ON THE
PATHOLOGY OF LUPUS,
WITH
SPECIAL REFERENCE TO THE APPEARANCES
DESCRIBED AS GIANT CELLS.

BY
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SUCH portion of our knowledge of lupus as is established beyond controversy both as to the facts and the theories explaining them is due to the investigations of Auspitz and Virchow. The former observer in a memoir on the cell-infiltrations of the corium, published in the Vienna *Jahrbücher* for 1864, sums up his views regarding the pathology of the disease, by stating that it is essentially a cell-infiltration which penetrates the corium uniformly throughout its entire depth. Beginning in the form of nodules which glimmer through the moderately swelled epidermis, it produces elevations which can usually be felt, although in some cases they appear as simple maculæ. Later, these nodules extend until they join each other, and form an extensive area of infiltration, whilst fresh nodules are formed at the periphery of the affected part.

Virchow in his work on Tumours, gives a similar account of the process, describing the cell-masses which are formed

as granulation-tissue, and on that account bringing lupus into the same category with leprosy.

The next work on lupus of importance is the memoir published by Friedländer in Virchow's Archiv in 1874. This observer called attention to the existence of nodules of a special kind, in the midst of the granulation tissue. The cells in the nodules are, he found, larger than the cells of the granulation-tissue, although their nuclei are about equal to those of the latter cells. The diameter of the nodule-cell is three times that of the granulation-cell, and the largest of these nodule-cells, pass by transition direct into giant cells, which are invariably to be found in the nodules. These giant cells are, he tells us, somewhat spherical structures, provided with delicate processes which taper to fine points. Their protoplasm has the same characteristics as that of the nodule cells; their nuclei are also similar, except that they are frequently oval instead of round, especially in the larger forms. The number of nuclei is always considerable and may exceed a hundred.

The importance of this description is best understood by taking it in connection with Schüppel's¹ investigations on tuberculosis of the lymphatic glands. "I distinguish in tubercle of the lymphatic glands," remarks this author, "three different forms of cells, namely, giant cells, large epithelioid cells, and small lymphoid round cells." Friedländer states that the giant cell probably never fails to be present in the lupus nodule; Schüppel that it is scarcely ever missed in tubercle. I have only further to add that a comparison of Friedländer's and Schüppel's plates shows that they had before them elements of an exactly similar nature.

Since the publication of Friedländer's memoir most of the investigators who have written on lupus, have confirmed his observations regarding giant cells. Professor Lang² of Innsbruck, forms, however, an exception. He observed appearances similar to those described by Friedländer, but

¹ 'Untersuchungen ueber Lymphdrüsen-Tuberkulose,' von Dr. Oscar Schüppel, Tübingen, 1871.

² "Zur Histologie des Lupus," 'Archiv für Dermatologie u. Syphilis,' 1875.

considers them to be degenerated sweat tubes and ducts. Stilling,¹ the latest German writer on the subject, so far as I know, believes that some of the appearances are, as Lang has advanced, due to degenerating epithelial structures, but maintains that the true giant cell also exists in lupus, and he figures examples similar to those drawn by Friedländer. Thoma, the author of an exhaustive and very valuable memoir on the pathology of lupus, in 'Virchow's Archiv,' in 1875, expresses his belief that all the cells of the lupus-infiltration are probably derived from the colourless blood-cells found in the perivascular spaces, these forming successively, in different stages of development, the granulation cell, the epithelioid cell, and the giant cell.

Although the discovery of giant cells during the last few years in very different kinds of diseased tissues has in one sense somewhat diminished the importance of Friedländer's observations, the interest attaching to the question is from another point of view only increased. As the "giant cell" is so frequently met by pathologists in whatever direction they are exploring, often turning up where least expected, further knowledge regarding this equivocal structure has become one of the pressing needs of medical science.

