THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME II JULY, 1926 NUMBER 4

A STUDY OF THE PROCESS OF CASEATION IN TUBERCULOSIS *

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The term caseation is applied to the gross characteristics of the necrotic material commonly seen in tuberculous infection. This necrotic tissue can be easily removed from the surrounding living tissue, leaving a cavity. It has no texture and varies in consistence from thick pus to a crumbly material not unlike cottage cheese. In these respects it differs from the necrotic tissue seen in a bland infarct or in a gumma, which cannot be readily removed from the surrounding viable tissue and which has a distinct rubber-like consistence. The necrotic material in an abscess differs from all of the above in that it is usually more liquid in character. Since these lesions are all, at times, seen in the same tissue and are either of an anemic or of an inflammatory nature, why should the necrotic tissue in tuberculosis differ from that seen in other conditions?

During the past four years an extensive study of the process of caseation has been undertaken. A large series of cases of both natural and experimental infection have been examined. Tuberculous lesions in the lung, spleen, liver, intestine, kidney, fallopian tubes and lymph nodes have been carefully studied by the serial section method. At least 200,000 sections have been carefully examined during this investigation and a large number of these sections have been examined for the presence of tubercle bacilli. Tissues from human cases obtained at necropsy and at surgical operations, from guinea-pigs inoculated with bovine and human tubercle bacilli and from fowl naturally infected with the avian strain of the tubercle bacillus have formed the basis of this study.

* Received for publication April 9, 1926.

Early in the study of the human tissues it became apparent that, if the natural sequence of events in the process of caseation was to be rightly understood, it would be an essential requirement to obtain tissues at known periods after infection. To obtain such tissues a series of guinea-pigs were inoculated on the same date with an equal dosage, approximately 20,000, of human tubercle bacillus, strain H37. The inoculation was made subcutaneously in the left groin. The skin over the area to be inoculated was carefully sterilized with iodine before inoculation and care was taken to avoid any contaminating infection. In none of the animals was there any evidence of acute inflammation on gross inspection at the site of inoculation at any time. Beginning with the tenth day after inoculation, animals were sacrificed every fifth day. The series gave tissues 10, 15, 20, 25, 30 and 35 days after the inoculation. Previous studies had shown that the spleen and the inguinal, iliac and par-aortic lymph nodes were the most uniformly infected following inoculation in the groin. These tissues were carefully studied for the presence of tubercle bacilli and the type of the inflammatory reaction.

Caseation in the Guinea-Pig

Since it is possible in the guinea-pig to follow the tuberculous process, step by step, from the earliest inflammatory reaction to the stage of typical caseation, a brief account of the process as it occurs in this host will be given first. This will be followed by a description, with an attempt at correlation, of the pathologic picture as seen in natural infection in the fowl and in man.

It is now common knowledge, dating back to the work of Yersin [1] and of Borrel,[2] that when tubercle bacilli are injected intravenously for the first time in the rabbit, the first inflammatory reaction occurs within the capillaries in the various tissues and organs where the bacilli lodge. This reaction is microscopic in proportion and consists of a varying proportion of polymorphonuclear and mononuclear leucocytes. Both types of cell phagocytize the bacilli. This first polymorphonuclear leucocytic reaction is never great and is of a transitory nature, hence abscess formation does not follow. The polymorphonuclear leucocytes which have been attracted die within a few days. From this stage on the mononuclear leucocytes continue to accumulate and the tubercle is formed.

This same reaction occurs at the site of the primary inoculation in the guinea-pig. This reaction, if the size of the dose be small, is never of sufficient extent to attract attention on macroscopic examination of the site. If the dosage be large the reaction may be sufficient in amount to cause slight ulceration of the overlying tissues. The ulceration is due, apparently, to the accumulation of polymorphonuclear leucocytes with resultant small abscess formation.

The distribution of the tubercle bacilli through the body from the primary locus has been so carefully and thoroughly studied by various authors that this phase of the subject will not be entered into. Suffice it to state that the bacilli are phagocytized by both the polymorphonuclear and mononuclear leucocytes which, by their wandering proclivities, first gain access to the lymphatics and later to the blood stream.

It is in these secondary foci of infection, where the bacilli are at first few in number, that the entire and probably characteristic reaction to tubercle bacillus infection can be found. Here it is possible to follow the development of the lesion from its beginning, step by step, to caseation and to healing, if the infection is overcome. This process can be followed in the various organs of the guinea-pig. The pathologic process as it develops in the spleen is here given. The spleen is chosen for three main reasons. In the first place it is of such size that serial section of the entire organ does not entail too great technical labor. Secondly, its infection with the tubercle bacillus is entirely hematogenous and, therefore, as remote as that of any organ from the original site of inoculation. And in the third place, it has no connection with the outside world, as do the lung and kidney, and consequently would be the least liable to be involved with infectious agents other than the one inoculated.

