals, as bearing more directly upon man, and wherever possible we have compared these with preparations from the human body, with the result of finding complete identity throughout. Contrary, however, to the opinion of many authorities, we have found the serous membranes the most useful for our investigation, being enabled to utilize these by virtue of special methods of our own, which we shall describe. Of these membranes the most serviceable is the growing broad ligament of pregnant rats and mice; for the growth of this thin structure during their short term of gestation is so rapid, that the developing cells and other structures remain isolated, having no time to form themselves into the dense masses which seem to have foiled other observers. Indeed, confining one's examinations to sections of tissue, as recommended, would render it impossible to see the most interesting of the phenomena in the life of the fat-cell, which can only be recognized in uninjured membranes, and at the extremes of cell promontories or isolated cell groups or islands in such membranes.



A, Upper ring; B, Lower ring; C, Membrane between them.

Before ever the membrane is excised from the body of the animal, it must be evenly stretched once for all, so as to keep the lines of vessels apart from each other, and consequently the tracts of fat-cells which lie close to them clear for examination. Moreover, while the various reagents are gently applied, and the membrane is being continually subjected to examination under the Microscope, no fold must ever ruffle its surface, nor any object be touched by it until it is permanently put up as a preparation.

These desiderata are obtained by using the histological rings invented by us, of which we show specimens. They will be found to be most simple and useful adjuncts in the biological laboratory. These rings are always made in pairs, one fitting tightly upon the other, with a certain amount of taper in each; and when a piece of membrane is jammed between them, the whole has the appearance of a tambourine. They ought always to be made of vulcanite, as metals are acted upon by acids; bone, ivory, and other animal substances throw down salts like chloride of gold from their solutions;

while glass, wood, &c., are too fragile for use. We have them made of all diameters, but the most useful size for ordinary glass slides is seven-eighths of an inch in diameter.

When, therefore, we wish to examine the serous membranes, the animal must be killed gently by chloroform; indeed, as soon as it is insensible it ought to be even drenched with the anæsthetic, which seems, when thus given in excess, to anæsthetize the individual cells as well as the animal. No time should be lost by injecting the animal, as by doing so at first we missed some most valuable indications; but immediately after death the abdomen should be opened up to the fullest extent, a portion of the uterus or intestine seized with the forceps, and gently lifted up, so as to stretch the membrane which attaches it to the back of the abdominal wall. Upon one surface of this membrane the smaller ring of the pair is applied, and upon the opposite surface the larger ring is adapted, and pressed gently with a slight circular motion upon the smaller ring, so as not to rupture the delicate membrane, until it jams itself upon that smaller ring, with the membrane lying between them. It may now be snipped off with fine scissors external to the rings, thus separating it from the rest of the body of the animal; and we have then a miniature tambourine formed, in which condition the membrane remains until finally disposed of.

Our next step is to apply to either or both surfaces, with the greatest care and without any preliminary washing, a half per cent. solution of nitrate of silver in distilled water, and after a few instants' exposure to its influence, the preparation is carefully washed with distilled water, and exposed for a short time to a dull northern light, until the desired action of the silver has been obtained, as shown under the Microscope. We may now expect that not only have the various cells forming the membrane been fixed in the condition or shape they possessed during life, but that the shoals of wandering cells, which are continually groping over the free surfaces of the abdominal organs, will, as far as they existed upon the free surface of our piece of membrane, be firmly fixed *in situ*, and the whole may now be subjected to various staining processes.

Of these, by far the most suitable and generally used by us for such tissues is the process invented by one of us, and described three years ago in the Journal of the Quekett Club.

The tambourine membrane is first soaked for a few minutes in spirit, to deprive it of water, and a 2 per cent. solution of perchloride of iron in spirit is filtered upon it. After the lapse of a few minutes a few drops of a 2 per cent. solution of pyrogallic acid in spirit is likewise filtered upon it, and in a few minutes more, according to the depth of tint required, the whole may be washed in ordinary household water; a few drops of glycerine placed upon the membrane render it transparent, and it is now ready for examination, or for being mounted permanently as a preparation.

Although this process of staining is by far the quickest and best for showing the development of fat in cells, it will be found advisable, more especially when studying their disappearance, to reverse the method, and, after treatment with silver solution, to treat the membrane first with osmic acid, to render the fat quite black, and then with logwood solution, to render the cells and their nuclei evident. But whatever processes the membrane may be subjected to, it will always be advisable to examine it from time to time under the Microscope, the membranous surface of the tambourine being placed uppermost on the stage; and, as may easily be conceived, it may thus be continually subjected to examination without touching anything or its receiving any injury whatever.

Instead of commencing with the ancestry of the fat-cell, we find it more convenient to start from the first appearance of fat-globules within one, and to trace their gradual increase until we reach the fully charged fat-cell. This condition is well shown in Fig. 1, from the broad ligament of the uterus in a well-nourished pregnant mouse. At *a* we see the first sign of fat making its appearance, as two minute oil-globules within a cell, one on each side of the cell-nucleus. At *b* we have a stage further advanced, and notice three fat-globules within a cell, each of the globules being larger than either of the two globules seen in the cell last described. In this way we may trace the progressive development of fat in *c*, *d*, *e*, and *f*, where the large fat-globules which fill the cells are on the point of running together to form the fully developed fat-cells seen in Figs. 4 and 6. Let us now return to cell *a*, and proceed in the opposite direction. All the cells we have referred to lie between the layers of endothelium covering both surfaces of the membrane, or, in other words, in the substance of the membrane itself. Now, there can be no doubt that cell *a* is of the same nature as cell *g*, in which no fat-globules have as yet appeared, and which lies like the rest in the substance of the membrane. But *g* is evidently similar to cell *h*, which is certainly a wandering cell lying external to the membrane, for it has placed itself in one of the natural holes which are so plentifully found in such membranes; it is evidently similar to the group of wandering cells seen near cell *e*, all of which, by the binocular Microscope, may be seen to lie on the free surface of the endothelium, over which they were travelling when the silver solution killed and fixed them in that position. Other minor features stamp these as being wandering cells; thus cell *i* possesses two nuclei, *h* has a purse-shaped nucleus where the one is about to become two, while at *j* we have the early stage or type of the newly born wandering cell; so that even without going further we might venture to conclude that fat-cells are developed from wandering cells in the substance of the membrane (in this case), and that these ancestral cells are not special in their nature, as held by Ranvier, but are purely and simply wanderers.

