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THE FATE OF THE GIANT CELLS IN HEALING TUBERCULOUS TISSUE, AS OBSERVED IN A CASE OF HEALING TUBERCULOUS MENINGITIS

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THE FATE OF THE GIANT CELLS IN HEALING TUBERCULOUS TISSUE, AS OBSERVED IN A CASE OF HEALING TUBERCULOUS MENINGITIS.

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Plate III.

The investigations into the nature and the importance of the giant cells of tuberculous tissue have not led to uniform results. The views differ more particularly with respect to the genesis and to the vitality of these peculiar elements.

While Rokitansky,* Virchow and others had observed, and in part described, the giant cell, it remained for Langhans, in 1868, to first give a full and satisfactory account of these cells, and to advance the two most prominent hypotheses in regard to their origin; namely, that they are the product of one cell, or formed by the fusion of many cells. The investigations of Langhans were soon followed by a very large number of studies concerning the giant cells of tuberculous and of other inflammatory, as well as of resorptive, processes. The literature upon the mode of formation and the nature of giant cells is very extensive, and it would not materially advance the object of this article to review it completely. I would, however, refer to the studies of Schüppel, Köster, Heidenhain, Weiss, Ziegler, Brodowsky, Marchand, Ranvier, Baumgarten, Cornil, Malassez, Martin, Arnold, Kiener, Weigert, Metchnikoff and his students, Taber, Kostenich and Wolkow, Krückmann, Welcker, and of many others, as indicating the amount of work bestowed upon the problems connected with multinucleated giant cells. The majority of these investigators review the pre-existing literature more or less thoroughly. Thus Marchand, in 1883, in his article on the giant cells that occur in connection with the absorption of foreign bodies, refers to no less than forty-five previous publications bearing on the subject of giant cells in general.

Koch's discovery of the tubercle bacillus, and the further demonstra-

* The references to the literature are arranged alphabetically at the end of the article.

tion of the important relations of this bacillus to the giant cell, gave rise to continued vigorous investigation and speculation concerning the Langhans cell. While the views of the authors in regard to the genesis of the giant cell of tuberculosis are so divergent and the possibility of different modes of development so marked as to indicate that, in all likelihood, the giant cells may indeed be the outcome of more than one process, the opinions concerning the vitality and the importance of this element have differed in a more precise and distinct manner, so that the investigators may be separated into two quite well defined schools, namely, those who, headed by Baumgarten and Weigert, regard the cell as an element on the way to destruction, as necrobiotic from its very inception; and, on the other hand, those who, led by Metchnikoff, are convinced that the giant cells of tuberculosis are living, active and defensive (mesodermal) cells.

Baumgarten, in his classical study of the histology of tubercle, concludes that the giant cell is the product of multipolar nuclear division in a single mesodermal or epithelial cell, the body of which fails to divide on account of degeneration in its interior, due to the necrobiotic action of the bacilli that it usually harbors. Weigert agrees with Baumgarten and has vigorously opposed the contradictory claims of Metchnikoff and his followers.

In his original communication concerning the bacillus of tuberculosis, Koch is inclined to regard the giant cells as somewhat permanent elements possessing more vitality than the bacilli they usually contain, and holds that the bacilli are able to persist in the giant cell simply because one generation succeeds another. He also points out that degenerate bacillary forms are not infrequently met with in the interior of giant cells. Later Koch seems to favor more directly Weigert's opinion. Metchnikoff has persistently championed the view that the giant cells are defensive, mesodermal phagocytes, produced in various ways, at times by direct nuclear division, at times by indirect segmentation of the nucleus, and still at other times by the fusion of epithelioid mesodermal cells without special nuclear changes. In one of his first articles on this subject he details the histological changes produced by the bacillus of avian tuberculosis when injected into the small rodent, Spermophilus guttatus, to which our gopher is related. He shows how the bacilli are taken up by the numerous giant cells that come into existence, and in the interior of which they undergo marked changes, both as to staining and to form, which must be regarded as clearly retrogressive in character. He furthermore demonstrates that giant cells may multiply by simple fission without mitosis, and also describes appearances that indicate that two or more giant cells may coalesce into a larger cell complexus.

Ssudakewitsch brought further proof of the activity of giant cells by showing that the giant cells found in the skin in an Eastern disease, pascha-churda, and in lupus, are capable of digesting elastic fibres.

Arnold, to whom we owe extended studies upon the manner of formation of, and the nuclear changes in, giant cells, was at one time inclined to divide giant cells into progressive and retrogressive forms, and to designate those of tumors as belonging to the former, and those of tuberculous tissue to the latter class; but after he had been able to demonstrate that even the tuberculous giant cells have the power of further development he no longer regarded any such distinction as justifiable. The fact that giant cells are destroyed in tuberculous tissue does not in any way invalidate this statement, because this fate they suffer in common with all the cells of this tissue—the point being that the giant cells do not have in them the seed of retrogressive metamorphosis from their very origin.

Welcker, not long ago, repeated the original experiments of Metchnikoff with avian tuberculosis upon Spermophilus guttatus. He did not find any evidences of multiple karyokinesis in the epithelioid cells and questions this mode of formation for giant cells. He regards direct nuclear division as the most frequent mode of formation, but does not exclude fusion. He could not demonstrate the amœboid movement of the giant cells which was claimed for them by Metchnikoff. He found in the interior of the giant cells peculiar sausage-shaped masses that he demonstrated to contain iron, and which he regards as bacilli changed by cellular activity.

The concentric, lamellated, calcareous concretions, described by Schüppel in tuberculous lymph nodes, and also briefly referred to by Ziegler in the seventh edition of his work on Pathological Anatomy (page 97), are regarded by Metchnikoff as due to the calcification of tubercle bacilli in the interior of cells. According to Metchnikoff the process of calcification can be well traced in the Algerian rat, an animal relatively insusceptible to tuberculosis, in which the tuberculous tissue, even many months after the experimental inoculation, consists of living epithelioid and giant cells, the latter enclosing dead bacilli in the form of the characteristic earthy bodies. He regards it as very probable that the phosphate of lime is laid down by the giant cell itself in the reaction against the bacillus. The final fate of the giant cells in this form of tuberculosis is not discussed by him.

The researches of recent years, carried out by Metchnikoff and his students at the Pasteur Institute in Paris, all warrant, according to their authors, conceptions quite similar to those first advanced by Metchnikoff

concerning the giant cells, and the general conclusion of this school is that it is of essential importance in the fight against tubercle bacilli that large protoplasmic masses with many nuclei are formed, so that the activity of the intracellular processes may be heightened because the bodies to be digested are very resistant. This would not appear to be at all a strange process when we remember that plasmodia are observed so generally in connection with cellular digestion in the lower as well as in the higher animals.

The modes of formation of giant cells, the many possible sources of their origin, their appearances, their relation to the bacillus of tuberculosis and to other parasites, as well as to foreign bodies, the degenerative changes that may occur in their interior, and many other interesting and important features have all been carefully and repeatedly studied. But the further definitive changes that may occur in these elements when the tubercle bacilli or other micro-organisms die or are absorbed before the cells have undergone necrosis, or after the foreign substances have been completely removed, have, strange to say, received but scant attention. Tuberculosis not infrequently heals, syphilis heals, actinomycosis heals, and foreign bodies are often completely absorbed. Are the giant cells, so generally present in these conditions and which sometimes persist even after the active cause that brought them into existence has been removed, capable of any progressive changes? Do they continue to exist as giant cells, or does complete healing or absorption mean their removal by way of disintegration? Manifestly a decisive solution of this rather neglected problem, in connection with the giant cells of tuberculous tissue, for instance, would materially aid us in arriving at some definite conclusion concerning their nature, whether they are to be regarded as purely necrobiotic elements, or as structures possessing an independent vitality that may outlast that of the tubercle bacillus, and in the destruction of which they perhaps play an active rôle.

The exact histological details of healing non-degenerated tuberculous tissue have been lost sight of on account of the general impression that the healing is accomplished, in the main, through necrosis and necrobiosis of the tuberculous tissue, together with calcification,

followed by more or less regeneration of the specific tissue elements, the principal part of the resulting defect being bridged over by cicatricial tissue.

That tubercle does not always undergo caseation was noted by Cruveilhier (quoted by Straus), who states that tubercles of the lungs, in particular, are curable at all periods of their development by means of a sort of fibroid encystment (tubercules de guérison). Again, Grancher states that all tuberculous granulations that develop slowly become fibrous and heal, that is, they are transformed into a sclerotic and inoffensive anatomical product in the form of a "fibro-caseous neoplasia."