A comparative study of tuberculosis of the spleen in the human and the guinea-pig will be reported at a later date. Here the only phase taken up will be the pathologic process as it concerns caseation.

At ten days the spleen shows no tubercle formation. By careful and persistent search one may find a single bacillus or a group of two or three bacilli about midway between the splenic artery and the periphery of the Malpighian corpuscle. These bacilli are usually within mononuclear leucocytes, although some of them are, apparently, free in the tissue. The small groups of bacilli are the ones most often found free.

From this point on one finds the greatest development of the tuberculous process in the Malpighian corpuscles, though as time elapses one also finds an increasing number of small lesions developing within the histologic unit of the spleen pulp as described by Mall.[3] There is a gradual increase in the number of tubercle bacilli up to the twenty-five day specimen. This increase is due in all probability to two factors, namely, the multiplication of the bacilli in the organ and the continued accumulation of the bacilli filtered out of the blood stream. The latter factor would appear to be the predominant one, for one finds the bacilli scattered singly or in groups of two or three, largely within mononuclear leucocytes, throughout the developing lesion. One finds the bacilli distributed in somewhat of a collar arrangement in the outer portion of the splenic corpuscle and in the histologic unit.

The cellular reaction in the fifteen and twenty day specimens consists almost entirely of mononuclear leucocytes. In many areas nearly the entire Malpighian corpuscle or the histologic unit is filled and greatly enlarged by the accumulation of these cells. This is the mononuclear or "epithelioid" tubercle as it develops in the guinea-pig. Lymphocytes are very rare in the tubercle of the histologic unit but are numerous in the area outside of the tubercle in the Malpighian corpuscle. Polymorphonuclear leucocytes are very uncommon in the tubercle but may be found in small numbers in the tissue surrounding it. There is no evidence of caseation. One does find, however, mononuclear leucocytes with vacuolated cytoplasm and very faintly staining nuclei. Mitotic figures are commonly seen in the splenic pulp and less frequently are found in the tubercle itself. There is abundant evidence that the mononuclear leucocytes migrate into the tubercle, for one very commonly finds these cells with their nuclei stretched out in a long sinuous process.

Beginning, at times in the twenty day but more marked in the twenty-five day specimen, and continuing in the thirty and thirty-five day specimens, one sees a gradual and increasing accumulation of polymorphonuclear leucocytes in the areas where caseation later becomes apparent. These areas are often near the center of the tubercle. They may, however, be eccentrically placed. They vary in size from a small focus to an area which eventually becomes as large as many tubercles. The immigration and the multiplication

of the mononuclear leucocytes by mitosis do not entirely cease but the accumulation of the polymorphonuclear leucocytes far overshadows the mononuclear infiltration, so that in many instances the inflammatory reaction resembles abscess much more than tubercle formation. Bacilli are present, more numerous in some instances and fewer in others, when compared to the fifteen and twenty day specimens. But in none of the areas where the inflammatory reaction is most intense does the typical picture of caseous material appear at this stage. Many of the smaller foci, especially in the histologic units, do show the typical picture of caseation and if the dead cells are not too closely packed together one can make out with a fair degree of certainty the outlines of the nuclei of the polymorphonuclear leucocytes. These areas also contain a varying amount of nuclear "dust." In the larger areas one sees the beginning of caseation at the periphery and in numerous instances cells in the process of disintegration. An interesting finding in these areas is the presence of mononuclear leucocytes which have ingested from one to half a dozen polymorphonuclear leucocytes. Tubercle bacilli are quite commonly found within the polymorphonuclear leucocytes which have been engulfed. Lymphocytes are rare.

In lesions of six, seven or eight weeks' duration, the picture of caseation is present in many of the larger lesions. The necrosis appears to begin at the periphery of the most intense inflammatory reaction and gradually to proceed toward the center. There is more or less solution of continuity between the viable tissue at the periphery and the necrosing inflammatory exudate within, so that a modified abscess formation is the end result.

In the inflammatory process as described, giant cells are not found. They do not appear to be an essential part of the early inflammatory reaction or of tubercle formation, at least as it is produced in the guinea-pig.

As these areas of caseation in the spleen cannot be discharged to the outside without rupture of the splenic capsule, the cellular reaction subsequent to caseation can be followed. Polymorphonuclear leucocytes are not further attracted after caseation has been produced. Mononuclear leucocytes continue to accumulate and they gradually invade the caseous mass. Lymphocytes also are attracted in increasing numbers and likewise invade the caseous material. At

this stage of the reaction giant cell formation begins to take place. The significance of this phase of the reaction will be discussed in a separate paper on giant cell formation in tuberculosis.