The relationship between the fat-cells and wandering cells may be even more clearly traced in Fig. 2, from the mesentery of a rat, where, lying between, or rather opposite the space between, two groups of fat-cells, we see a portion of one of those shoals of wandering cells, which may always be found on the free surface of such membranes, lying sometimes like the lines of drift rubbish from a receding tide, and at other times in clusters or buds attached by a pedicle, if sufficient care has been taken not to rub or ruffle the surface of the membrane or rudely to wash them away.

The fact that these cells are to be found scattered over the free surface of such membranes, and unconnected with other structures, is clear proof of their being wandering cells; and when we can trace identity between them and similar cells becoming, or about to become, fat-cells lying between the endothelium-covered surfaces, the direct relationship between the two becomes evident.

In Fig. 2, with three or four exceptions, all the wandering cells depicted there lie on the upper free surface of the membrane; on the opposite free surface of the membrane there were quite as many, but to prevent confusion we have not drawn them. For the same reason, we have only drawn the endothelium outlines on the upper surface, except at cell *a*, where we have inserted in dotted lines the outline markings of the endothelium on the lower surface of the membrane, in order to show clearly that cell *a* lies between the surfaces in the substance of the membrane, and that it is identical with cells *c* and *d* lying on the free surface, and forms a link between these and cell *b* lying, like itself, between the endothelium-covered surfaces, and which, as is shown by the two fat-globules within it, is rapidly becoming a fat-cell belonging to the group of which cell *f* is a fully developed fat-cell.

It has been urged as a reason for holding the progenitor of the fat-cell to be a special form, distinct from the wandering cell, that the latter is globular and the former flat and round; but a glance at such a group of wandering cells as is shown in Fig. 2 lets us see both forms, with every variety of gradation between them. Young wandering cells like *d* have so little protoplasm round their nucleus, that they retain the globular form when exposure to cold or to silver solution has forced them to retract their amœboid processes and die on the spot.

Full-grown wandering cells, on the other hand, with abundance of protoplasm round their nucleus, like cells *c*, *c*, remain spread over a certain extent of surface when subjected to the same conditions as those affecting cells *d*, *d*. Every gradation of form may be seen between these two extreme types, and we may also note that, when-ever a wandering cell is about to become a fat-cell, it develops a considerable amount of protoplasm or cell-substance proper, which increases likewise *pari passu* with the growth of the fat within it, so as to form a strong envelope for the great globe of fat in the fully developed fat-cell.

Wandering cells, therefore, like *e* and *f* and especially *a*, with a comparatively large amount of protoplasm, although apparently round when viewed from the front, are also flat, and when viewed edgeways they appear like long or spindle-shaped cells, thus causing and accounting for a certain amount of confusion in the views and descriptions of different observers; for in the thick subcutaneous tissue (unlike this thin membrane) in which it has been recommended to study the development of fat-cells, these cells are seen as often edgeways as any other way.

If we have succeeded in showing that fat-cells are developed from wandering cells, and that the hastily assumed difference between globular and flat round cells gives no ground for supposing that the progenitors of the fat-cell were special even from their origin, and if we have also succeeded in reconciling the views of Rollett, Ranvier, Czajewicz, and others, who have held respectively that fat-cells were developed from flat and from round cells, are we therefore to hold that Flemming and others, who have insisted that fat was developed in branched cells, are wrong in their views? By no means; and we hope to be able to show that they also are correct, and that perhaps the chief cause of disagreement between observers lies in the fact that, by different methods or modifications in methods of preparation, the same elements were shown in all the different forms referred to. Even at the risk of appearing prolix, we shall point out how slight modifications in preparation have changed our views slightly, and appear to justify the opposite opinions held by different observers.

When we first commenced this research some years ago, we were careful to bleed the animal to death, after making it insensible by chloroform, and after the blood had been withdrawn as much as possible, the blood-vessels were filled with a coloured injection, and the body was left to cool before we opened it to procure the membranes for our preparations. In this way the preparations from which Figs. 1, 2, and 4 were drawn, were made, and we believed that fat-cells were specially developed from round or flattened wandering cells. Some time afterwards, being in a hurry, we dispensed with the preliminary bleeding, injecting, and cooling, and found that we thus obtained singularly beautiful and illustrative specimens, especially when the animal had been drenched with chloroform after it was insensible. The vessels were still distended by fluid blood, and all the wandering cells within the membrane were found in a more or less branched condition, even when a large number of fat-globules had become developed within them. In this way the preparation from which Fig. 3 has been drawn was made from the broad ligament of a pregnant mouse; and as an example of the rapidity with which such a specimen can be made by our special process, we may remark that within twenty minutes after the animal had been brought to us to be destroyed, it was killed by chloroform, opened, the membrane stretched on rings, silvered and stained black, clarified, and mounted as a permanent preparation.

Strange to say, when the first modification (by injection) was practised, the wandering cells were found in great numbers on the free surfaces of the membranes, as if during bleeding, injecting, and cooling they had endeavoured to make their way from the blood-vessels or their neighbourhood to the serous cavities; on the contrary, when the animal was quickly killed by chloroform and opened, they were seldom seen on the free surfaces. In this case, the jamming of the one ring upon the other keeps the blood-vessels distended by fluid blood, and the first preparation thus obtained is generally faultless, yet the very act of excising the rings with membrane attached opens the blood-vessels left behind, and thus a thin sheet of blood-corpuscles, scarcely noticeable to the naked eye, comes to be spread on the surface of the remaining membrane, and when silver solution is applied, the sheet of red blood-corpuscles becomes fixed *in situ*, and completely obscures the preparation. If, however, a jet of water is directed upon this membrane before applying the silver, these will all be washed away, but of course leaving the various cells in an altered condition, to be fixed by the subsequent application of silver. This shows the great advantage to be gained by using the silver on clean preparations, without preliminary washing, as this not only washes away the cells on free surfaces, but it also alters the forms of those left behind.

Fig. 3 may therefore be regarded as a typical specimen of wandering cells fixed in their branched condition, and in that condition they are becoming fixed cells wherever fat is seen developing within them. We there see the various stages of the development of fat within branched cells as clearly as they were seen within round cells in Fig. 1, and the different amounts of protoplasm developed round the branched wandering cells is as varied and distinctive as in the round wandering cells seen in Fig. 2. In short, we claim not only to have shown that fat-cells are specially developed from wandering cells, but that these wandering cells may appear to be round or branched cells, according to the process or modifications of processes by which they have been prepared; and we believe we have thus reconciled the views of different observers, as far as the shape of the parent-cell of the fat-cell is concerned, those views being erroneous principally because they were too exclusive in their limitation to only one form of the parent-cell.