The results of an examination of lupus tissue, for which I am indebted to the kindness of Mr. Morratt Baker, have proved interesting chiefly in relation to this question of giant cells. A careful analysis of these objects, in their different stages and forms, has led me to form the conclusion that the giant cells of lupus are not independent organic structures, but that, on the contrary, the wall of the so-called cell is the altered coat of a diseased blood-vessel, that the appearance described as protoplasma is produced by a disintegration or red blood-corpuscles, that the nuclei on the periphery are nuclei of the vascular walls, and that the nuclei of the centre, when they are present, are the nuclei of colourless blood-corpuscles.

¹ "Einige Beobachtungen zur Anatomie und Pathologie des Lupus," von Dr. Med. Heinrich Stilling, 'Deutsche Zeitschrift für Chirurgie,' Band viii, 1877.

Before, however, entering on this, the main subject of my communication, I shall state briefly the evidence which is furnished by the case I have examined regarding some other points in the pathology of lupus which are still *sub judice*.

The lupus tissue was procured from a boy, æt. 9, who was under Mr. Baker's care in St. Bartholomew's Hospital. He had an isolated patch of lupus on the anterior surface of the left thigh, measuring about two inches in its long diameter; it had a raised border and was nowhere ulcerated. There was also a small lupus tubercle on the skin of the penis. Both patches were excised by Mr. Baker. I examined part of the patch from the thigh and sections of the whole of the tubercle from the penis.

The distribution of the cell infiltration in this case corresponds exactly with that found by Thoma in a number of cases which he examined. In the apparently sound skin, for a considerable distance beyond the developed disease, the superficial blood-vessels of the corium are invested with a thin covering of cell-infiltration. There is no cell-infiltration here between the bundles of the connective tissue. Coming nearer the extensively diseased area the external root-sheaths of the hairs and the sebaceous glands are found disintegrated and their place occupied by a mass of cell-infiltration from the vessels of the hair-follicle, the surrounding connective tissue being still unaffected. Approaching the centre of disease we find nodules of cell-infiltration developing around the blood-vessels and displacing the connective tissue, until finally we come to a point where the papillary layer of the skin has completely disappeared, its place being occupied by a large mass of cell-infiltration, in which the areas of the nodules, by whose coalescence it has been formed, can mostly still be recognised.

Deeper in the corium, and mostly separated from these superficial masses by unaltered bundles of the *pars reticularis*, we find large oval or round nodules of cell-infiltration, and by examining these deeper nodules in different stages it is seen that the seat of disease here is the territory of a sweat coil. It has been stated by Lang that in lupus the sweat

glands take on new growth. In this case it has certainly not been so. The cell-infiltration begins around the vessels of the coil, and the glandular epithelium simply passes from one stage of disintegration to another.

Localised nodules had also begun to form amongst some of the superficial flat vesicles.

The appearances which I have described support the views of those observers who describe lupus as a cell-infiltration which spreads outwards from the blood-vessels.

I have found no evidence in favour of Lang's opinion that the cell-infiltration originates in a growth of the protoplasm of the capillary wall, nor anything to support the conjecture that there is proliferation of the connective-tissue cells. The explanation given by Auspitz and Virchow of the connective-tissue origin of the cell-infiltration was advanced at a time when the presence of several nuclei in any space between the bundles was believed to afford proof of cell-proliferation. Since that period the discovery that in morbid conditions the colourless blood-corpuscles enter the interfascicular spaces, and the better knowledge we now possess regarding the nature of connective-tissue cells, have revolutionised our conceptions regarding the origin of cell-infiltration.

As a matter of fact the connective-tissue cells of the corium are exceedingly difficult of demonstration, and I know of no text-book in which an attempt is made to show more than that there are cell-nuclei on the bundles. Any endeavour, therefore, to discuss assumed morbid changes in these cells is premature.

I agree with Thoma in thinking that the size of the cells in the lupus-infiltration, the positions in which they are first found, and, I may add, their behaviour under staining agents, concur to render it very probable that they are colourless blood-cells undergoing various stages of development and degeneration.