In many of these areas of caseation, stainable bacilli are very few or absent. In other areas one finds colonies of stained bacilli. This presents a picture quite different from the even distribution of the bacilli, individually or in small groups throughout the lesions, in the earlier stages of the tuberculous process.

Quite often the inflammatory reaction is so extensive in the larger lesions that infarction of splenic tissue not primarily involved in the tuberculous process is produced. The size of the infarction varies with the size of the artery involved, but at times involves as much as half of the organ. This point is of considerable importance in the consideration of the essential tuberculous lesion. One has, however, little difficulty in distinguishing between the infarcted non-tuberculous tissue and the areas of tuberculous involvement. In the infarcted tissue one can distinguish easily between the areas of tuberculous inflammation and the non-tuberculous splenic areas which show the outlines of the sinuses and trabeculae of the dead splenic tissue. In fact, if the infarct be large, one finds several areas of tuberculous involvement within the infarcted area. These areas can be identified with certainty by the finding of tubercle bacilli, whereas the uninvolved infarcted tissue shows no bacilli.

Caseation in Avian Tuberculosis

Since one cannot determine the date of infection in cases of natral infection, it was impossible in the fowl to follow the development of the inflammatory reaction to the tubercle bacillus in time sequence as it was done in the guinea-pig. However, it seems logical that if stages of reaction corresponding to those observed in the guinea-pig can be found, the identity of the development of the inflammatory reaction to tubercle bacillus infection in the guinea-pig and in the fowl would be established. In the various fowl tissues studied it was possible to demonstrate numerous examples of typical mononuclear, or "epithelioid," tubercles without caseation, giant cell formation or polymorphonuclear leucocytic invasion. It was also possible to find numerous examples of tubercles without caseation but with polymorphonuclear leucocytic infiltration which

varied from a few to a large number of these cells in the areas where caseation occurred; and examples of different stages of caseation were numerous. In brief, all the stages leading up to the typical picture of caseation present in the guinea-pig were easily demonstrated in the fowl tissues naturally infected with the avian strain of the tubercle bacillus.

While it is not pertinent to go into a full discussion of the pathologic picture as seen in avian tuberculosis, there are a few facts worthy of comment. In the first place tubercle bacilli are far more numerous in the lesions than have been found in either guinea-pig or human lesions. In the caseous material large masses of bacilli in colonies are very commonly found; and in these same areas one finds large numbers of "phantoms" of unstained bacillary forms which correspond in size, shape and distribution to the stained bacilli.

In the fowl the leucocyte which corresponds to the neutrophilic polymorphonuclear leucocyte in man has an abundance of eosinophilic granules. This fact makes for easy recognition of these cells and when they are massed together in the midst of a tubercle they take an intense eosin stain which contrasts markedly to the blue-staining of the mononuclear leucocytes clustered around the periphery of the mass. The caseous material early takes a much more intense eosin stain than it does in man or guinea-pig. This fact is strongly suggestive of the important part played by the polymorphonuclear leucocyte in the production of caseous material in the fowl.

As in the guinea-pig, the polymorphonuclear leucocyte does not appear to be attracted by the caseous mass after it is once produced. In fact it is quite common to find large areas of polymorphonuclear infiltration directly adjacent to an old area of caseation with no evidence of the polymorphonuclear leucocytes attempting to invade the old caseous mass.

The mononuclear leucocyte appears to play the same rôle in the inflammatory reaction in naturally acquired avian tuberculosis as it does in the guinea-pig experimentally infected with the human or bovine tubercle bacillus. In freshly fixed tissues, one finds abundant evidence of its motility, as shown by greatly elongated nuclei. In the mononuclear tubercle, it is found to have tubercle bacilli within it. Mitotic figures in these cells are fairly easy to find in and about the tubercles.

The lymphocyte is very commonly found in the tissues surrounding the tubercle and the caseous material. It does not appear to take any active part in the formation of the tubercle or in the process of caseation.

Giant cells are usually far more numerous than in the guinea-pig tissues or in the human material I have studied.

Caseation in Human Tuberculosis

As in the case of the fowl, the human cases were those of natural infection and no date of the initial infection could be established. It would seem that the same logic which applied to the correlation of the avian and guinea-pig tuberculous reactions would obtain in man. Stages from the mononuclear tubercle without giant cell formation, polymorphonuclear infiltration or caseation to the typical picture of caseation were found, not once but many times, in the spleen, lymph node, kidney, liver, fallopian tube and lung. So that it would appear that there is close similarity between the inflammatory reaction and the appearance of caseation in guinea-pig, fowl and man.