When, however, we pass from the mere expression of shape to the opposite opinions held by different observers regarding the essential nature of the parent-cells, we find it impossible either to reconcile these opinions or to agree with any one of them. We agree as little with Ranvier in supposing those parent-cells to be special in their nature, as we do with Toldt in supposing that only fat-cells can give origin to future fat-cells. Klein's idea of peri-lymphangeal nodules developing into fat-tracts, and fat-tracts being appanages of the lymphatic system, appears to us too far-fetched, so that there only remains for us to discuss how far it is correct to consider fat-cells as developed from the fixed cells of the connective tissue or from the adventitia of blood-vessels.

What is the connective tissue, and what are its branched cells? These are questions which we admit we are unable to answer, unless it be to the effect that we believe both terms to be no longer applicable to the cells or tissue to which they were at one time attached.

The term connective tissue, since it was first applied by Johannes Müller, has been modified out of all its original meaning by succeeding histologists, until at the present day no two histologists of eminence are agreed upon what constitutes that tissue.

Held at one time to include such structures as cartilage and bone, in whose fixed cells no one ever supposed fat to be normally developed, it is now almost confined to gelatinous, or what are called fibrous tissues in general, such as tendons, the subserous and subcutaneous tissues, &c. For our part, even if we acknowledge the branched cells in tendon, the cornea, and similar structures to be fixed cells, yet here also no one supposes that they can normally become fat-cells; and as regards the subcutaneous and subserous tissues in which fat-cells are generally found, we cannot admit that the branched cells found there are anything other than wandering cells, moving through the soft gelatinous matrix to enter into the formation of blood-vessels, fat-cells, or any of the other definite fixed cells found there, or leaving them in retrogression when that phase supervenes. Even should the term connective tissue be retained for the matrix or tissue referred to, we must hold the term fixed branched cells to be incorrect and inapplicable, and so far we are at variance with Flemming, Klein, and others, who speak of these as fixed branched cells. But in so far as we believe the wandering cells and the branched cells they refer to to be identical, we agree with them as to the parent-cells of the fat-cells. It is rather a curious commentary on the term fixed branched cell of the connective tissue that Ranvier, one of the latest and best of histologists, entirely denies the existence of such a cell, and endeavours to show that the fixed cell of the connective tissue is a broad flat cell, "*cellule plate,*" which, when applied to fibres, has the appearance, but only the appearance, of being a branched cell. Of course we are equally at issue with him in his conception of a fixed cell of the connective tissue, and believe that his "cellule plate" is only an exhausted fat-cell, such as we have drawn in Figs. 9, 10, and 11; and if anyone takes the trouble to compare our drawings with the drawings given by Ranvier at page 340 of his 'Traité d'Histologie' of his "cellule plate" (of which we have seen the original), he will see a wonderful identity between them, an identity which does not stop with appearance, but is continuous even in the physiological attributes he ascribes to it.

All these considerations show how dangerously vague a term is that of the connective tissue, and as we have already held that in those divisions of it which we have been considering there are no special fixed branched cells, it is clear that in our opinion no fat-cells can be formed from them.

The hypothesis advanced by Flemming that fat-cells are developed from the branched cells of the adventitia of the blood-vessels, seems to have met with general and, it seems to us, unmerited condemnation, for we have evidently here only an error of name and not of fact.

In the first place, as Flemming is not responsible for the term *adventitia of blood-vessels,* let us inquire what really constitutes this adventitia. Anyone who studies silvered preparations of the skin in mammals, cannot fail to be struck by the numerous and well-marked branched cells which lie specially upon the veins forming their so-called adventitia and stretching out from them for a considerable distance into the neighbouring gelatinous matrix, or, as it is called, white fibrous tissue.

The number of these branched cells seems to be considerably affected by various pathological conditions, so much so that we feel unable to admit that they are anything else than wandering cells clustering about the vein as if they were either about to enter or to leave it.

That fat should be developed in such wandering cells lying in so close proximity to nutrition, is not only reasonable, but in general accordance with our observations; for, as a matter of fact, fat-cells in a fat-tract found close to the lines of blood-vessels, seem to be developed from the wandering cells nearest to the vessel, and which would probably be called cells belonging to the adventitia of the vessel.

In Fig. 5 we have an illustration of the manner in which a fat-tract extends along a blood-vessel. In the cells there shown, the fat seen within them had been deposited to our certain knowledge within a period of twenty-four hours, and, although deposited in previously existing exhausted fat-cells, it shows well the general plan of development. These fat-cells had developed peripherally along the blood-vessel *a*, first as a single row of cells *b, b*, lying along or upon the vessel, and afterwards externally to that single file as in the case of cells *c, c* and *d, d*.

The branched wandering cells from which these cells had originally been developed, might fairly have been considered as belonging to the so-called adventitia, although at the same time they were only wandering cells clustering round the vessel. So far, therefore, we are inclined to agree with Flemming in the identity of the cells and locality he refers to, although we cannot agree with him in holding that these are fixed branched cells, or that the development of fat-cells only takes place in the so-called adventitia, and in being too exclusive as to the locality of development; for, as seen in our drawings, fat-cells may develop either singly (Figs. 1, 3), or in islands (Figs. 7, 9, and 11) unconnected with any vessel whatever, although it is quite possible that the parent-cells only a short time previously formed part of the so-called adventitia of the nearest veins.

It is a matter of common observation that the tracts or masses of fat-cells lie close to the lines of blood-vessels, or, in other words, close to the centres of nutrition, and considerable importance has been attached to the question of the direction in which their development proceeds. This we consider to be a wholly unnecessary question, only brought forward by way of supporting certain erroneous hypotheses, and we only now notice it lest our silence be mistaken for acquiescence in them.