Scattered through the lupus growth, and more especially situated (generally excentrically) in the nodules that compose it, are the structures that will now engage our attention—the "giant cells" of Schüppel and Friedländer. I find in my

preparations numerous examples of appearances identical with the giant cells figured by these and subsequent observers. This identity will be apparent to any one who compares my figures with theirs (see, *e. g.* figs. 3 and 5).

The appearances in question can be made very apparent by a particular mode of preparation. The dye eosin has a special elective affinity for some tissues, red blood-corpuscles and blood-vessels sharing with horny epidermis and striped and unstriped muscle this preferential selection. The giant cells of lupus stain as deeply by eosin as blood-corpuscles or muscular fibre do, and by judicious manipulation with the dye a section of lupus tissue can be made to show these structures coloured a deep orange red in an almost colourless ground. Subsequent staining by logwood brings out the nuclear elements present in the mass.

The fully-developed giant cell is usually seen in section as a circular or oval mass with a well-defined contour, which, for the purposes of description, I shall term its wall (fig. 3 *a*, fig. 5 *a*, fig. 12). The mass is granular, and, as I have already remarked, stains deeply by eosin. The wall is generally lined on the inner surface, more or less completely, by nuclei. In the substance of the mass, there are frequently no nuclei, or they may be present sparsely or in great numbers in one part and not in another, or be found only in the periphery, or only in the centre. From the bounding wall of the mass process-like prolongations pass outwards into the tissues which surround it (fig. 3 *a*). Sometimes there is a space between the mass and the surrounding tissues, and the prolongations are seen very distinctly crossing it. When this space exists oval nuclei, which have the character of the nuclei of connective-tissue cells, are found on both its bounding walls. But from this typical giant cell there are many departures. Oblong membranous-looking patches, long narrow strips, some of them very small, others very large, are found, more or less granular, with more or fewer nuclei, and staining exactly like the giant cell (fig. 5, *c*, *d*).

Further, if we search for the early stage of development of

the giant cell in parts of the healthy or comparatively healthy tissue adjoining the lupus infiltration, we find the following transition stages:—Giant cells are found in which the contents of the cell are homogeneous at one part and granular at another (fig. 7); others in which the contents are entirely homogeneous, whilst the wall and processes fulfil the characteristic requirements of the giant cell, the nuclei, in this case, being limited to the wall, but still differing in no respect from the nuclei on the wall of the granular giant cell. In some of these cells with homogeneous contents the likeness of the whole structure to a blood-vessel becomes apparent, and occasionally the wall is found to show the characteristic muscular coat of an artery. Going another stage backwards, we find a giant cell with homogeneous contents and red blood-corpuscles in the centre of the homogeneous mass—sometimes in considerable numbers—the wall and its relations still answering to the requirements of the giant cell (fig. 6). In all these cases the characteristic staining by eosin is maintained, and the conclusion becomes forced on us that the peculiar staining of the granular mass in the typical giant cell is due to the substance stained deriving its origin from the red blood-corpuscles.

In other sections of giant cells we find the coats of the original blood-vessels still represented, the inner coat being represented by the nuclei of its endothelium, and the middle and outer coats by considerable thicknesses of characteristic tissue (fig. 9).

When we find a giant cell bounded by a single wall, which is fringed on its inner surface with a line of nuclei, the resemblance of these nuclei to those of the vascular endothelium must strike every one. Similarly, in sections in which there is considerable thickness of wall a number of elongated, narrow nuclei are found in it, which I believe to be equally characteristic of the coats of the blood-vessels, of the size of the larger vessels usually found in the corium.