The caseous material in man is composed in large part of dead polymorphonuclear and mononuclear leucocytes, but it appears that the bulk of the necrotic material is made up of polymorphonuclear leucocytes. In many of the areas the inflammatory cells are so closely packed together that it is impossible to make out the outline of individual cells. The intense hematoxylin stain which these areas take during the process of cell disintegration is another fact which is evidence of the marked cell accumulation during the most active inflammatory phase. The large amount of nuclear "dust" seen in the later phase of the process can readily be explained in the same way. In the later phases of cell disintegration it is impossible to determine the types of cell which compose the compact caseous mass. But if one may judge from the earlier steps in the process the lymphocyte plays little or no part.

The cellular reaction which occurs after the process of caseation is complete, that is, when the caseous material no longer shows nuclear "dust," differs in some respects from that which takes place before caseation is produced. Around these areas one finds many mononuclear leucocytes and a varying number of lymphocytes. Both of these cell types wander into the caseous material and can

be found all the way through it if the area is not too large. Polymorphonuclear leucocytes are not present in the reaction at this time and appear to take no part in the removal or organization of the caseous material. At this stage giant cell formation begins.

Among the human tissues examined were several cases of the hyperplastic type of tuberculosis. The majority of these were in lymph nodes removed surgically. A study of the inflammatory reaction in these cases showed a variation from the process described above in several respects. Mononuclear or "epithelioid" tubercles are much more common than in the caseating type of tuberculosis. Lymphocytes are more plentiful in the tubercles, often having accumulated in considerable numbers in the small areas of necrosis of the mononuclear leucocytes and in the rare areas of typical caseation. Polymorphonuclear leucocytes are extremely rare, except where typical caseation is being produced. Areas of caseation are rare and are small when present. Fibrosis is very common, many of the tubercles showing little but hyaline collagen fibers. Giant cells are present but are not numerous. Tubercle bacilli are scarce, the finding of a single tubercle bacillus being a laborious task.

Discussion

If the steps in the process of caseation in the guinea-pig, fowl and man as described above are a correct interpretation of the development of the tuberculous process, then it would appear that the process is the same regardless of the type of tubercle bacillus causing the infection or of the host infected. When caseation appears it is an indication of the virulence of the infection, of the lack of resistance of the host, of the dosage or of all three. When hyperplastic tuberculosis without caseation develops it is an indication of low virulence on the part of the bacillus, good resistance on the part of the host, small dosage or a combination of these factors. When caseation develops in a situation where it is possible for the necrotic material to be extruded from the body, as in the lung, kidney, skin or intestine, cavitation or ulceration ensues. If caseation occurs in a place, such as bone, where the caseous material cannot be extruded, a cold abscess will develop if the process is not successfully walled off. In case the caseous area is successfully walled off, it will either become calcified or be organized and a scar produced.

The term "mononuclear leucocyte" used throughout the description of the tuberculous process is, perhaps, not the best term to denote the cell. It is the ameboid phagocytic cell which has to do with tubercle and giant cell formation. It is apparently the same cell met with in typhoid fever, blastomycosis and other diseases and pathologic conditions where the function of phagocytosis of material that cannot be successfully handled by the polymorphonuclear leucocyte, is of vital importance. It is the cell of varied terminology. It has been designated as the epithelioid cell, the wandering mononuclear leucocyte or phagocyte, the macrophage of Metchnikoff, Evans and others, the endothelial leucocyte of Mallory, the polyblast of Maximow and the monocyte of Cunningham and Sabin. While its exact origin is perhaps still unsettled, its activities are fairly well understood. Its participation in the tuberculous process is generally accepted. A cell capable of ameboid motion, such as this cell possesses, could migrate to the site of the tubercle bacillus from the blood stream or from the surrounding tissues with equal ease. If one may judge by the presence of mitotic figures, it also multiplies after arrival at the site of infection. Whatever its name or its origin, it appears to be the greatest single factor in the destruction of the tubercle bacillus that the body possesses. It is my belief that the number of tubercle bacilli destroyed by cells of this type during tuberculous infection is but little realized.

It is the chief intent of this paper to direct attention to the rôle which the polymorphonuclear leucocyte seems to play in the process of caseation. In the mononuclear or "epithelioid" tubercle, the polymorphonuclear leucocyte is not seen until there is evidence of damage to the mononuclear leucocytes. This damage is shown by a slightly greater eosin staining of the cytoplasm, by loss of nuclear structure and oftentimes by vacuolization of the cell cytoplasm. This does not resemble caseous material. In these small areas one can often make out bacillary forms which do not stain with carbolfuchsin. This can best be demonstrated in fowl tissues where tubercle bacilli are numerous in the tubercle. Whether the polymorphonuclear leucocytes are attracted by the necrotic mononuclear leucocytes, by opsonins, by substances liberated through the death of the tubercle bacillus or by substances produced in the tissues by the multiplying bacilli is not understood.