Laying aside Toldt's idea that the fat-tracts are developed as glands from special centres in the embryo, as being too extreme and palpably incorrect for serious discussion, let us pass to Flemming's hypothesis * that the fat-cells near blood-vessels develop first close to the vessels and are then pushed to the periphery by the growth of succeeding fat-cells, in other words, that development is from the centre of nutrition to the periphery. This view seems to be insisted

* Since the above was written, we have found that Flemming has recently published another article on fat-cells in vol. xii. for 1876 of the 'Archiv für Mikroskopische Anatomie.' That article seems to be in great part a defence of his former opinions, which had been attacked by Klein and others. He has, however, modified his views as to the development of fat-cells close to and from the adventitia of blood-vessels, in somewhat the same sense as we have put it. He also acknowledges that he was wrong in speaking of the whole of the protoplasma of the fat-cell outside the fat-globule as the cell-wall, and he corrects himself so far as to speak of it only as protoplasm, outside of which, however, he describes in very vague terms another, or, as he calls it, a secondary cell-wall or membrane not always necessarily present. In short, he has adopted Ranvier's idea of a fat-cell-wall, pure and simple, in which what remains of the original protoplasm is still to be seen on its internal surface, only he describes it differently as a secondary membrane formed outside of the protoplasm, a condition even more complicated and more untenable than his former opinion.

upon as a necessary corollary to his hypothesis that fat-cells are developed from the adventitia of blood-vessels, and Fig. 4 gives fair support to it, where cells *g*, *g*, in the early stage of development into fat-cells, lie at the very centre of nutrition, while the fully developed fat-cells *a*, *a* lie at the periphery. That this mode of development should be very common is easily accounted for by the fact that both wandering cells and surplus nutrition are most plentiful immediately external to the blood-vessels, from which they indeed probably come, and consequently fat-cells may most readily be developed there. But Fig. 1 shows equally well the more advanced fat-cells lying nearest the vessels, and the earliest stages of development of fat in cells at the periphery. All this shows that it is incorrect to limit the direction of development to one course as Flemming has done, or indeed to make a special question of direction of development, as we have shown that it may proceed from opposite directions or from any direction.

In Fig. 4 it will be observed that the fat is developing or being formed in two different conditions within cells, that while in cells *a*, *a* and *g* only one large globule exists, in cells *b*, *b* we have a large number of comparatively small globules appearing within one cell.

This really points to an important difference in the time or manner of fat formation within cells, which we did not perceive when the drawing was made, but which subsequent observations explained. If in a fat-cell the fat is slowly but steadily deposited, or has existed there for a long time, even if originally deposited in globules which have subsequently run together, we find in such cases only one large fat-globule filling and distending the cell. If, however, nutrition has been excessive and fat rapidly formed, we generally find it deposited as numerous globules, more especially if the cells in which it is deposited possess much protoplasm or were previously existing fat-cells which had become exhausted. Fig. 5 is an example of this condition, in which the exhausted fat-cells were probably in the condition of those shown in Fig. 9; but if the cells have passed into the granular condition shown in Fig. 10, the globules then appear to be imbedded in a granular matrix, as shown in specimens which we exhibit under the Microscope.

We mention these points on account of the importance they may have in medico-legal cases, such as the late Penge case; for the appearance of the globule not only gives us an idea of the quickness of its formation, but the pellucid or granular character of the matrix in which the globules are imbedded gives us an idea of the degree of exhaustion which had preceded the re-development of fat.

The latter conditions are very common in mice which have entered a trap while in a starving condition, and afterwards gorged themselves on the bait employed. In this way we have procured several specimens similar to Fig. 5, where in no case had the trap been set above ten hours previously, showing how rapidly fat may become formed within previously exhausted fat-cells in these little animals.

It may also be well to state here that the normal shape of a fat-cell, when it is not distorted by the pressure of contiguous structures or fat-cells, is generally oval and sometimes round, as shown in Figs. 4 and 6, the irregularly polyhedral shape drawn and insisted upon by Ranvier being due entirely to distortion by pressure of contiguous cells, and therefore in no way representing the normal shape. The influence of pressure in distorting fat-cells may easily be traced in Fig. 6, where cells *a*, *a*, *a*, at the border of a fat-tract lying along the blood-vessels in the mesentery of a guinea-pig, have their free borders rounded off, while on the sides pressed upon by contiguous fat-cells *b*, *b*, they are becoming angular and irregularly polyhedral in shape, of the form indeed in which they are generally represented.

Hitherto there has been no question of a cell-wall or membrane, for all histologists agree that the wandering cell does not possess one, and indeed it is generally presented as the type (often under some other of its names) of a wall-less cell, whereas the fat-cell is almost invariably presented as the type of an animal cell possessing a true wall or membrane, and it therefore becomes of importance to inquire how far we are justified in accepting it as such a type. Ranvier and others, in tracing the development of the fat-cell from a wall-less cell, go so far as to localize the time when the wall is formed, and state that it is only when the fat-globules have pushed the nucleus from the centre of the cell to its periphery that the cell-wall begins to be formed.

Now, with all due deference to the opinions of other observers, we feel called upon to state that, even after careful searching and studying the fat-cell in all its phases, we find no evidence whatever of the existence of a special cell-wall, that is to say, in the sense in which the term is generally understood. We cannot admit that there is any change whatever in the nature of the cell-substance or protoplasm, although in fully developed fat-cells like those in Fig. 6 it has become so distended and attenuated by the mass of fat growing within it, that it appears to surround the latter like a thin sheet. Still that thin sheet is only unaltered protoplasm, and we shall afterwards see that, when absorption of the fat from the fat-cell occurs, the so-called membrane contracts upon the lessening fat, becoming thicker as the fatty contents become smaller in a way a formed membrane would not do, and when the fat wholly disappears, the cell-substance remains behind in the same protoplasmic condition in which it existed in the parent-cell. If any observer has observed before us the behaviour of the cell-protoplasm during absorption of fat, we cannot understand how he could reconcile that behaviour with the existence of a formed cell-membrane, and indeed no better proof could be required of the entire groundlessness of the belief in a cell-membrane than that afforded by fat-absorption. This belief in a cell-membrane has arisen and been maintained by false analogy and erroneous histological methods, or through the interpretation of the appearances they produced. As a vegetable cell often possessed a cell-wall, so it was supposed that an animal cell ought to possess one, although the complete organisms of plant and animal are entirely unlike. Histologically it was, or rather it is at the present time, considered sufficient to treat fat-cells with ether, which dissolves out the fat from the fat-cells and leaves the empty envelopes behind, and these are held to be complete evidences of the existence of a cell-wall. It is somewhat surprising to find histologists at the present day, who make a *sine quâ non* of the use of fixing agents, admitting such a proof. Ether, like alcohol, is a fixing agent which first fixes the protoplasmic envelope and destroys its power of contraction, then dissolves out the fat within it.

Certainly the histologist in this case has made a membrane where one did not naturally exist, but the explanation is so simple that it is surprising that no one ever noticed the worthlessness of the test. Ranvier, while saying that this test is perfectly demonstrative, adds another of his own invention, which is equally misleading. By his well-known method of interstitial injection of a solution of nitrate of silver among the fat-cells lying in the subcutaneous tissue, he holds that he has been able to demonstrate the existence of a cell-membrane external even to the protoplasm distended round the fat. Under this treatment a dark membranous layer seems indeed to surround the cell, but here too the appearances are deceptive and the interpretation incorrect. When a solution of silver is allowed to come into direct contact with such cells, it forms such a layer where none existed before. This may easily be demonstrated upon an endothelium-covered membrane, as we have often done. If at one part the endothelium be removed where it covers fat-cells, and the silver solution be then applied, it will be found that the unprotected fat-cells show the dark pseudo-membrane where the silver solution had come in contact with them, while the contiguous fat-cells which were protected by endothelium show no such membrane, thereby proving that the supposed membrane is only an artificial production. Where the silver has thus only penetrated to a certain distance into the protoplasmic wall, the unaffected portion retains its normal appearance, and thus gives rise to the supposition that a part of the original protoplasm may often be seen lying on the inner surface of the supposed membrane.