D. J. Hamilton, in his Text-Book of Pathology, says that sometimes the tubercle does not caseate, but continues to live on and to develop into what seems to be its ultimate stage of organization. In or quite near to the centre is usually a giant cell, around which there may be found smaller giant cells. From the periphery of the giant cell processes come off that by subdivision produce a reticulum which is more condensed at the margins of the tubercle. In the meshes lie lymphoid corpuscles and one or more giant cells. This is the reticular tubercle first described by Wagner. As this tubercle becomes older the reticular giant-cell system is replaced by a simple mass of fibrous tissue; the giant cell becomes more and more fibrous at its periphery, and the protoplasm of the cell becomes transformed into or secretes the fibrous margin, which is covered with nuclei that appear to be derived from the giant cell. During this process of fibrous transformation the bacilli have vanished.

The investigators that have studied the action of dead tubercle bacilli upon the tissues make no statements as to the ultimate fate that befalls the giant cells that may form in the cell accumulations around the dead bacilli (Straus).

The precise manner of healing of tuberculous peritonitis after laparotomy has been made the subject of a considerable number of investigations, the results of which differ somewhat, the variations depending, it would seem, upon the stage of the process at which the operation was performed. Osler reports the results of the microscopic examination in the case of a woman who died of acute pneumonia 4½ months after a laparotomy which had been followed by marked improvement of the abdominal condition; the peritoneal tubercles were changed to fibrous masses containing giant cells with fatty granules, abundant bacilli, but no caseous material. Pichini, Bumm, Riva and D'Urso found that in healing tuberculous peritonitis after laparotomy (in man) the tubercles are replaced by fibrous tissue, and, according to Bumm and D'Urso, the

giant cells are destroyed by wandering cells. Among those who have studied the question experimentally may be mentioned Kichensky and Stchégoleff, both of whom regard the improvement and healing that may follow laparotomy in experimental tuberculous peritonitis in guinea-pigs, dogs and rabbits as due essentially to phagocytosis, to infiltration with round cells, to the formation of fibrous tissue while the "specific elements of the tubercle" disintegrate and undergo absorption. Mazzoni, Nannotti and Baciocchi, and especially Gatti, emphasize dropsical degeneration of the epithelioid cells as an essential step in the healing. Gatti, who studied this problem in guinea-pigs and rabbits, but principally in dogs because of their greater resistance and of the more marked chronicity of the tuberculosis, comes to the conclusion that the perfect healing, macroscopic, histological, and biological, that unquestionably does follow simple opening of the peritoneal cavity, when the tubercles of the peritoneum have reached a certain stage—the fibroid but not the caseous—does not depend upon inflammatory reaction nor upon proliferation of the connective tissue, but upon a dropsical degeneration of the epithelioid cells, which melt together to form small spaces, while the nuclei are dissolved, and finally the remnants of these cells disappear completely, together with the lymphoid cells, leaving simply the preexisting stroma; fibroblasts and karyokinetic figures do not occur. Gatti reasons that the poison that kills the epithelioid cells does not attract leucocytes; that the bloody serum, which forms after the laparotomy, kills the bacilli or so weakens them that the resulting proteins cause slow degeneration of the cells; and that, therefore, the prime factor in the operative healing of the peritoneal tuberculosis is the exudation of serous fluid into the abdominal cavity. When the tubercles have become caseous laparotomy may arrest further caseation, but has no direct influence upon the removal of caseous masses.

It will have been observed that practically all of the authors quoted fail to record any observations as to the exact changes in the giant cells in healing tuberculous peritonitis—Gatti rarely mentions the giant cells in his articles—and, furthermore, that none of the investigators attribute any active part in the healing process to the cells of the tuberculous tissue itself, all speaking solely of degeneration, disintegration and absorption of the cells of the tubercles.

In his work, "Die causale Behandlung der Tuberculose," Klebs devotes a chapter to the consideration of the histology of the healing tubercle, as observed in guinea-pigs suffering from experimental tuberculosis and treated more or less successfully with the products of the tubercle bacillus. He advances the view that the proliferation caused by the

tubercle bacillus protects the bacillus against the bactericidal action of the fluids of the tissues, hence the latency of many local tuberculous infections. When the tuberculous tissue loses its protective properties on account of degenerative changes, the bacilli may die or they may multiply, depending upon various local and general conditions. Under the influence of the tuberculin and its purified modification, tuberculocidin, there is produced an exudation which deprives the cells of the tuberculous infiltration of their protective powers and the bacilli are killed by the serum. Now, the cells of tuberculous proliferations do not possess unlimited powers of proliferation, and hence tuberculous tissue is susceptible of healing. After the death of the bacilli, the tuberculous tissue may disappear partly by necrosis, regeneration and cicatrization, partly by transformation into mature tissue. While the capabilities of many of the cells are exhausted, so that they are merely useless elements that are best removed, tuberculous tissue may yet contain various cells of connective tissue as well as epithelial origin that possess an independent vitality and outlive the tubercle bacilli. Such cells may, in the course of further events, become component parts of apparently quite normal structures. Thus the giant cells in the alveoli of healing pulmonary tuberculous areas may subdivide into small uninuclear cells; the nuclei become richer in chromatin, karyokinetic figures form, and the cells apply themselves to the alveolar walls and become part and parcel of its lining. The cells that do not form, or are not needed to assist in the formation of the alveolar lining, are thrown out. In the healing of tubercles in the periportal tissue of the liver, the giant cells which, according to Klebs, are formed from the lining of the bile ducts, separate again into individual cells. In healing splenic tubercles of guinea-pigs the giant cells, which are all intravascular, become reduced in size by contraction of the protoplasm and remain for a long time after the disappearance of the bacilli, but Klebs thinks that they are finally divided up into endothelial cells. The giant cells in tubercles in the lymph nodes are formed by the endothelial cells of the lymph vessels, and may, after the destruction of the tubercle bacilli, separate and revert to endothelial cells again; such giant cells, therefore, are closely related to the intravascular giant cells.

Klebs regards the non-epithelial giant cells in connective tissue as coming from the angioblasts. He observed in a case of recurrent tuberculous pericarditis that the miliary tubercles were surrounded by wide vessels which passed into the tuberculous tissue, where they disappeared, their place, however, being taken by very large giant cells which were surrounded by round cells. The protoplasm and the processes of the

giant cells stained more deeply with the ponceau dye than the surrounding cells. The nuclei were arranged with their long axes vertical to the surface and usually around a clear centre. While not able to trace a distinct and immediate connection between the giant cells and the vessels, Klebs seems to believe that as the vessels are compressed by granulation tissue they may fall into fragments or pieces that remain filled with various substances, that the endothelial cells multiply and the angioblasts form giant cells which may subsequently divide into endothelial cells, although the only evidence he has seen of this latter change was not found in human tuberculosis, but in the tuberculous spleen of guinea-pigs.

While studying the vascular changes in the leptomeninx in a case of clinically anomalous tuberculous leptomeningitis of an unusually long duration, my attention was directed to the relatively excessive number of giant cells present and to certain peculiar changes presented by them, that seemed to point quite clearly to the occurrence of other than merely retrogressive processes in the specific proliferations. I consequently utilized the opportunity to study more particularly the giant cells of this form of healing meningitis. The results of this part of my work are embodied in this article; further observations made in connection with suitable experiments are reserved for publication later.

Tuberculous leptomeningitis may, like tuberculous inflammations of other serous membranes, heal spontaneously. Dujardin-Beaumetz, Bauer, Sejournet, Weir, Nilsson, Martel, Klein, Freyhan, as well as many others, describe cases diagnosed clinically as tuberculous meningitis which ended in recovery. Ord describes a case diagnosed as cerebral tuberculous meningitis in which recovery followed after drainage through a trephine opening into the subdural space.

While the diagnosis in such cases as the above may be open to criticism, Fütterer examined post mortem a patient who had suffered two years before death from a disease diagnosed by Leube as spinal tuberculous meningitis, and found the spinal leptomeninx to contain shrunken, calcareous, miliary tubercles, *i. e.* he furnished the anatomical proof of a healed degenerating tuberculous leptomeningitis.

Atypical, subacute, and chronic, sometimes latent, forms of tuber-

culous meningitis also occur. Whereas, according to Strümpel, the average duration is between three days to one and one-half weeks, Seitz mentions two cases of forty-two and fifty-four days, Ludwig Meyer one of forty-nine days, Neudörffer one of fifty-six days, and Busse one which lasted at least sixty days. These cases occurred in adults.