The idea which one gains from the literature is that if the poly-

morphonuclear leucocyte is present in the inflammatory reaction to the tubercle bacillus it is there because of secondary infection. Mallory [4] states that these cells are present only when the tubercle bacilli are very numerous. He also states that caseation is due "chiefly or entirely to endothelial leucocytes plugging the lymph or blood vessels, thus cutting off nutrition" and that "the necrotic material consists largely of endothelial leucocytes." MacCallum [5] states that even in acute tuberculous inflammation "polymorphonuclear leucocytes seem to be very little attracted, their place being taken by lymphoid cells and large mononuclear wandering cells." Aschoff [6] does not mention the polymorphonuclear leucocyte in connection with caseation which he considers to be caused by the necrosis of the epithelioid cells which form the tubercle. Wells [7] quotes Schmoll as finding that caseous material, even when it breaks down and forms a cold abscess, shows much less evidence of autolysis than pus. Maximow [8] claims to have produced caseation in tissue culture where the polymorphonuclear leucocyte, because it is not regenerated in such cultures, could have but little to do with the process. He obtained in tissue culture necrotic "epithelioid" cells but it is doubtful whether this can rightly be compared to the process of caseation as it occurs in living tissues where all types of cell have free access to the site of infection. Smith [9] states that the polymorphonuclear leucocyte does not play any recognizable rôle in the tuberculous process. He also states that the appearance of the polymorphonuclear leucocyte in the early reaction to cultures inoculated intravenously is due in all probability to the suspending fluid and to disintegrating bacilli which are always present in the cultures of a few weeks' growth.

Kostenitsch and Wolkow [10] speak of a primary polymorphonuclear leucocytic infiltration which occurs a few hours up to three days after the primary inoculation of tuberculous material, and of a secondary polymorphonuclear leucocytic infiltration which occurs at the time of caseation. As tubercle formation can take place up to the stage of caseation without the polymorphonuclear leucocyte participating, it appears that the polymorphonuclear leucocyte does not in reality make a primary and secondary appearance. It is evident that there is a phase in the reaction to the tubercle bacillus where a substance is produced which definitely attracts this cell. They also state that the primary reaction is more intense than the

secondary reaction. I have found the polymorphonuclear leucocytic response much more intense after well established infection has been produced.

There is abundant evidence that the polymorphonuclear leucocyte is not attracted by caseous material after it is once formed. This can be easily demonstrated in both experimentally and naturally infected tissues. The active participation of the polymorphonuclear leucocyte in the steps leading up to caseation can be as readily demonstrated if the tissues are examined at the proper stage of the lesion. The most conclusive demonstration of this can be made in avian tuberculosis because of the easy differentiation with certainty between the polymorphonuclear leucocyte and the mononuclear elements. The eosinophilic granules in the polymorphonuclear leucocyte of the fowl allow of this sure differentiation. Although there are no eosinophilic granules in the guinea-pig or human polymorphonuclear leucocyte, these cells can be identified with certainty until they are so closely packed together in the inflammatory reaction that cell outlines can no longer be determined.

Miller [11] and others have conclusively shown the existence of reticulum which is continuous with the surrounding tissue, as a constant feature of the well formed "epithelioid" tubercle. As long as this reticulum is intact, even if death of the mononuclear leucocytes occurs, it hardly seems possible that cavitation could be brought about. During the process of caseation, however, this reticulum may be more or less destroyed and its continuity with the surrounding viable tissue broken. Because of this fact it can readily be understood why caseous material in some cases is discharged to the outside when opportunity occurs and cavitation or ulceration results. The persistence of this reticulum, even in caseous material, would also explain why in other cases cavitation or ulceration is not produced. It would seem quite probable that the destruction of this reticulum is brought about by the polymorphonuclear leucocyte with its proteolytic enzyme rather than by the mononuclear leucocyte which appears to be very closely associated with the production of the reticulum in the mononuclear tubercle.

A certain parallelism between the lipoid content of pus and of caseous material would indicate that they are probably composed largely of the same cellular elements. According to the chemical analysis of dried pus by Hoppe-Seyler,[12] the lipoid content was

21.78 per cent and 22.34 per cent in two specimens. Bossart [13] reported the lipoid content of pure caseous material as 20.75 per cent of the dried stuff. The cholesterol content varied from one-third to one-fourth of the lipoid content in the caseous material, while in pus it was approximately one-third of the lipoid content. In the dried pus there is 7.2 per cent of lecithin and in dried caseous material there is 3.83 per cent according to an analysis by Schmoll and F. Müller.[14] While the lipoid content is not identical in pus and caseous material, there is sufficient similarity to suggest that their composition is quite alike. As the ages of the pus and caseous material chemically examined without doubt were different, the caseous material being the older, it would not be surprising if the lipoid content had differed more than the analysis showed.