The expression referred to, that the cell-wall only gets formed when the fatty contents have pushed the protoplasm and nucleus to the periphery, is inaccurate, from the fact that protoplasm and nucleus are always peripheral to any fat-globule within the cell; and when by excessive distension the nucleus and protoplasm appear like a signet ring, the relation between the two still remains the same, and after absorption of the contained fat the nucleus appears to return to the centre of the cell-substance, as seen in Figs. 7, 8, 9, 10, and 11, although in reality the relationship has never altered throughout the cell life. We have now traced the fat-cell into its fully developed condition, as shown in Fig. 6, and seen that its parent-cell was the wandering cell, under which name we of course include white-blood cells, lymph, lymphoid, or lymphatic cells, migratory cells, embryonic cells, leucocytes, amœboid cells, and to these, by our own showing, the so-called fixed branched cells of the connective tissue and of the adventitia of blood-vessels; and we have also seen that these cells may be either globular, round, flat, spindle-shaped or branched, according to the position in which they are viewed, or whether they are fixed before or after they have had time to contract or retract their processes. With the fully developed fat-cell we reach the end of the first half of our studies, a task which ought to have been simple and short, but for the fact that it was encumbered with the divergent opinions of different observers. We have endeavoured to reconcile those opinions where possible, by explaining the causes of divergence, and in this, we believe, we have been not unsuccessful.

We now pass on to the second part of our studies, to show how the fully developed fat-cell returns into its original condition of a wandering cell, a task which will prove much easier and interesting than that of following development, for few observers have traced even the first part of the decline of the fat-cell, and none to our knowledge have witnessed the interesting appearances which herald its disappearance, so that we shall here only require to state the appearances observed by ourselves, and not to reconcile the divergent opinions expressed by others.

Part II.—*Retrogression of the Fat-cell.*

During the development of fat-cells we noticed that, as the fat increased within the cell, the cell-substance also increased *pari passu* with the amount of fat which it had to envelope. In absorption or retrogression of the fat-cell, we have thus two substances to get rid of before the cell can return into its original condition; but although these two substances, namely, fat and excess of cell-substance, developed at the same time, their absorption occurs separately; indeed the decline or break up of the cell-substance does not commence until some time after the complete disappearance of the cell-contained fat.

Both processes in retrogression can best be studied in the bodies of rats and mice or other small mammals; indeed the latter process can only be studied well in such subjects. Flemming and others have starved dogs and other large mammals for a long period, with the result that they have failed to observe the most interesting and essential part of the process. In rats and mice, more especially the latter, which are often trapped in a starving condition, the system seems to be so exceedingly sensitive to excess or deficiency of nutrition, that they may either fatten or starve within the space of twenty-four hours; the little animal from which Figs. 9, 11, and 12 were drawn, was found almost dead in a jar, into which it had fallen, and in which it could not have remained above twenty-four hours, yet the whole of the different stages of retrogression in fat-cells could be followed upon one preparation of its mesentery.

This great susceptibility to variation in nutrition is apt to introduce an element of uncertainty or confusion into the study of the process of retrogression upon them, for it often happens that the remains of fat-cells, which had been broken up some time previously, are to be found in a preparation where well-developed fat-tracts point to even excessive nutrition. The first changes, during the absorption of the contained fat, seem to occur in the condition of the fat itself, which, from being of a yellowish-white colour and thick consistency, becomes more transparent, watery, and slightly red in colour. These changes have been previously noted by other observers, who have compared the resulting fluid or fat to serum, although there is nothing of the nature of serum about it, for we find that under the action of osmic acid it blackens even more intensely than in the case of newly formed fat. When once absorption has fairly commenced, if nutrition continues deficient, it follows a steady course, characterized by diminution of the fatty contents and the contraction and thickening of the protoplasmic envelope containing them *pari passu* with each other. This process is illustrated by Figs. 7, 8, 9, and 10, showing different stages in different animals of the process of fat-absorption from fat-cells, and it will be found that in all the mammalia the process and appearances are the same throughout. Fig. 7 is from the body of a young man who died of cancer of the skin, under the care of one of us, at St. John's Hospital. He had entered the hospital only two months before his death, a plump and well-nourished individual, and said that previously he had never had a single day's sickness. His downward progress was rapid, as the whole of the skin of the left side of the thorax became gangrenous, and during the last few days of life he was kept under the influence of morphia, on account of his sufferings, and as he took little or no food latterly, he died much emaciated. Fig. 7 represents a part of his omentum, taken by permission immediately after death, and stained by silver and pyrogallate of iron. It may be taken as a typical specimen of steady and unbroken absorption of fat from fat-cells, and it will be noticed that, owing to the locality and the absence of distorting pressure from neighbouring cells, as well as from their lying parallel to the surface, all the cells are assuming the oval, almond-like shape.

Fig. 8, again, is from the subcutaneous tissue of the body of a young man, who died after an illness of thirteen years and in the last stage of leprosy. It is prepared by treatment with osmic acid and picro-carminate of ammonia. It represents a more advanced condition of fat-absorption than that seen in Fig. 7; and although selected from a spot in a perpendicular section, where the fat-cells were by no means closely packed, yet evidence of distortion (rapidly disappearing, it is true) is to be seen in the angular shape of one or two of the cells. At other parts of the group not included in the drawing, many fat-cells were seen entirely destitute of fat. In neither case had the disease under which the patients suffered affected in any way the fat-cells. Although some observers have tried to make out a distinction between the fat-cells found under the skin and those found in serous membranes, recommending only the former for examination, yet it will be seen that the fat-cells in Fig. 8 only differ from those in Fig. 7 inasmuch as the former have been distorted by pressure of contiguous structures, while the latter show the normal and true shape of the fat-cells. Fig. 9, from the broad ligament of the mouse formerly referred to, shows a still further stage of absorption of fat, which has entirely disappeared from several of the cells *c, c* in the drawing. Some of these cells also have been exposed to some slight distorting pressure, and it will be specially observed that in general appearance they are identical with the fat-cells of the human body, as seen in Fig. 7, they having been prepared by the same process.