In the case described by Busse, which occurred in a woman thirty-seven years old, the pia was adherent to the cortex and contained numerous flattened and hard elevations of irregular size and outline. In the Sylvian fissures were small, grey, translucent nodules. Caseation was absent. The areas of thickening consisted of interlacing bundles of fibrous tissue, containing here and there masses of cells and also occasional giant cells. Tubercle bacilli were found in small numbers inside as well as outside the giant cells. Evidently there was here a chronic tuberculous inflammation in process of arrest and healing.

The present case was that of a man, white, aged 25, admitted into the service of Dr. Norden, at the Cook County Hospital, December 13, 1895, with a history of having been sick for 35 days before admission with headache, some nausea and pain in the stomach. He had been working in a rolling mill before he became sick. He had never had any serious illness before and denied all venereal infection. Precise information could not be obtained because he was stupid and dazed.

Physical examination showed a medium-sized, rather slender and poorly nourished man; the organs of the chest and abdomen were quite normal. The tongue was dry and coated. There were some spots on the arms that were thought to be rather suspicious of syphilis. The cervical glands were enlarged. The temperature, pulse and respiration were normal at the time of admission. He was placed upon iodide of potassium, one gramme four times daily.

During the days succeeding his admission he complained at times of very severe headache, more so at night, and would clutch his head with his hands and moan. There were no focal cerebral symptoms. After a week or so the potassium iodide was increased to two grammes four times daily, and further notes of headache were not made. The record shows that while his pulse and respiration remained normal the temperature would occasionally mount up to 101° F. There was marked costiveness and much nausea, the appetite being poor. After December

30th his temperature but rarely rose above 98.5°. Examination of the urine was negative except for hyaline casts. Examination of the eyes with the ophthalmoscope on February 15, 1896, by Dr. Wescott, showed the disk to be poorly defined on the right side, less so on the left. No tubercles were found in the iris.

The emaciation increased somewhat; the symptoms and signs of pneumonia appeared shortly before his death on March 6, about four months after the beginning of his sickness.

The clinical diagnosis was cerebral gumma and chronic nephritis.

Post-mortem examination.—Ten hours after death.

Anatomical diagnosis.—Chronic tuberculous leptomeningitis; chronic tuberculosis of the peribronchial lymphatic glands; acute bronchitis; lobar pneumonia; adhesive pleuritis; adhesive perihepatitis, perisplenitis and periappendicitis; chronic gastritis; parenchymatous nephritis; venous angioma of the liver; decubitus.

The body is poorly nourished and of rather slender build. The rigor mortis is marked. There is a small bed-sore over the sacrum.

The peritoneal cavity is empty; there are adhesions between the liver and the diaphragm and between the gall bladder, the duodenum, and the colon, also around the spleen and around the vermiform appendix.

The pleural cavities are empty; adhesions are present posteriorly over both lungs. The pharynx, larynx and trachea are normal. The parenchyma of the lungs is spongy and pale grey in color, except the lower right lobe, which is solid, and rather homogeneous; from its cut surface, which is of a red color, small whitish casts are scraped away. The bronchi contain muco-pus. The peribronchial lymphatic glands are enlarged, containing caseous areas, calcareous masses and small yellowish nodules.

The pericardium is empty and the surface of its layers is smooth. The heart weighs 240 grammes, the endocardium is smooth, the muscle uniformly firm and greyish brown in color. The aorta is smooth.

The spleen weighs 200 grammes and on section is seen to contain much fibrous tissue.

The kidneys weigh 230 grammes together; the capsules are free, the cortical markings distinct, the medullary rays being especially plain, the consistence firm. The ureters, seminal vesicles, and prostate are normal.

The liver weighs 1400 grammes; of firm consistence; near the anterior surface of the left lobe is a venous angioma about 2 cm. in its longest diameter. The gall bladder is normal.

The œsophagus is normal. The mucous membrane of the stomach is thickened and red. The large and small intestines are normal. The pancreas is normal.

The scalp, the skull and the dura are normal. At the base of the brain there is much turbid serous fluid and a thick layer of rather firm, translucent, gelatinoid material matting the structures together quite firmly. Along the arteries in both Sylvian fissures are numerous whitish and greyish yellow nodules, of pin-head size and larger, imbedded in the translucent material with which they seem to be infiltrated. The ventricles are dilated, containing much turbid fluid, the lining being rather soft. The brain substance is normal.

Both ears are normal; the sphenoidal sinuses are normal. The spinal cord was not examined.

Bacteriological examination.—The lungs were found to contain, in the pneumonic lobe, the Micrococcus lanceolatus, which was present in cover-glasses prepared from the exudate and was also isolated in the pure cultures.

The liver contained a coccus corresponding to the staphylococcus pyogenes albus, but cultures made from the spleen and the kidneys remained sterile.

Cover-glasses prepared from the meningeal exudate did not contain any micro-organisms when stained with ordinary dyes, and special stains for tubercle bacilli failed to reveal any bacilli (4 cover-glasses). A glycerine-agar tube inoculated with a liberal quantity of meningeal exudate remained sterile after having been in the thermostat for four days; at the end of this time it was sealed and returned to the thermostat, and on May 26, 1896, it was found that a pure growth of tubercle bacilli (mammalian) had developed in typical form.

Histological examination.—There is marked degeneration and desquamation of the epithelial cells lining the convoluted tubules of the renal cortex.

The changes in the leptomeninx and its vessels presented many features of interest and they were, therefore, extensively studied in serial sections prepared in the following manner: The tissue had been fixed and hardened in nearly absolute alcohol; small pieces from various parts of the basal leptomeninx, usually cut so as to have one or two vessels running through the centre of the longer diameter, were cleared in cedar oil and imbedded in paraffin; extensive ribbons of sections at right angles to the vessels were made and fastened on the slide with albumin fixative; the different series of sections would vary in thickness; some were 4μ, others 6μ, others 10μ, depending upon the exact minimal thickness at which perfect series could be obtained. The majority of the slides were stained with Delafield's hæmatoxylin; differentiated with 1 per cent. aqueous HCl solution, washed carefully and for a long time in water,

dehydrated in absolute alcohol, cleared and counterstained with oil of cloves containing in solution enough eosin to give it a rich red color, the excess of the oil being removed by xylol. Van Gieson's hæmatoxylin and picric-acid-fuchsin method was also used, and a number of slides set aside for the staining for tubercle bacilli were either colored with hæmatoxylin, stained with carbolfuchsin and dehydrated with xylol-aniline oil after a short bath in the iodine-iodide-of-potassium solution, or stained directly with carbolfuchsin, decolorized with 20 per cent. sulphuric acid and counterstained with methylene blue.

The inability to obtain the ponceau dye, used and recommended by Prof. Klebs for the purpose of counterstaining sections of healing tuberculous tissue, prevented its employment.

The changes were now studied in the various series of sections which were found to include in a perfect manner very many larger and smaller miliary tubercles; the appearances of the giant cells could be easily followed through the whole thickness and extent of the cell.

The vascular changes.—The intima of the larger arteries at the base of the brain may show a more or less well-marked thickening, due to the presence of a sparsely nucleated fibrous tissue situated between the lumen of the vessel and the tunica elastica. This thickening is best marked where the adventitial and extravascular changes to be described are most intense. In many instances this intimal thickening contains districts of hyaline degeneration which assume a faint bluish-violet tinge when stained with hæmatoxylin and eosin. The thickening in the larger arteries is usually semicircular in its extent and tapers from the thicker central part towards the ends of the semicircle, the elastic layer below it being intact and the endothelial lining quite distinct.

The smaller arteries further out in the Sylvian fissures also exhibit, more especially at points corresponding to the larger adventitial foci, quite extensive chronic fibrous thickening of the intima that at times greatly narrows the lumen of the vessel. In some of the series of the sections the deeper parts of the subendothelial fibrous tissue are the seat of advanced typical hyaline degeneration, but distinct caseation is not present. In other places the parts near the muscular coat are quite rich in cells, the amount of fibrillation being much less than in the strata nearer the endothelial lining, so that here the tissue is composed of round or oval cells with quite deeply stained nuclei, lying in a very loosely meshed stroma. In one instance an indistinct giant-cell-like body that is recognized through three sections, each 5μ thick, is found lying among the fibroblasts (Fig. 5, Plate III); this cell is small and seems to consist of a mass of very closely aggregated nuclei with a minimum amount of

cell body. In some places, again, the deeper parts of the proliferation contain spaces without any recognizable endothelial lining, but nevertheless filled with blood.