From the study of the inflammatory reaction early in the process of caseation in the guinea-pig, it is apparent that the polymorphonuclear leucocytes are injured before disintegration takes place. One can easily find mononuclear leucocytes which have phagocytized from one to half a dozen well formed polymorphonuclear leucocytes. Stewart, Long and Bradley [15] have recently reported this observation in tuberculin and reinfection reactions. This phenomenon appears in the areas of primary infection as well as in the reinfection and tuberculin reactions. This picture is quite comparable to the phagocytic action which the mononuclears display for lymphocytes and erythrocytes in typhoid fever. This early injury to the polymorphonuclear leucocyte might explain why autolysis and softening do not take place in the process of caseation as in an ordinary abscess. Several investigators have failed to find any evidence of autolytic ferments in caseous material. Jobling and Petersen [13] suggest that this inhibition of autolysis is due to the presence of unsaturated fatty acids derived from the tubercle bacillus. As the autolytic ferment of the polymorphonuclear leucocyte requires an alkaline medium to enable it to bring about liquefaction, it would seem plausible that an acid reaction might be the cause for the failure of the leucocyte to bring about liquefaction as it does in a pyogenic infection. It would seem that some such phenomenon rather than a marked difference in the cellular content of caseous material and pus would be a logical explanation for the difference between caseation and abscess formation.

Conclusions

Caseation, cavitation and ulceration in tuberculosis appear to be due to the active participation of the polymorphonuclear leucocyte in the inflammatory reaction to the tubercle bacillus.

The process of caseation appears to be the same in naturally acquired tuberculous infection in fowl and man and in laboratory animals experimentally infected.

The presence of the polymorphonuclear leucocyte in tuberculous inflammation is not an indication of secondary infection with pyogenic bacteria. It is an indication of the production by the growth or death of the tubercle bacillus or by the action of the tubercle bacillus upon the tissue in the tubercle, of a substance which strongly attracts the polymorphonuclear leucocyte.

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EXPLANATION OF PLATES

Plates 55–61

Fig. 1. Guinea-pig spleen. Mononuclear tubercle in histologic unit of the pulp. Twenty days after groin inoculation. The tubercle is composed of mononuclear leucocytes, probably of reticulo-endothelial origin. In such a tubercle lymphocytes and polymorphonuclear leucocytes are extremely rare. No caseation. x 350.

FIG. 2. Guinea-pig spleen. Twenty-five days after groin inoculation. This tubercle is in the same anatomic position as the one in Fig. 1. Note the considerable number of polymorphonuclear leucocytes in the central portion. Lymphocytes are rare. There is no evidence of caseation. x 350.

FIG. 3. Guinea-pig spleen. Thirty days after inoculation in the groin. The lesion is in a histologic unit of the pulp. The dark mass is composed very largely of polymorphonuclear leucocytes. Lymphocytes very rare. No evidence of caseation. x 350.

FIG. 4. Guinea-pig spleen. Thirty-five days after groin inoculation. The lesion is in the outer portion of a Malpighian corpuscle. The dark mass is made up largely of polymorphonuclear leucocytes. Caseation is beginning as is shown by the hazy appearance of the tissue at the periphery. Lymphocytes are present in small numbers in the tissue around the caseating area. x 350.

FIG. 5. Guinea-pig spleen. Thirty-five days after groin inoculation. The lesion is in a histologic unit of the pulp. There is considerable nuclear "dust" in the center with typical caseation in the periphery. Note the predominance of mononuclear leucocytes around the area in the periphery of the caseous material. Several of these cells show elongated nuclei, presumably in the process of migrating into the caseous area. Lymphocytes are more numerous than in the preceding figures. Polymorphonuclear leucocytes while present are few in number. x 350.

FIG. 6. Avian tuberculosis. Typical mononuclear tubercle in turkey liver. Natural infection. Acid-fast stain. Corresponds to Fig. 1. x 350.

FIG. 7. Avian tuberculosis. Natural infection. Spleen of chicken. The dark staining cells are polymorphonuclear leucocytes. There is beginning caseation. x 350.

FIG. 8. Avian tuberculosis. Natural infection. Spleen of chicken. More marked accumulation of polymorphonuclear leucocytes than Fig. 7. This corresponds to Fig. 3. There was no evidence of caseation in the entire lesion which was serially sectioned. x 350.

FIG. 9. Avian tuberculosis. Natural infection. Liver of chicken. The dark area in the center is a compact mass of polymorphonuclear leucocytes. There is beginning caseation at the periphery. Note the vacuolated mononuclear leucocytes surrounding the area of polymorphonuclear leucocytes. This lesion corresponds to Fig. 4. x 350.