It occurred to me that if the so-called giant cells are in reality disintegrated blood-corpuscles in degenerated blood-vessels, it should be possible to isolate the mass in some

length. And this I have succeeded in doing. Figs. 10 and 11 are drawings of an elongated, hollow, granular mass thus isolated, the shape affording evidence that it is the cast of a dilated blood-vessel. This mass consisted of a finely granular substance, which stained by eosin precisely the same tint produced by the dye on the granular substance of the giant cells, and in other respects the similarity was complete. Embedded through the whole thickness of the mass scattered colourless blood-cells were observed. On the edge of the cast, and on its external surface, formed elements were found at several points. These were not granular, and were probably detached portions of the wall of the vessel, which had remained adherent to the granular contents. I found no other elements in my preparations except the so-called giant cells, whose characters corresponded to the mass I have just described.

I have also figured part of a preparation in which a group of giant cells was found in one microscopic area of the nodule from the penis (figs. 4 and 5). On studying this group it became evident that all the structures composing it belonged to one or two blood-vessels. Between two of the giant cells blocks of a substance containing nuclei, and coloured orange red by eosin, but not granular, connected one cell with another. By careful regulation of the fine adjustment it was seen that the giant cells corresponded to parts of the vessel in which the wall and its contents had been cut transversely or obliquely, and that the non-granular communicating links consisted of longitudinal sections of the wall of the vessel alone.

I think it is probable that the formation of this appearance in the vessels is attended by great distension of the diseased wall. In a thick section I have several times been able by using the adjustment to follow a giant cell of considerable size into a comparatively small vessel without contents. My experience on this point is, however, not sufficiently large to warrant the expression of a definite opinion, and in these cases I may have been misled by a branch of the diseased vessel.

Friedländer has described the giant cell as a constant element in the minute nodule, the presence of this cell being relied on as evidence of the relationship of lupus and tubercle. The outlines of these nodules are distinct in the preparations I have studied (figs. 2 and 3). Instead of the expression giant cell, however, I substitute the term diseased blood-vessel. In many of these nodules the blood-vessel from which the limited cell infiltration has taken its origin still remains recognisable, but mostly it is found as a typical giant cell. The area of the nodule is often bounded by a distinct layer of fibrillated connective tissue (fig. 3, *b*,) and a comparison of areas in different stages of development leads me to infer that this connective tissue represents the adventitia of the vessel. The effusion from the vessel detaches the adventitia from the other coats and pushes it outwards, the gradually enlarging area in which the cells of the nodule are observed being thus formed.

Such a growth of the adventitia as is implied in the formation of a bounding wall of the area must be, of course, considerable. It has been observed and described by Thoma, who compares the layers of new growth in extreme cases to the membranes of the Pacinian corpuscle.

In eosin-stained preparations the nodules take on the dye more strongly than the cell-infiltration surrounding them, indicating the existence there of some substance which is not present in parts where the diseased process has not reached the same degree of specific change.

The process-like fibres which in many cases pass from the giant cell into the surrounding tissues (fig. 3), and which have been described as processes of the cell, answer to the tests of connective-tissue fibres. They have the appearance and position of fibres which in healthy blood-vessels connect the vessel with the connective tissue in which it lies, and are, I believe, specially related to the adventitia.

Having completed this analysis of the "giant cells" in lupus, I will, in conclusion, permit myself a few general remarks on the subject of the diagnosis of cells in so far as it refers to giant cells. In lymphoid and some other cells a

more or less granular appearance is detected by the microscope. Hence has arisen a natural tendency to associate any granular substance in which a nucleus or nuclei are embedded with the conception of a cell. If this substance is in a mass, and if many nuclei are embedded in it, the difficulty is surmounted by the conception of giant cells. The correctness of this mode of reasoning depends on the accuracy of the assumption which really underlies it, namely, that degenerating tissues do not become granular, and that nuclei may not be easily demonstrated in them after every trace of the cell-substance proper has disappeared. Both these assumptions are contradicted by facts.

The conclusion at which I have arrived has some analogy with that to which M. Cornil¹ has lately come after an examination of tubercular lymphatic glands. This pathologist states "that the giant cells of Schüppel and German authors always develop in the interior of the vessels after the circulation in them has been arrested, when the lymph-corpuscles or endothelial cells accumulated in the lumen of the vessel continue to live and to grow at the expense of the fibrin and red corpuscles which are in contact with them." The foci or areas found surrounding one of these "giant cells" in tubercle are simply, he believes, "the contents of a small obliterated vessel whose wall has been destroyed."