The endothelial lining over the thickenings is quite distinct and usually composed of small, closely set, rather typical cells. The cells in the layers immediately under the endothelium are not distinguishable, so far as shape and size are concerned, from the cells of the endothelial lining proper.

The elastic layer is everywhere intact, but the connections between it and the intimal thickening are apparently so loose and free that the thickened intima has often become more or less detached.

The extravascular changes.—The translucent material mentioned in the macroscopic description as surrounding the basilar vessels and other structures is composed, generally speaking, of a loosely arranged, richly cellular, very young fibrous connective tissue, throughout which are scattered a remarkably large number of variously shaped giant cells, often enclosed in small nodules of an indistinct concentric arrangement that might be considered as changed miliary tubercles. Caseation is almost absent; only in one or two places are small districts of caseation found in the adventitial foci of smaller arteries, and the caseous material seems to be enclosed in a capsule of more dense though quite cellular connective tissue. The adventitia of the smaller arteries in the Sylvian fissure and elsewhere present very small nodal enlargements made up of similar young fibrous tissue which also contains very many giant cells.

Many of the cranial nerves are the seat of interstitial changes similar to those above outlined.

The tissue referred to as young fibrous connective tissue may present a plainly fibrillated, sometimes lamellated, more often perhaps a very loosely arranged indistinctly fibrillated, granular or homogeneous matrix. Plain fibrillation, with occasional lamellation, is found at the periphery of the adventitial foci of the arteries, and this tissue is not so richly cellular; in such areas the endovascular thickening may be very pronounced. Mostly, however, this tissue consists of a matrix that stains more or less deeply reddish with eosin, being often composed of loosely and irregularly arranged bands of a fibrillar or granular structure of varying width and density; or the matrix may be quite homogeneous.

In this matrix lie various kinds of cells; usually the cells are scattered, but occasionally the cell infiltration is so marked that the intercellular substance can hardly be made out. In addition to the giant cells already mentioned, two other kinds of cells are distinguished: (1) Cells with rather large, lightly staining, occasionally almost vesicular

nuclei, that are oval, oblong, spindle-shaped, or of long drawn-out and irregular forms. The cytoplasm of these cells often blends with the intercellular substance so that the exact limits or shape of the cell body cannot always be made out; usually the cell body corresponds somewhat in shape with that of the nucleus; it is finely granular, almost homogeneous and stains faintly with eosin. (2) Cells, small in size, with relatively large, round or oval, very deeply staining nuclei surrounded by a small rim of reddish cytoplasm; these cells, which are the most numerous, would correspond, in many instances, in shape, size, and appearance, to the lymphocytes of the blood. There are foci and areas of cell infiltration composed almost entirely of these cells.

In addition there are not a few cells which contain two nuclei, and indistinct or poorly preserved karyokinetic figures are found once in a while. Such cells cannot be recognized as belonging to either the one or the other of the two kinds of cells described above. There are also cells that might be regarded as transition forms between these two classes. Polymorphonuclear leucocytes are not present except as occasional single cells.

The tissue here described in general contains many small blood-vessels, the greater number of which are evidently of new formation. Embryonal capillary loops can be found in very many places, and the location and the number of the vascular channels with thicker walls indicate that they also are newly formed structures. The endothelial cells are often very large and oval and are provided with swollen nuclei. It may be stated at this point that while many of these vessels occur in close proximity to the giant cells to be described, yet the most thorough examination of the series of sections has failed to disclose a single instance in which one could say, with reasonable certainty of being correct, that the giant cells played a direct part in the formation of the vessels. Direct connection between the lumen of the vessel and the giant cell or its remnants could not be demonstrated.

In some places the vessel wall is diffusely thickened and very small vessels may appear almost completely obliterated.

Tubercle bacilli were conscientiously searched for in a large number of suitably prepared specimens. In the sections stained with hæmatoxylin and carbolfuchsin some of the well preserved giant cells contain minute sausage-shaped and irregular forms that are colored black and resemble somewhat the bodies described by Metchnikoff, Welcker and others as changed and degenerate bacilli; but it would be difficult in these specimens to differentiate between such masses and nuclear fragments. In some of the sections stained with carbolfuchsin and methylene blue be-

tween the cells are found small aggregations of bright red granular masses containing bodies not unlike cocci, and also larger irregular forms that may be altered tubercle bacilli or remnants thereof, as well as a very few quite typical bacilli; isolated bacilli were also found between the cells, but only in very occasional instances.

The giant cells (Figs. 1–4, Plate III).—Imbedded indiscriminately in the granulation tissue are, as stated, a remarkably large number of variously appearing multinucleated giant cells, which, speaking generally, seem well preserved and free from evidences of extensive degeneration. The giant cells may in some instances seem small and appear immediately surrounded by ordinary young connective tissue; or they may lie in small cavities, as it were, a distinct though irregular space separating the cell from the surrounding tissue; more frequently, perhaps, they are immediately encircled by very loosely arranged cells with a tendency to a concentric arrangement, the whole resembling to a certain extent, on first view, a miliary tubercle; there are also small foci occupied by loosely scattered cells with an imperfect, concentric peripheral disposition, producing sometimes an indistinct central lumen or space, which may be quite empty, or in which, as well as in its walls, may lie giant-cell remnants, nuclear fragments, and endothelioid nuclei imbedded in protoplasmic masses similar to those of the fragmented giant cells with which they may or may not be connected.

The protoplasm of the giant cells is often almost homogeneous, or it may be uniformly finely or, in parts, more coarsely granular; the more coarsely granular parts are, as a rule, found near the centre of the cells and may contain, when more extensive, irregular chromatic fragments, while the surrounding nuclei may stain quite well. Generally the body of the giant cells sends out irregular and branching prolongations that pass among the surrounding cells and seem to fuse inseparably with the homogeneous or granular intercellular substance; at times, however, the outlines of the cell are very sharp, distinct and regular. Under all circumstances, but more particularly in the latter instances, the main protoplasm of the giant cells stains a little more deeply with eosin than the intercellular substance, and on this account it is possible to trace the origin of the many larger and smaller multinucleated and uninucleated fragments into which the giant cells are often separated. In many instances the giant cells are vacuolated; those vacuoles are produced in part by nuclei that stain very faintly; especially is this the case when the borders of the nucleus only take the stain, the vacuoles being then quite distinct in spite of their small size. In part the vacuoles seem to result from the disappearance of the protoplasm of the giant cell im-

mediately about round nuclei, which are often deeply stained; the vacuoles sometimes contain nuclear detritus and occasionally they are very large (Fig. 4 B, Plate III).

The size and the outline of the giant cells naturally vary much. In the various series of sections the majority of the cells can be traced through a very considerable number of specimens, and in this way it can be estimated that in some diameters many cells may equal as much as 60, 80, 100 and even 200μ or more; it may also happen that the other diameters are not very much less, and consequently in some sections the giant cells are almost recognizable with the naked eye. On account of the branching prolongations usually present, the outline, as a rule, is very irregular. At the periphery of many cells, and especially at the poles, there are often found scattered cells and cell masses that have nuclei and protoplasm similar to those of the main giant cell, and that consequently are either in the act of fusion with or separation from the giant cell.

The number and the arrangement of the nuclei also vary greatly; cells are observed with probably hundreds of nuclei. In a large majority of the comparatively unchanged cells studied, the nuclei are arranged in the manner characteristic of the typical Langhans giant cells, and form a more or less complete circle near the periphery of the main part of the body of the cell. They often seem to have the long axis vertical to the surface of the cell. The nuclei are usually quite small, oval or spindle-shaped; they are often rather poor in chromatin substance and stain somewhat faintly; not infrequently they are vesicular, and when only the borders of the nucleus stain, and that rather faintly, the nucleus may appear like a distinct vacuole; at other times the giant cells contain oval or round nuclei that are rich in chromatin and stain deeply. The nuclei also frequently present very atypical forms; they may be dumb-bell-shaped, flask-shaped, or very long and drawn out; budding processes connected with the main nucleus by a slender thread or stem are also present, and irregular, bizarre shapes are not infreqeunt. Occasionally fairly well preserved karyokinetic figures are also found in a single nucleus of a giant cell. In some cells there are also found, as already stated, nuclear fragments and detritus.