Certain observers have also stated that the difference between the fat-cells in man and the smaller mammals was so great, that the latter could not be taken as types of the former. To this statement we wish to give a complete denial; we have never been able to detect any difference whatever, not even sufficient to enable us to tell which animal they belonged to.

As from several of the cells shown in Fig. 9 the fat has completely disappeared, we may consider that in them we have reached the end of the first stage in the retrogression of the fat-cell, that, namely, which concerns the absorption of fat only; so before passing on to the second stage, let us make a few remarks relative to fat-absorption.

We find no reason to suppose that the different stages seen in the development of fat are represented in its absorption. We saw, for example, that fat was first deposited in several or many globules within one cell, which afterwards ran or melted into one mass in the fully distended fat-cell.

In absorption of fat we find no breaking up into several globules of the one mass; but where the fat-cells contained only one mass, the mass grew smaller, but did not break up into globules, as seen in most of the cells of Fig. 7. When, however, the fat-cells were only in course of development when nutrition failed, as seen in several of the cells in Figs. 9 and 10, where the developing globules had not melted into one mass, these globules diminished together; in other words, single masses diminished as single masses, and multiple globules diminished as multiple globules.

The course or direction of absorption among fat-cells is better marked than the direction of development. The fat-cells of the mesentery, and more especially at the upper part near the pancreas, become empty before the fat-cells of the broad ligament, while in each membrane the cells farthest from the blood-vessels and from the neighbourhood of the parts of the blood-vessels farthest from the centre of the circulation, are the first to become emptied of fat. After the fat has disappeared from the cells, and the first stage of decline is completed, a period of quiescence ensues, during which little change appears in the condition of the exhausted cells.

It may be observed, however, that they seem to diminish slightly in size; they become more regularly oval or almond-shaped, and when viewed edgeways the fat-cell is seen to have become thicker in the centre, like an almond viewed edgeways.

Within the cell-substance the granules are seen becoming better defined from the transparent matrix containing them, and at the same time increasing in number. Suddenly, and without any particular change or warning, the granules begin to leave the cell in every direction, as if they had become endowed with the power of automatic locomotion which their mother-cell had lost on becoming a fat-cell. Not only does the sharp oval outline become lost in that mother-cell, but the nucleus also becomes nearly hidden by the mass of granules clustering round it like a swarm of bees round their queen. The swarm passes away on every side and in apparently no definite direction, the granules becoming fewer and more isolated the farther they pass away from the mother-cell.

This condition is well seen in Fig. 10, from the same animal as Fig. 9. We have there a small group of fat-cells forming an island apart from the great fat-tracts that lie along the contiguous blood-vessels. While the fat has disappeared from all the cells of the group, three of them, *a*, *b*, and *c*, have entered upon the condition of granular exodus, and the granules may be seen passing away from them in every possible direction. We see none of that appearance shown in drawings of an ovum which has been burst by mechanical pressure, and where the vitellus is seen pouring out through the rent in the vitelline envelope. On the contrary, there is clearly no membrane here to rupture, and the granules appear to emerge from every point of the surface of the mother-cell; and we here desire to state that each of the departing granules has been drawn *in situ* by the aid of the camera lucida, and that we have in no way drawn upon our imagination in depicting this phenomenon. In Fig. 10 it will also be observed that there are stages in the granular exodus; cell *b*, for example, has retrograded further than cell *a*, and cell *c* further than cell *b*; or, in other words, the granular exodus has been going on longer, and a greater number of granules have left cells *c* and *b* than cell *a*, but the continuous change onwards in absorption can be better studied in Fig. 13, from the same animal and preparation as Figs. 9 and 10. In this Plate we are brought to what may be considered as the last chapter in the life-history of the fat-cell. In it the least advanced in retrogression are cells *a*, *a*, still undergoing the granular exodus. Cell *b*, however, has almost reached the last stage of this process, and in it a definite outline is again appearing, and the nucleus is again becoming distinct, being no longer hidden by the swarm of granules clustering round it, as in the case of the less advanced cells. Beyond cell *b* we have a group of cells *e*, which have probably belonged to a group of fat-cells similar to that seen in Fig. 10. From them the granules have almost entirely departed, leaving them in the condition of branched wandering cells, similar to those seen in Fig. 3, the faintly tinted protoplasm in both cases being almost destitute of granules, and visible apparently more in consequence of difference of refraction between them and the gelatinous matrix in which they lie than by any distinct colour or tint.

In fact, we have now come upon debatable ground, where there is room for discussing whether such branched cells are really the offspring or result of the granular exodus from fat-cells or *bonâ fide* wandering cells.

A certain number of granules can still be detected here and there within their protoplasm, but it is difficult to say whether these are a residuum of the original fat-cell or eaten as pabulum by the wandering cell. By long and careful examination, we have come to the conclusion that those cells *c*, *c*, are the remains of the fat-cells which we have thus traced back to their original condition, but we have considered it advisable to place the *contras* as well as the *pros* of the question before our readers.

It ought also to be borne in mind that other cells besides these contain granules, and that granular exodus is not confined to fat-cells, which are shown here as typical of a condition, and not as undergoing a change special to themselves. The blood capillaries and vessels which had developed *pari passu* with the outlying groups of developing fat-cells, as indeed the special nutritive adjuncts of the latter, have no longer any *raison d'être* when their nurslings perish, and they consequently obliterate their canal, and the constituent cells separate and undergo a similar granular exodus to that seen in the retrograding fat-cells, although in a much smaller and otherwise almost imperceptible degree, as at *f*, *f*.

During the process of granular exodus in the fat-cell, a change was taking place in the condition of the nucleus, which only becomes apparent when, as shown in cell *b*, the greater part of the granules which obscured the nucleus have left and allowed the nucleus to become visible.

In the wandering cell, the nucleus stains intensely by colouring agents, and is generally more or less globular in shape, except when proliferating. When the wandering cell becomes a fat-cell, we see that, as the protoplasm becomes distended by the fat within, the nucleus also seems to become stretched out into a flat circular or oval form, being thinner if greater in superficies, and staining much less intensely than formerly by staining agents. Even in retrogression the nucleus maintains its flat and circular condition, as it seems to pass back to a position in the centre of the cell-substance, and continues in that condition till the granular exodus obscures it. When it next appears, as in cell *b*, it has become globular, and smaller in superficies, and begins to stain more intensely, comes back indeed to the condition of the nucleus of the wandering cell, so that no distinction can be made between them.