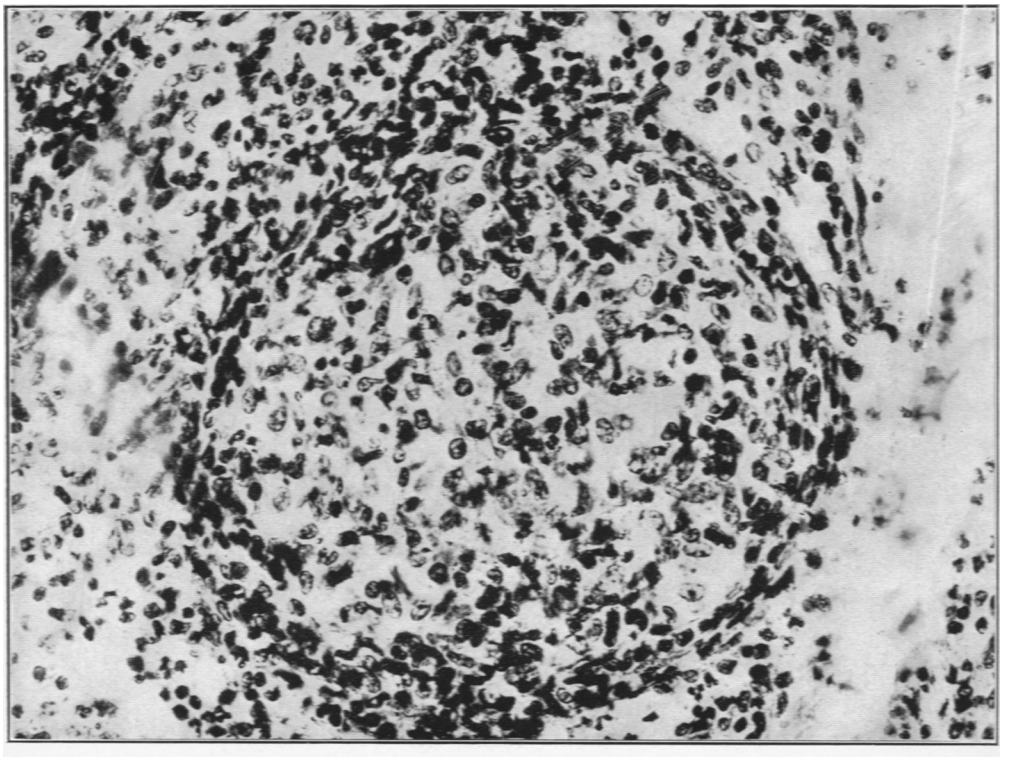
FIG. 10. Avian tuberculosis. Natural infection. Turkey liver. The lesion to the left shows old caseation and corresponds to Fig. 5. The lesion to the right shows a much greater accumulation of polymorphonuclear leucocytes but is about the same stage as Fig. 9. The polymorphonuclear leucocytes do not appear to be attracted by the older caseous material. Note the sharp line of demarcation between the two lesions. x 100.

FIG. 11. Human tuberculosis. Human spleen. Mononuclear tubercle. There is no caseation. Note the zone of polymorphonuclear leucocytes in the periphery of the tubercle. x 200.

FIG. 12. Human tuberculosis. Fallopian tube. Compare with Fig. 3. Note the elongated polymorphonuclear and mononuclear leucocytes, presumably migrating into the tubercle. There is no evidence of caseation. Lymphocytes are very rare. x 350.

FIG. 13. Human tuberculosis. Lymph node. The edge of a large lesion corresponding in age to Fig. 4. There is a lymphocytic zone above, a mononuclear zone in the middle and polymorphonuclear leucocytes below. Compare the nuclear shapes below with the nuclei of the polymorphonuclear leucocytes in Fig. 12. x 350.

FIG. 14. Human tuberculosis. Kidney. A small area of caseation. Compare with Fig. 5. Note the mononuclear leucocytic zone around the area of caseation, the nuclear "dust" in the area of caseation and the rarity of polymorphonuclear leucocytes at this stage. x 350.