While the above description would answer in a general way, yet closer examination with the high powers of the microscope reveals also many other interesting appearances in the nuclei and the protoplasm of the giant cells that, although presenting difficulties in the way of concise and systematic description, as well as satisfactory interpretation, nevertheless merit some attempt thereat.

Division of the giant cells with nuclear disintegration.—It has been

mentioned that a considerable number of the giant cells seem to be in the course of division into or, possibly though not probably, fusion with smaller multinucleated masses and uninuclear cells. At times this process is associated with the formation of more or less detritus of nuclear origin and a splitting up of the cytoplasm into more minute fragments, together with the appearance of cells or phagocytes that are loaded with the remnants. Such manifestations are most noticeable in the vicinity of foci of caseation, but they are also found elsewhere. It is also observable that the bodies of the cells and cell fragments under these conditions are usually more coarsely granular. In many cases the giant cells seem to have split up into two or more separate and unequal parts, and the centre of the place that was occupied originally by the giant cell may be strewn over with nuclear fragments, occasional polymorphonuclear leucocytes and other cells filled with detritus. In other places the interior of the still intact or partially fragmented giant cell may contain much nuclear detritus, as well as vesicular and more deeply stained nuclei, while there may be arranged at its periphery cells with deeply staining nuclei which lie in more or less distinct lacunæ in the surface of the cell that then has a scalloped appearance; in a few cases these cells seemed to contain in their interior smaller and larger pieces like the substance of the body of the giant cell. In this way there may be formed, as it is easy to trace in the serial sections, a small area in which the matrix stains brighter red than that of the tissue immediately around it; the area is occupied by rather loosely scattered cells with the appearance of a concentric arrangement, especially at the periphery, producing here and there an indistinct, irregular central space or small cavity without any direct connection, however—and this was looked for very closely—with the blood-vessels. The small cells are usually oval, curved, spindle-shaped, or irregular, with a reddish, finely granular, frequently indistinct protoplasm and spindle-shaped or oval, quite lightly stained nuclei; distributed among these cells may be other round or oval cells with more chromatic nuclei and also a varying amount of free and intracellular small, deeply colored nuclear fragments, often shaped like cocci or rods; furthermore, there are not infrequently found irregular portions or remnants of the giant cells with typical or with very peculiar, flask-shaped, club- and dumb-bell-shaped nuclei, and also cytoplasmic fragments without any nuclei; polymorphonuclear leucocytes are present in rather insignificant numbers, but more particularly when the disintegration is rather well marked. Often such a mass as above outlined may be surrounded by a small capsule of a more condensed tissue, and under the low power many of them may resemble miliary tubercles.

In the above described process the amount of nuclear disintegration, the irregular splitting up of the giant cells, the coarseness of granulation of their protoplasm, and the presence of phagocytes all indicate that one is dealing with structures that are undergoing retrogressive changes and disintegration. But even in these cells there are abundant evidences of the fact that not all the nuclei of a partly necrotic giant cell are doomed to destruction. In many places the appearances point to a direct separation of apparently viable cells from the giant cells; the nucleus in the part wholly or partly separated may become rich in chromatin and stain deeply; one can also observe that the nuclei in the interior of a disintegrating giant cell, or of a fragment thereof, become more deeply stained, surrounded with a faint rim of protoplasm outside of which a vacuole with a faint network may form (Fig. 4 A, Plate III); now, when a number of nuclei undergoing such a change as this are arranged across a giant cell there may result a complete separation of the cell into unequal parts; during the time that some nuclei in the giant cell are undergoing progressive changes, others have suffered disintegration, as shown by the irregular chromatin fragments scattered about. At the poles and circumference of such giant cells there are also frequently found groups of more or less deeply stained nuclei, surrounded by a small amount of protoplasm, that give the impression of having become separated from the giant cell.

Division of giant cells without much disintegration (Figs. 2 and 3, Plate III).—There remain to be described a large number of giant cells which seem to have separated, or to be separating, into a number of small cells with but slight or no evidences of concomitant nuclear necrosis and disintegration of the protoplasm.

In quite a number of giant cells, with a finely granular cytoplasm and a more or less perfect peripheral wall of rather faintly stained nuclei, there is found a varying number of deeply stained round nuclei, many of which may lie in vacuoles in the cell substance, others upon the protoplasmic processes of the giant cell, while still others may be recognized immediately outside the cell and provided with a cell body (Fig. 1, Plate III). An apparent connection between the lightly and deeply stained nuclei can be traced through transition stages. Rather poorly preserved karyokinetic figures are also present in a very few of these cells; budding processes are also seen arising from some of the nuclei. Towards the periphery and the poles of such a cell there are found quite a number of deeply stained nuclei with rather indefinite cell bodies and still enclosed within the body of the old giant cell. The nuclei of some of the new cells, especially the ones that are free, may assume a spindle-

shaped form. There are no appearances indicating that cells are in the act of wandering into the giant cell from without. Polymorphonuclear leucocytes are not, as a rule, seen in the vicinity of giant cells undergoing such changes as these, and there are but few nuclear fragments. When these changes have advanced throughout the whole giant cell, or throughout a whole segment of one, there is formed a focus of loosely scattered oval and spindle-shaped cells with deep or lightly stained nuclei, occasionally presenting mitotic figures, and with indistinct cell bodies situated in a loosely meshed stroma; immediately around such a centre may be a more closely arranged wall composed of cells imbedded in a distinctly fibrous matrix. In general, these areas, in some part of which portions of the giant cell are usually still present, remain distinguishable from the surrounding tissue also by the fact that they have a more reddish intercellular substance, that they are not so cellular and that the nuclei of the cells are less deeply stained. In the most advanced districts, where the fibrillation of the young connective tissue is most marked and the cellular infiltration less pronounced, the areas described are usually small and wholly occupied by cells, many of which cannot be distinguished, as regards shape, from the cells in the recent fibrous connective tissue around the area. Appearances indicating the transformation into blood-vessels of such districts of cells derived from the disunited giant cells are not present.

Undoubtedly the loosely filled spaces above referred to would later on become filled or obliterated in part, perhaps, by cell proliferation, but principally, most likely, by contraction of the intercellular substance.

SUMMARY.

From the foregoing description of the histological changes in the leptomeninx it is quite evident that we are dealing with a chronic, stationary, healing form of tuberculous inflammation.

This statement is substantiated, in the first place, by the clinical history. The only reasonable interpretation of the symptoms would establish the duration of the process as four months. The imaginable contingency that there existed first a meningeal syphilitic lesion that was dispersed by the iodide of potassium only to be followed by a tuberculous infection is so remote and unlikely that it need not be discussed. At all events the tuberculous leptomeningitis, which presented a typical distribution, began insidiously, existed at times in a latent condition, and pursued a very anomalous course, marked by a

relative mildness of all the symptoms, and thus it came about that when an apparent or real improvement followed the administration of iodide of potassium able observers were induced to make an erroneous diagnosis. Death occurred as a result of an intercurrent infection.

The long duration of the process is also shown, anatomically, by the thick layer of firm, translucent and gelatinous material that matted together the structures at the base, and also by the evident adhesions between the pia and the brain.

The histological examination furnishes proof positive of the correctness of the conclusion in regard to the peculiar character of this process because it shows:

(1) That the tuberculous proliferation is uniform in development and has reached nearly the same stage of evolution throughout the entire extent of the leptomeninx involved; it is not a process that has advanced by exacerbations and irregular extensions; the lesions are, generally speaking, of nearly the same age everywhere and must have begun at about the same time.

(2) That only a very limited degree of caseous degeneration is present, pointing to an early arrest of the activity of the tubercle bacillus or to a very decided diminution or attenuation of its virulence.

(3) That the subendothelial intimal proliferations of epithelioid cells, so generally found in acute tuberculous leptomeningitis,* have in this case become more or less completely changed into distinct fibrous tissue in which but very slight, if any, direct evidence of its tuberculous origin can be found. It is only by recognizing that the chronic endarteritis is most marked in correspondence with the most advanced adventitial tuberculous changes, and by finding an imperfect, much altered giant cell in one district of intimal thickening, that we were able to establish the direct kinship of the endovascular changes with those of the pia in general.

(4) That acute inflammatory changes, in the form of emigration of polymorphonuclear leucocytes and of fibrinous exudation, are en-

* See an article by the writer entitled "The Vascular Changes of Tuberculous Leptomeningitis, especially the Tuberculous Endarteritis," in this Journal, Vol. I, No. 1, 1896.

tirely absent in all parts of the district involved. The presence of a turbid serous fluid is of course not at all inconsistent with the view that the anatomical changes are of long duration.