The point of greatest importance in this inquiry is the nature or character of those granules which we see leaving the cells and travelling through the gelatinous matrix of the membrane, apparently by virtue of their own power of locomotion. Indeed the end of these studies only opens out to us the commencement of other more minute, more delicate, and more important researches. What, in the first place, is the typical shape of the granules? The powers of the Microscope used in making the drawings 800 diameters only showed them as bright refringent points, staining slightly by the black staining fluid used in the cases mentioned.

Moreover, to be able to fix their natural shape, they ought to be studied in their living condition, upon the warm stage under the Microscope, to see if, like wandering cells, they alter their shape during life or during their locomotion, if such can be observed. Even during their dead condition (chloroform having been plentifully used in killing the animal, so that we might hope that, like the wandering cells, they were fixed in their living shape), with specially high powers of the Microscope, we can see that many of them are oblong in shape but round when seen edgeways, and sometimes two or three are attached together like beads. All these points, however, ought to come into a special inquiry into their life-history, so that we have considered it advisable at present merely to draw them in their general positions, shape, and size, as seen under the power used in making all the drawings in this research.

But of far greater importance than their shape is the character of the substance composing these granular bodies, and this, we think, we have been able to ascertain satisfactorily, as far as their biological character is concerned.

As may well be conceived, the first point of importance to settle was whether these were fatty or protoplasmic in their nature. If, as was likely, they were fat-granules, little importance was to be attached to them; but if, on the contrary, they were protoplasmic in character, they were all-important as a key to the past and an explanation of the future.

To decide this point we had to vary our methods of preparation and, instead of using the pyrogallate of iron, we treated our membranes with ether, logwood, carmine, indigo, purpurine, and eosine, with and without osmic acid, and the result was unmistakable. Osmic acid did not blacken, while colouring agents stained, logwood being prominent among the rest in the intensity of its staining, showing that these granules were protoplasmic in character and not fatty.

The character stamped upon them by staining tests, as well as the power they appeared to possess of moving off at pleasure from the parent-cells by their own inherent power, and as we shall afterwards see of probably moving back again when the conditions were reversed, show us that we have here to do with something specific in biology, something vastly more minute, and a stage more elementary than the composite body called a cell; something which lives and moves and has its being independently of the cell, and to which we are called upon to assign a specific sphere in nature. Have we here germs, the micrococci, the zooglœa, the spores, fungi, bacteria, or the spores from which bacteria are developed in these living atoms? It is impossible to evade the conclusion that had these been observed in sections of tissues, where their connection with the cell or its nucleus could not be traced, more especially in any specific disease, they would indubitably have been ascribed to some of the foregoing classes, and (perhaps not without reason) the most serious conclusions might be drawn from their presence. We have no doubt that they furnish a key to the alleged discoveries of some of the above-named classes of organisms in certain specific or infective diseases in the past, and they may probably furnish an explanation of many infective processes in the future.

We may also mention here, with reference to a recent biological mistake in the character of germs that, whether treated with or without alcohol, and indeed by all kinds of modifications of method, the result was always the same. At page 13 of his work 'On the Lower Organisms,' in endeavouring to account for the presence of bacteria within the living body, Dr. Bastian says:—"We must imagine that when the vital activity of any organism, whether simple or complex, is on the wane, its constituent particles (being still portions of living matter) are capable of individualizing themselves, and of growing into the low organisms in question. Just as the life of one of the cells of a higher organism may continue for some time after the death of the organism itself, so in accordance with this latter view, may one of the particles of such a cell be supposed to continue to live after even cell life is impossible."

This hypothesis of Dr. Bastian's is so exactly applicable to the granular bodies we have described, that we have ventured to quote him, as he expresses even better than we could ourselves the opinions we hold and wish to put on record.

We believe that in them we supply the missing link between cellular and germ pathology, and its bearing on the causation of disease will become more apparent when, at another time and place, we have an opportunity of showing that granular exodus is not confined to healthy cells, but that at least in one virulent disease we have characteristic granular breaking up of its cells throughout the body, and in that the explanation of its eminently contagious character.

But the interesting phenomena to be observed in the life-history of these organisms by no means cease with their leaving the parent-cell in the condition of the wandering cells seen in Fig. 13. Even in that direction they may pass beyond the stage seen there, and thus we find that the whole of the fat-cells forming a great fat-tract may pass away, leaving the vascular network which supplied them still existing, or they may still be observed there as numerous granular patches, each with its own nuclear centre which it is about to leave, and which in turn is about to leave the neighbourhood of the blood-vessels, as in Fig. 12.

Even at this juncture, if nutrition becomes again abundant, a complete change takes place in the action or plans of those granules. In that case they seem at once to return to the nucleus they were leaving or had left. They surround that nucleus on every side, and, when logwood staining is used, we find that, although that nucleus (where it can be seen) is stained as intensely as the neighbouring nuclei, yet the clustering granules stain so intensely purple as completely to hide the nucleus from view, as shown in Figs. 5 and 14. Then comes another consideration: the granular cells staining intensely by logwood come to be seen not only near vessels where no fat-cells had ever existed, but also far away even from vessels, in the centre of non-vascular tracts, which they could only have reached by journeying as wandering cells. That they have this property, we think we can demonstrate satisfactorily by means of specimens which we show to-night.

If, in the first place, we start with cell *a*, Fig. 10, which seems to have left the group of fat-cells shown there, we can pass on to another example, Fig. 16, where four of such granular cells can be seen lying within a natural hole of a membrane, like cell *h*, Fig. 1, and lying, moreover, within a group of wandering cells for which they cannot possibly be mistaken; for the large oval contour filled with granules, a nucleus sharply defined and of a reddish colour (when stained by pyrogallate) contrasts strongly with the blue-black polynuclear condition of the wandering cells surrounding them.

Only one link is missing, and that also we supply, by showing in *a*, Fig. 15, such granular cells in the branched condition, moving along by the side of blood-vessels, and contrasting strongly with the transparent delicate branched cells *b*, *b*, near them.