The points of difference between my views and those of M. Cornil are that I find no evidence of growth in the endothelium of the vessel, and no reason to believe that the lymph-corpuscles are nourished and multiply at the expense of the red corpuscles.

Lang² has described and figured diseased blood-vessels in lupus, identifying the morbid change as similar to that described by O. Weber under the term vitreous swelling. "The vascular elements, he observes, swell, becoming shining, stiff, and brittle. Such a vessel gives the impression of a hard tube, the intima appearing splintered, whilst the cellular elements are distended and glassy, and the connective tissue acquires an unyielding or uniformly opaque aspect."

This morbid appearance has been so fully described and

¹ Robin, 'Journal de l'Anatomie,' No. 3, 1878.

² Op. cit.

figured by the author I have just quoted that I shall not report in detail the examples of it which I have observed. I shall content myself with remarking that I have both isolated and observed in sections examples of blood-vessels in which the walls had undergone this transformation, and that I regard it as an early stage in the process that leads to the formation of the "giant cells" and the nodule which forms around the latter.

The term giant cell is, it may be fairly contended, an unfortunate one, inasmuch as it not only prejudges the nature of an appearance whose origin has not been sufficiently traced, but it has grouped together structures which are manifestly dissimilar. If the giant cell of lupus is compared with the *myéloplaque* of growing bone, which is also described as a giant cell, it is impossible not to be struck by the points of difference, even more than by the points of similarity. This diversity has been insisted on by Professor Charcot, who¹ has recently stated "that the giant cells of tubercle must be held as absolutely distinct from similar elements found in other neoplastic growths, as sarcomata, granulations, inflammatory exudations of serous membranes, &c." The first are, he tells us, multipolar, with branching processes and peripheral nuclei, whilst the second have none or few processes, and their nuclei are scattered in the body of the cell, and not at its periphery. This difference applies equally if we substitute the giant cell of lupus for that of tubercle, and its explanation will be found in the observations which I have laid before the Society. When the giant cell is produced by a diseased blood-vessel with disintegrated contents, the adventitia supply the multipolar processes, and the nuclei of the endothelium of the intima the peripheral nuclei. Into the nature of the other form of giant cells, of which the *myéloplaque* of Robin may be taken as the type, it is beyond the scope of this paper to enter. It is distinguished by the absence of the special features which would connect it with a blood-vessel.

¹ Quoted by Malassez et Ch. Monod, 'Archives de Physiologie,' 1878, No. 4, p. 398.

That in diseases which clinically differ so much as tuberculosis and lupus a characteristic morbid product, like the "giant cell," should form so conspicuous an element in both is undoubtedly a fact of great interest, but it leaves the question of the identity of the two morbid conditions untouched. Assuming the correctness of my interpretation, the cause of the disease of the blood-vessels in the two instances may be widely different, and there is in each of them amorphous morbid material in the affected areas, which may have much to do with the extension and virulence of the maladies, but regarding which the microscope affords us little or no information.

So far as positive evidence justifies an opinion, the case of lupus with which I have been dealing is a case primarily of disease of the walls of the blood-vessels. The cell-exudation, the molecular disintegration of the fibrillated connective tissue, and the mode of extension of the disease, are all explicable by the degeneration of the vascular coats. This opinion is not incompatible with any of the facts contributed by previous observers; on the contrary, it is supported by them.

EXPLANATION OF PLATES VII AND VIII.

(Pathology of Lupus. Dr. George Thin.)