(5) That the granulation tissue present is, in general, undergoing fibrillation and contains a rich supply of embryonal capillary vessels as well as of larger blood-vessels of evidently new formation. The absence of any considerable extent of polymorphonuclear leucocytic infiltration in this tissue has already been referred to. The cells in the granulation tissue correspond to the cells of embryonal or formative connective tissue. Vacuolation is rarely present.

(6) That the unusually large number of giant cells present are remarkably free from evidences of necrosis and degeneration of the character ordinarily observed in tuberculous proliferations, that they do not contain in demonstrable form tubercle bacilli, and that the majority of the giant cells seem to be separating into individual cells and smaller masses often with, but sometimes also without, evidences of nuclear disintegration. The possibility that these phenomena may signify fusion instead of the sundering of cells will be discussed below.

For these reasons there can be no doubt that the general claim that we are dealing with an instance of chronic, healing tuberculous meningitis must be regarded as established beyond dispute.

The growth of tubercle bacilli in the glycerine-agar tubes, inoculated with the fluid from the pial meshes, and the demonstration of tubercle bacilli, though in very small numbers, between the cells of the embryonal tissue, furnish the positive evidence that we are actually dealing with a tuberculous process due to living and not to dead bacilli.

The degree of virulence of the cultures of tubercle bacilli was, unfortunately perhaps, not studied. The presence of living tubercle bacilli in a tissue free from active and acute changes characteristic of tuberculosis demonstrates that, whatever the actual degree of virulence of the bacilli may have been, the tissue in which they were found was at this time relatively immune from their action. The manner in which this immunity was produced, and in which the process of healing was initiated, need not be discussed at this time any further than to again direct attention to the fact that the bacilli lost

their virulency as regards the cells in this leptomeninx before these cells underwent any marked degree of degeneration. The cells of the tuberculous proliferations survived the further action of the bacilli whose original effect it was to initiate cell accumulation or proliferation; the cells also retained sufficient vitality to develop, in some instances at any rate, into formative cells according as their origin would dictate, *e. g.* into fibroblasts. That fibroblasts are formed only by embryonal connective tissue cells, and not by wandering cells, such as the large mononuclear leucocytes, we are well aware, is possibly still a disputable assumption, and we do not consider it pertinent to discuss the question any further in connection with this study, but would only emphasize the point that some of the cells of tuberculous proliferations may, under favorable circumstances, become formative cells, and, furthermore, that the amount of formative tissue produced may be far in excess of what is actually needed for purposes of repair only. Surely the appearances here noted indicate that the bacillus of tuberculosis has the power to stimulate fixed cells to multiply, unless one assumes that all, or almost all, the formative cells here seen are derived from wandering cells attracted by the presence of the bacillus and its products.

As to the ultimate fate of the formative and other cells in this healing tuberculous tissue no final statements can be made. It must be remembered that it is only one stage in the process of healing that is dealt with. The well marked evidences of fibrillation, the quite extensive formation of new vessels, the absence of evidences of degenerative changes in the uninuclear cells, all point to the production of new fibrous tissue as sure to occur, but it seems quite probable that occasional epithelioid cells may undergo or have undergone dropsical or other forms of degeneration, although it is certainly apparent that so far as the small cells are concerned the involution of the tuberculous tissue is not occurring through disintegration.

Perhaps the most interesting feature in this case is the opportunity it affords to study the changes in the giant cells of healing, non-degenerated tuberculous tissue. In the first place, the large number of giant cells is quite remarkable. The general characters of the tissue

in which they are found recall the fact that giant cells are regarded as quite constant elements in chronic mild tuberculosis; often the giant cells are the only cells that contain bacilli (Koch). In this instance the giant cells do not contain bacilli that are demonstrable by the usual methods; neither do they contain bodies that can be definitely interpreted as degenerate forms of bacilli such as those found by Metchnikoff, Stchastny, Welcker, and others, in the giant cells of Spermophilus guttatus, in avian and in human tuberculosis. Metchnikoff states, however, that he knows of the occurrence of such degenerate forms only in the Spermophilus guttatus under the circumstances mentioned, and in the rabbit and guinea-pig in mammalian tuberculosis, but not in man; consequently, the manner in which the giant cells rid themselves of the bacilli undoubtedly present in their interior at some time during their existence, must as yet remain without any explanation.

In the description of the histological changes the various appearances presented by the giant cells are described somewhat minutely. The essential observations made concern, in my opinion, the further fate of giant cells which are still found to persist in healing non-degenerated tuberculous tissue. It was, I believe, quite conclusively shown that the consecutive changes appear to consist in the breaking up of the nuclei, the removal of the detritus by phagocytes, and the formation of a few apparently viable uninuclear cells in the case of more degenerated, exhausted giant cells, while other, and, as it would seem, better preserved or younger giant cells, separate into a number of individual, uninuclear cells with but little or no nuclear disintegration.

Objection might be raised to this interpretation of the appearances in the giant cells. While no one could very well dispute the view that part of the giant cells are undergoing retrogressive and absorptive changes with the production of some viable cells, a question might well be raised concerning the nature of the process taking place in those giant cells that have been spoken of as splitting up or dividing into uninuclear cells and smaller multinucleated masses without much evidence of nuclear disintegration. It might be claimed that the pro-

cess is one of fusion of many cells to form giant cells, and not one of division of fully formed giant cells into small cells. But a broad view of the processes described speaks against fusion. In the first place we are not dealing with a stage of tuberculous proliferation (Baumgarten), or cell accumulation (Metchnikoff), in which one would look for the production of giant cells, no matter which view concerning the histogenesis of tubercle be assumed as the correct one, because it has been demonstrated that, from whichever point of view the lesions are examined, the same positive conclusion that they are in the process of healing is reached; there is, therefore, no occasion for the formation of new giant cells in such wide-spread degree throughout the district involved.

It might be claimed that the cells became arrested and, as it were, fixed in the act of fusion which was taking place in the early stage of the meningitis, but it would be difficult to understand the nature of the stimulus that could hold the cells together in such a peculiar manner for such a long time. It must be remembered that bacilli or bacillary detritus could not be found among the incomplete or in the complete giant cells.

In the second place the difference between the cells that are undergoing disintegration and those regarded as dividing is essentially, to a certain extent at any rate, one of degree, because in the first instance there is not much, if any, doubt but that viable smaller cells are also formed, and in the second instance some, though often very slight, evidence of nuclear fragmentation is nearly always present; it would also be correct to infer that in advanced subdivision of a giant cell much, and perhaps all, of the nuclear detritus produced might have been removed up to the last trace; finally, the two extremes of these changes in the giant cells are connected by transition stages passing by gradation from the one to the other. Hence it is justifiable to conclude, for the time being, that *in healing non-degenerated tuberculous tissue, the multinucleated giant cells may in part disintegrate and undergo absorption, in part form viable small cells; that both these changes may, and usually do, affect the same cell, but that in one class of cells—presumably the older or the more exhausted—the retrogres-*

sive process is predominant, while in a second class of cells—presumably the young and vigorous—the progressive changes are the more marked.

In this connection it may be pointed out that while there cannot very well be any question but that we are dealing only with dividing and not coalescing cells, yet if this conclusion should be disputed and found incorrect, then the only remaining alternative would be to infer that this tissue furnished a unique and striking example of the formation of plasmodial masses by fusion in human tuberculosis, a conclusion to which many pathologists would refuse to subscribe, if for no other reason than because it is not in accordance with the almost universally accepted teachings of Baumgarten and Weigert in regard to the mode of formation of the giant cells in tuberculosis.

Believing as I do that the giant cells under consideration are in the act of division and not at all of fusion, there remain to be discussed some of the histological and other features presented by the dividing cells.

Many of the giant cells, perhaps the majority, contain larger and smaller vacuoles in the protoplasm. The exact significance of this vacuolation is not always clear. When the vacuolation accompanies an evident solution of the nucleus (karyolysis), there cannot be any doubt but that we are in the presence of a distinctly retrogressive process. Vacuoles are also most numerous in the giant cells that present other evidences of degeneration, such as coarseness of the granules in the protoplasm and extensive nuclear disintegration, but they occur as well around nuclei that stain deeply, around cells that seem to be separating from the giant cell, and even about nuclei that present mitoses. The formation of vacuoles seems to be responsible, to a certain extent at any rate, for the diminution in the volume of disintegrating and dividing giant cells, as shown by the clear spaces that form about them; these spaces are too large and occur too uniformly to be attributed solely to artificial shrinking produced by the hardening in alcohol.