It would, therefore, appear that when from a fat-cell all the fat has become absorbed and it has passed into granular retrogression, the faculty of locomotion is restored to it, that indeed it is in the condition of a wandering cell, plus the granules which it contained. But it would further appear that, while wandering and while its own granules are moving off from it, a supply of nutrition checks the granular exodus without checking the cell wandering (or exodus as regards the fat-tract), and then the granules may cluster round the nucleus in every possible form of irregularity, looking like the peripheral crystals in a lump of sugar. Gradually, however, these granules seem to melt into the substance of the cell, and it is again finally seen as a round or oval flat cell with sharp border and granular contents, which gradually become less granular, until the granular cell, the quondam fat-cell, becomes indistinguishable in appearance from any other wandering cells and, as we already have seen from its presence in the natural hole of a membrane and therefore on its free surface, it has also the same nomadic faculty, and indeed with that faculty we see no reason why it should not be discovered within blood-vessels where we have not yet looked for it. The time taken to effect all these changes is comparatively long, and we have not yet been able to fix a limit. We believe that a fortnight is not sufficient, and this fact is apt, as we have already noted, to introduce a complication into the study of this question; for just as it seems the rule that a mouse may be reduced often to the point of starvation while at large, the vestiges of such granular cells are scarcely ever entirely absent from some preparation, although we are able to show two or three in which they have not been found to exist. When, moreover, we take into consideration the fact that other cells beside fat-cells have the power or fate to become granulr, and, moreover, that other processes besides starvation will reduce even the fat-cell into the granular condition, we may form a fair idea of the difficulties surrounding this research and the liability to errors which it possesses.

Apart from the question of disease, if a tame rat be put into a cage with some strangers, these latter, if they are powerful enough, will often so maltreat the new-comer as to reduce it to a skeleton, or even kill it outright, and then the same phenomena of fat-cell absorption may be witnessed. Although young rats while they are being suckled are generally plump and fat, they rapidly become lean when weaned and forced to provide for themselves instead of being dependent on the mother's milk. In such cases, even although food had been continuously supplied, we have found the fat-cells exhausted and granular cells abundant, which could only be accounted for by the change in nutrition subsequent to weaning. Even more interesting is the condition of the fat-cells during excessive lactation, and the bearing which this has upon the same condition in the human female. In rats and mice, pregnancy is accompanied by a great accumulation of fat in the tracts near the blood-vessels, as if in preparation for the demands about to be made upon the mother by her nurslings. A short time ago a female mouse, having been trapped, was brought to us to be destroyed, and we afterwards noticed that it was extremely lean, and that its teats were pendent and flaccid, as if it were nourishing a large litter of well-grown young ones, which we afterwards proved to be a fact. From this animal's broad ligament and mesentery specimens were prepared which showed all the stages of retrogression, similar to those seen in Figs. 9, 10, and 13, although, from the immense number of exhausted fat-cells near the lines of blood-vessels, it was evident that, shortly before, the animal had been extremely fat, but it had been brought down to a condition identical with that found in starvation, by the excessive demands of its young upon it. We have thought it unnecessary here to enter upon any speculation as to the channels by which the granules of protoplasm move off from their parent-cell; by the aid of the binocular Microscope and one preparation whose endothelium is marked by silver on both surfaces, it is easy to decide that the granules are moving off through the soft gelatinous matrix which forms the membrane. They move off in every direction and by no definite channel, and lest some one should invoke the presence of lymphatic radicles as a channel of exodus, we can only say that, after having made a speciality of the search for lymphatic radicles or vasa serosa, such channels are purely mythical, and have no foundation in fact. They may possibly pass away finally by the blood-vessels or lymphatics, or even more probably they may be absorbed or appropriated by the wandering cells, and we can from this easily imagine how, by the absorption of granules from diseased cells by wandering cells, a specific disease might quickly become generalized throughout the system.

One word more as to the behaviour of the exhausted fat-cells not yet passed into granular exodus, when nutrition again becomes abundant. If in the condition of the cells seen in Fig. 9, they simply fill the already prepared mass of protoplasm with numerous fat-globules, as seen in Fig. 5. But if the cells have become granular, like those seen in Fig. 10, when about to break up, then they still fill up, as in Fig. 5, only that in this case the fat-globules seem imbedded among granules. Of this condition we show a specimen, Fig. 11, which affords inverse proof of the connection between granular cells and fat-cells.

In terminating this long paper, we wish to observe that we do not pretend to have completed this question of retrogression, but rather to have only opened it out. Conscious of our many imperfections, we are prepared to find our conclusions modified or reversed subsequently by others or by ourselves. We are also aware that several collateral conditions remain to be investigated; such, for example, as whether the supply or deprivation of water affects the retrogression of the fat-cells in starvation, or whether gradual or sudden deprivation of nutrition has the same result or effect on the fat-cells. These are points which would require to be settled by direct experiment, if one has not the patience to wait for accidental circumstances. We have the patience to wait rather than experiment, and when opportunity offers and we find anything new or anything incorrect, we shall not be so tardy in making it known as we have been with this research, which has been spread over an interval of above four years, but which we have endeavoured to bring up to date.*

While the foregoing was passing through the press, two remarkable communications were made on May 6th and 20th to the Pathological Society. The first of these, "On the Occurrence of Micrococci underneath Antiseptic Dressings," by Mr. Cheyne, a pupil of Mr. Lister, and supported by him, mainly concerned the cultivation in vegetable infusion of micrococci from the matter obtained from wounds treated antiseptically, while the second was the report of the Committee on Pyæmia, and was largely illustrated by microscopical specimens of tissue in that.

In the preceding pages we have spoken vaguely of the identity of the granules we have described with many of the so-called specific organisms, because we were aware that different people held different opinions as to what constituted those supposed organisms. The high authorities who brought micrococci before the Society, however, gave us a definite standard of comparison, and we now assert with confidence that all those micrococci were nothing other than the

---

* A short account of this research with microscopical demonstrations was given by Mrs. Hoggan before the Naturforscher Versammlung at Cassel in September, 1878, and her remarks were published *in extenso* next day, on pp. 53 and 57 of the 'Tagblatt.'

granules formed from cell protoplasm in the manner we have described. The specimens illustrating pyæmia especially, showed micrococci both in free masses and within cells of the kidney, almost identical with those shown in our preparations.

In the discussion of the questions referred to, it was assumed that the so-called micrococci were specific independent organisms from without the body, and the chief interest turned on such questions as how they managed to enter underneath the dressing or into the body, whether they could exist in the body, or what specific influence, if any, they might have there.

All reasoning therefore might, however, seem superfluous if it could be shown that, instead of being specific independent organisms from without, the so-called micrococci were merely minute atoms of the protoplasm of the cells within the body, formed as we have described, and that according as they were the result of a physiological or a pathological process, so would their effect be when introduced into the system. In more specific terms we might consider that the particles resulting from the disintegration of the protoplasm of fat-cells would be harmless, while those resulting from the protoplasm of cells in glanders, where we have also observed this process, would be most malignant in their effect when introduced into the system; and the same might be said of those particles so clearly shown within and outside the cells in pyæmia.

London: Printed by William Clowes & Sons, Stamford Street and Charing Cross.