FIG. 1.—Vertical section through the hypertrophic edge into the apparently healthy tissue. *a*, Epidermis; *b*, large mass of cell-infiltration produced by the coalescence of nodules; *c*, hairs; *d*, a sebaceous gland (seen by a higher magnifying power to be degenerated and filled with exudation cells); *e*, a sweat coil (seen by a higher power to be infiltrated by cell-exudation; the upper part of the coil is disintegrated, the lower part is little changed); *f*, cell-infiltration occupying the position of the external root-sheath of a hair. At this part the epidermic cells are almost entirely destroyed; the upper part of the root-sheath (indicated in the drawing) is unchanged. *g*, Cell-infiltration limited to the perivascular space in the vessels of the corium; *h*, fat; *i*, an artery. $\times 8$.

FIG. 2.—*a*, One of the nodules or areas from which the lupus growth extends (several nodules are still recognisable in the mass; the black marks within them are "giant cells" or degenerated blood-vessels; all the dark objects in the figure, except the two hairs marked *b*, are giant cells); *b*, hairs; *c*, connective tissue of the corium; *d*, fat; *e*, cell-infiltration. $\times 14$.

FIG. 3.—Giant cell with its nodule (marked *a* in Fig. 2). *a*, The "giant cell;" *b*, fibrillated connective tissue bounding the nodule; *c*, one of several small blood-vessels which can still be traced in the nodule. $\times 260$.

FIG. 4.—About one half of the small lupus patch excised from the penis. *a*, Epidermis; *b*, connective tissue of the corium; *c*, lupus cell-infiltration; *d*, a giant cell (*a* in Fig. 5), forming one of several which make up the group shown in Fig. 5 (all the darkly marked objects in the cell-infiltration, except *e*, are either typical giant cells or parts of the coats of diseased blood-vessels in which the granular appearance is not present); *e*, section of a small hair; *f*, two large giant cells of typical appearance when seen under a high power (from their position probably parts of an artery and vein.) $\times 30$.

FIG. 5.—The group shown in Fig. 4 more highly magnified. *a a'*, At one focus typical giant cells; on changing the focus the appearance is found to be continuous with the vessels shown in the figure); *b*, "giant" cell, evidently part of the vessel next it, marked *d'*; *c*, longitudinal sections of the degenerated walls of blood-vessels. $\times 260$.

FIG. 6.—Section of a vessel showing the first stage of formation of a giant cell. *a*, Homogeneous coagulum; *b*, still unaltered red corpuscles; *c*, nuclei of the endothelium of the lining membrane of the vessel; *d*, normal connective tissue next the vessel; *e*, cell-infiltration appearing between the wall of the vessel and the adjacent bundles of connective tissue. $\times 260$.

FIG. 7.—Section of a vessel showing a more advanced stage towards the formation of a "giant cell." *a*, Homogeneous coagulum; *b*, nuclei of the intima; *c*, granular matter beginning to form in the coagulum; *d*, healthy connective tissue. $\times 260$.

FIG. 8.—Giant-cell formation developing whilst some unchanged red corpuscles are still found in the coagulum. *a*, Homogeneous part of the coagulum; *b*, granular part; *c*, unchanged red blood-corpuscles; *d*, normal connective tissue; *e*, small blood-vessels, with formation of lupus cell-infiltration around them. $\times 260$.

FIG. 9.—"Giant cell," in which the walls of the vessel, *a* and *b*, are still distinguishable. $\times 260$.

FIG. 10.—Cast of vessel isolated from lupus tissue, and showing all the characteristics of the supposed giant cells. $\times 45$.

FIG. 11.—Part of the cast represented in Fig. 10, more highly magnified to show the granular formation and the colourless blood-cells throughout it; *a* and *b*, adherent elements of the blood-vessel. $\times 260$.

FIG. 12.—Giant cell. *a*, colourless blood-corpuscles in connective tissue; *b*, nuclei of the endothelium; *c*, mass of colourless blood-corpuscles accumulated in the centre; *d*, granular product of disintegration of red blood-corpuscles, so-called "protoplasma."

(All the figures have been drawn to scale by camera lucida.)