Further undoubted evidence of retrogression in certain giant cells is the occurrence of nuclear disintegration, or karyorhexis, which sets

free larger and smaller chromatin masses that are recognized in the giant cell as well as in the interior of the phagocytes usually found around such cells.

Almost all the polymorphonuclear leucocytes found in this tissue are met with around giant cells with broken-up nuclei. In many nuclei of disintegrating giant cells can be noted appearances that correspond well to certain stages in the complicated karyorhexis observed in anæmic necrosis by Schmaus and Albrecht; some of the nuclei with budding processes correspond particularly well with those in certain of their drawings; the interior of giant cells of tuberculous tissue may, it would seem, present conditions favorable to the development of this series of postnecrotic nuclear change. Vacuolation, karyolysis and karyorhexis are the essential steps that lead to destruction of the whole or parts of some of the giant cells; associated with these processes there is usually observed a splitting up of the body of the giant cell into irregular fragments with as well as without nuclei; and, as described, more or less phagocytosis of the resulting remnants of various kinds is seen.

But evident degenerative and necrotic processes in a giant cell may be associated with progressive changes. While some nuclei undergo vacuolation or break up, others seem to become richer in chromatin and to stain more deeply at the same time that they seem to acquire cell bodies quite distinct from the protoplasm of the giant cells; this hyperchromatosis does not, therefore, seem to be a stage in karyorhexis. A very few but undoubted karyokinetic figures were found, together with evidences of division of the cell body formed in the giant cell protoplasm. Precisely similar changes are described by Klebs in healing pulmonary tuberculosis of the guinea-pig; the nuclei of the giant cells became rich in chromatin and karyokinetic figures occurred. Krückmann among others has found occasional mitoses in giant cells around foreign bodies, as well as elsewhere, but it would seem that such mitoses have always been interpreted as indicating the probable mode of formation of the giant cells rather than of their involution.

The question of mitosis in existing multinucleated cells has recently been studied by Krompecher, who concludes that the individual nuclei

of such cells may undoubtedly divide by mitosis, either simultaneously or at separate times. Division by amitosis can also occur, but mitosis is the only progressive form of division, amitosis being a retrogressive, disintegrating process that must be looked upon as an evidence of degeneration of the nucleus. Ziegler states that in division of giant cells whose nuclei have multiplied by mitosis it may happen that the separating cell remains enclosed in the protoplasm of the mother cell.

A singular phase in the involution of the giant cells in this pia is to be found in the existence of progressive changes side by side with nuclear necrosis and with degeneration; this finding indicates that giant cells may contain many independent elements which, though apparently fused into one large cell, may preserve their individuality so that while some nuclei die, others proliferate and perhaps feed on the remnants of their dead brethren and form new, viable small cells. The nuclei in giant cells may be looked upon as representing independent centres, capable at times of existing even though the cell protoplasm is disintegrated. Many of the giant cells separate into individual cells, unaccompanied or unassociated with much evidence of necrosis. These cells may be regarded as the more vigorous forms. Here also are observed occasional mitoses—but on the whole extremely few—and very constantly an evident increase in the amount of chromatin in the nuclei of the new cells as compared with the amount ordinarily found in the nuclei of giant cells.

These deductions concerning the persistence of the vitality of some of the nuclei, even in the presence of molecular and morphological changes in the cytoplasm and in other nuclei of the giant cell that lead to disintegration, are not entirely without the support of previous observations on cells, which, although made under different conditions, are nevertheless, it would seem, applicable to cells in general. Thus the brilliant investigations of Loeb upon the effects of various unfavorable surroundings, such as absence of oxygen or reduction of the amount of water, upon the cleavage of eggs of many kinds, show that the conditions which arrest development are qualitatively alike for nucleus and protoplasm, but quantitatively less for the protoplasm; when the irritability of the protoplasm is suspended the nucleus may

segment without segmentation of the protoplasm, but upon re-establishment of favorable conditions the protoplasm may divide into about as many spheres as there are nuclei preformed—the nucleus persists, preserves the irritability of the cell and stimulates the protoplasm to segmentation. From the appearances of the giant cells here described it would seem, then, that some nuclei are able to maintain their vitality longer than others in the same cell, and under certain conditions to stimulate parts of the protoplasm to segment; in other cells all the nuclei have, as a rule, preserved their irritability.

The groups of cells formed by the dividing of the giant cells can be traced by studying the process at the different stages in the different parts of the tissue. They assume an oval or spindle-shaped form, becoming more and more like the formative and endothelioid cells of young connective tissue, but their ultimate fate cannot be determined because it concerns essentially only one limited period in the involution of the tissue. It may be said with reasonable certainty, however, that the new cells do not form blood-vessels, but as regards their forming lymph-vessels nothing definite can be concluded.

It would not be safe to draw any definite conclusions, from the appearances described, with regard to the origin and the mode of formation of the giant cells. The resulting small cells in general resemble very much endothelial and formative cells, but some of them are, at certain stages at any rate, not unlike large mononuclear leucocytes; their final fully developed or mature condition being unknown, no positive inference can be drawn as to their pre-giant-cell origin. The evidence points to the fact that the most probable origin of the giant cells, as indicated by their form and the apparent future career of their descendants, would be the fixed mesoblastic cells of the pia. In regard to the mode of formation of the giant cells it is quite clear that it must involve some process which is not incompatible with the viability of the small cells which may spring from the giant cells. Whether this would speak more in favor of formation by fusion than by karyokinesis of a single cell without division of the cell body cannot be well determined, and as long as authors are not agreed upon the question of the production of living, procreative cells by amitosis

(direct segmentation, direct and indirect fragmentation) it would not be profitable to discuss the compatibility or incompatibility of the views of those investigators who trace the origin of giant cells to amitotic division, with the progressive changes that giant cells have been shown to be capable of.

The fact that giant cells in tuberculous tissue, under certain conditions, undergo progressive changes and separate into small, living cells proves that they are not, as claimed by Baumgarten, Weigert and others, necrobiotic elements that are doomed to destruction from their very inception. On the other hand it lends more strength, if that were necessary, to the teleological view urged by Metchnikoff that they are living, defensive cells (whatever their origin may be), formed for the distinct purpose, like plasmodial masses in general, of isolating and removing foreign, harmful bodies, in this case the tubercle bacillus, and, having accomplished their object without being destroyed or exhausted, or the cause of their formation being removed or neutralized in some way, they, or their nuclei, may retain enough irritability to form a larger or smaller number of living, small, uninuclear cells.

I wish to thank my friend Dr. J. D. Freeman for his excellent drawings.

DESCRIPTION OF PLATE III.

Fig. 1.—A giant cell in one portion of which many of the peripheral nuclei are rich in chromatin and stain deeply; there are vacuoles about some of these nuclei. To the left is a small fragment that has separated from the giant cell proper and which contains a few deeply staining nuclei as well as an indistinct cell with two nuclei. Zeiss, obj. 4°, ap. 0.95 apochr.; oc. 8 (compensat.); tube-length 160.

Fig. 2.—The same giant cell as in Fig. 1, but at a different level. The cell is separating into uni- and multinuclear cells and masses of varying forms. Magnification same as Fig. 1.

Fig. 3.—In the central part of the drawing are spindle-shaped and irregular cells and masses derived from the splitting up of a giant cell, as shown by study of the serial sections. Same as Fig. 1.

Fig. 4.—*A*, a section of an irregular, finely granular giant cell with faintly stained and vesicular nuclei, some chromatin granules, occasional deeply staining nuclei; and lying in a vacuole a distinct cell, the nucleus of which seems to have divided and the cell body of which presents a central constriction as though about to divide. At the lower margin of the cell are

separated protoplasmic masses, one of which contains a deeply stained nucleus.

B, giant cell with huge vacuoles, containing fine granules. Same as Fig. 1.

Fig. 5.—Chronic fibrous thickening of the intima.

A, subendothelial fibrous tissue covered by closely arranged nuclei.

B, imperfect or dividing giant cell (?) in the deeper, more cellular part of the thickening.

C, intact elastic layer.

Adventitia the seat of considerable infiltration. Zeiss, apochr. obj. 4°; ap. 0.95; oc. 4 (compensat.).

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FIG. 1.

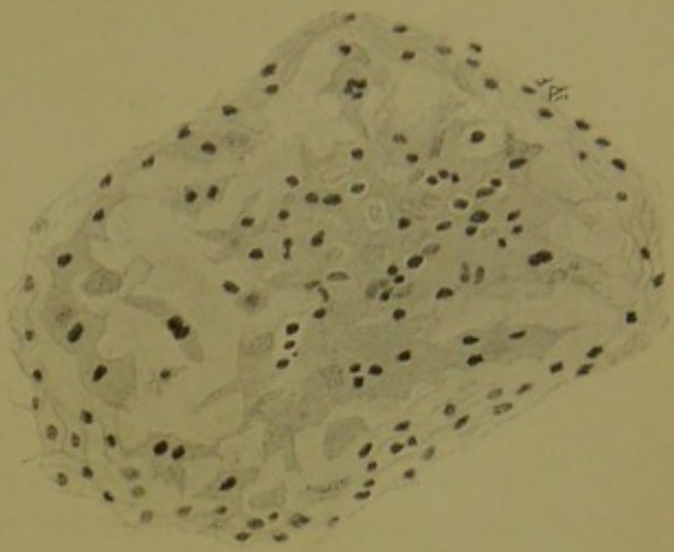


FIG. 2

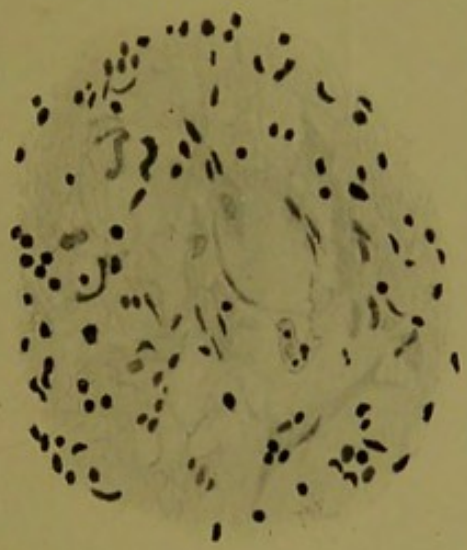


FIG. 3.

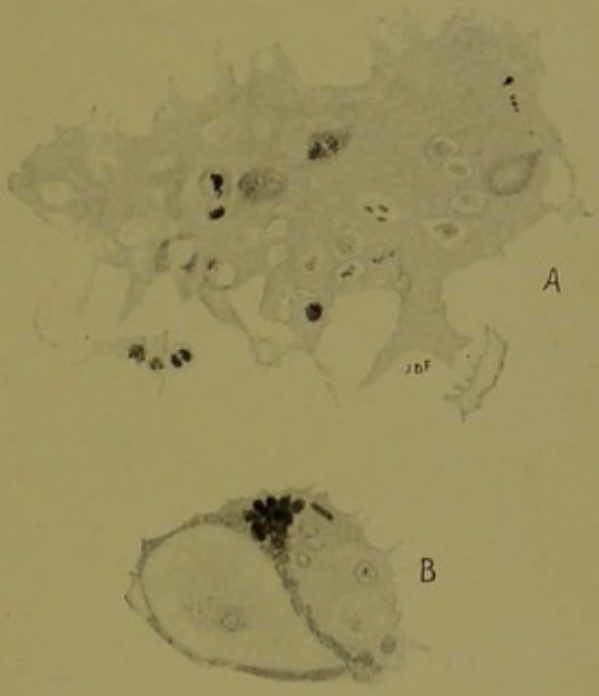
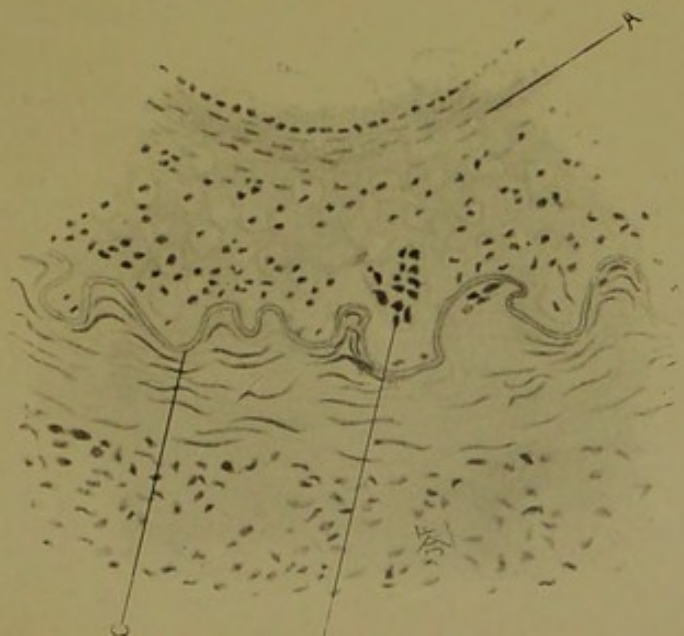
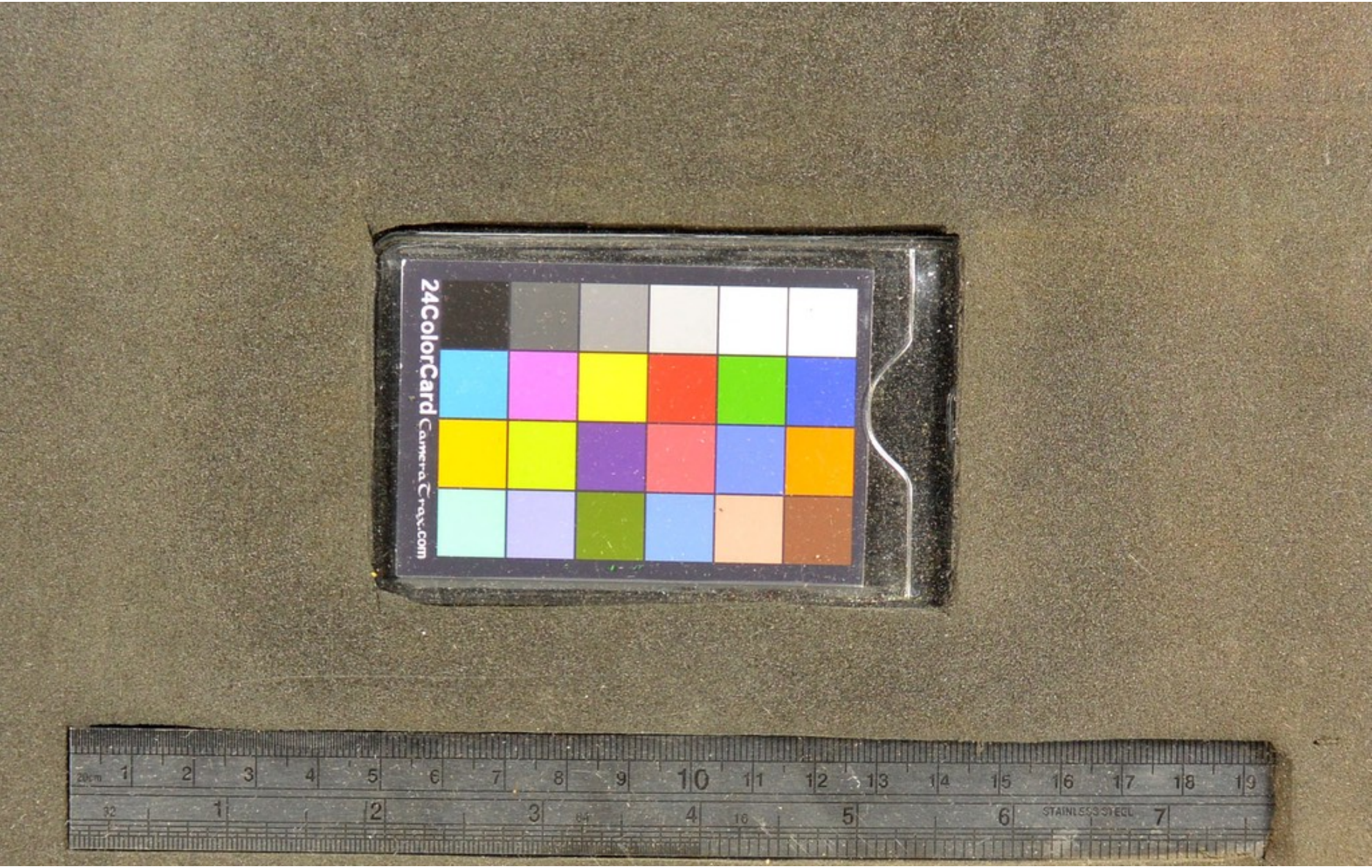


FIG. 4.

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