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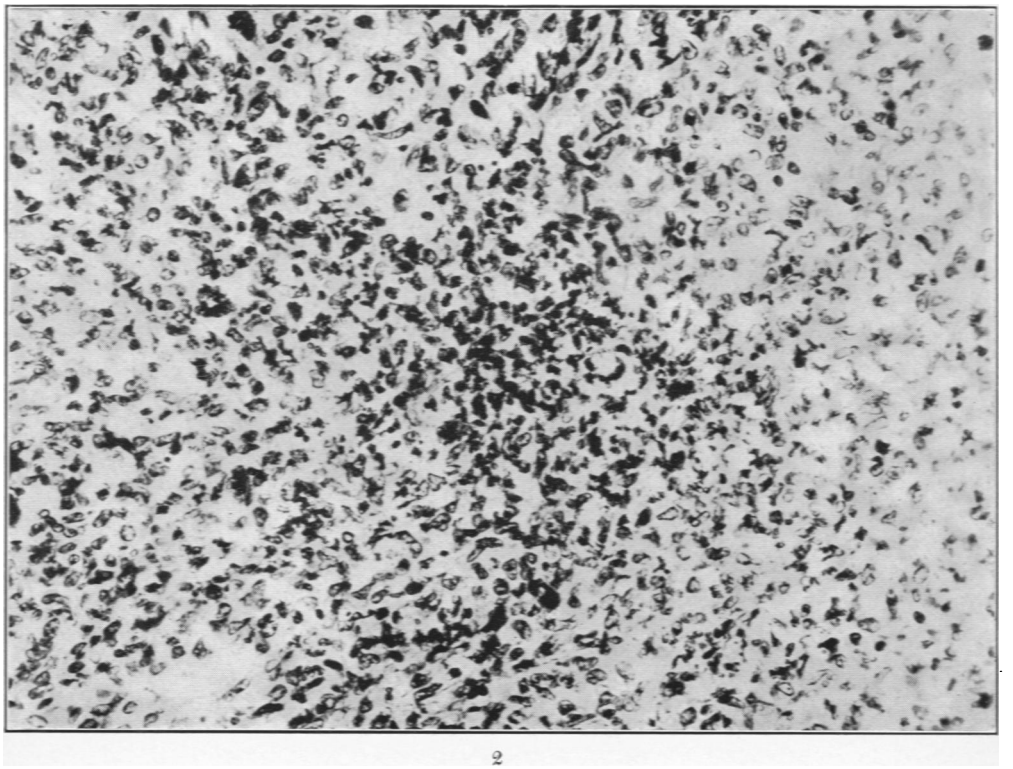
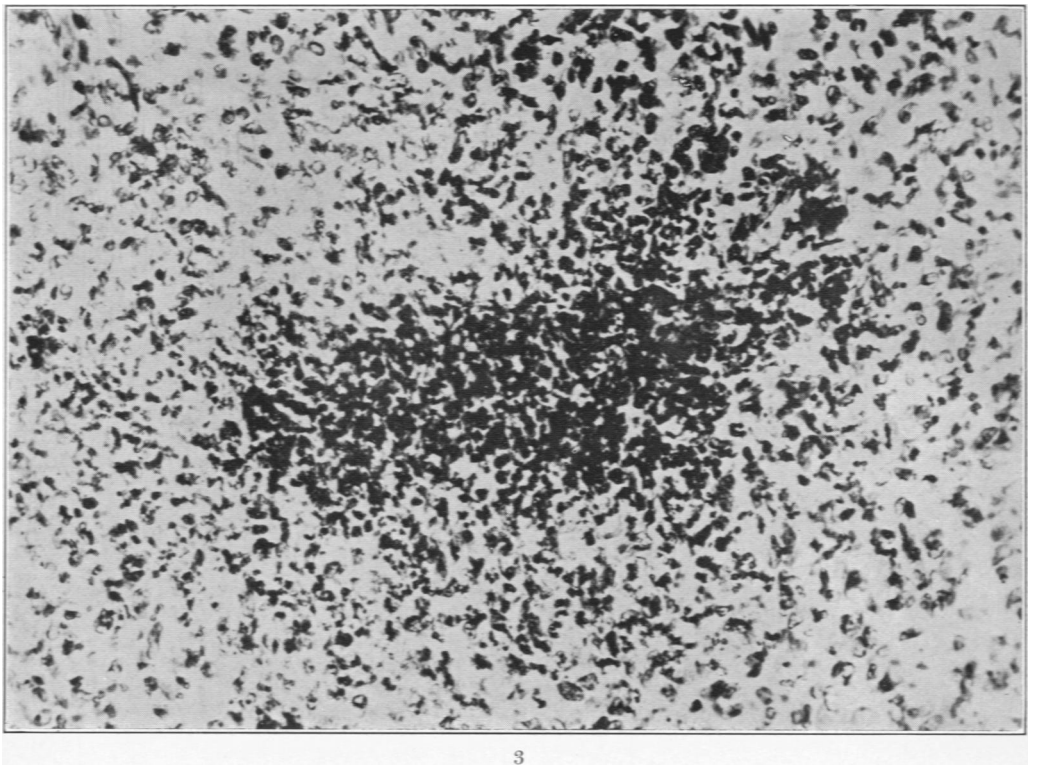


2

Medlar Caseation in Tuberculosis



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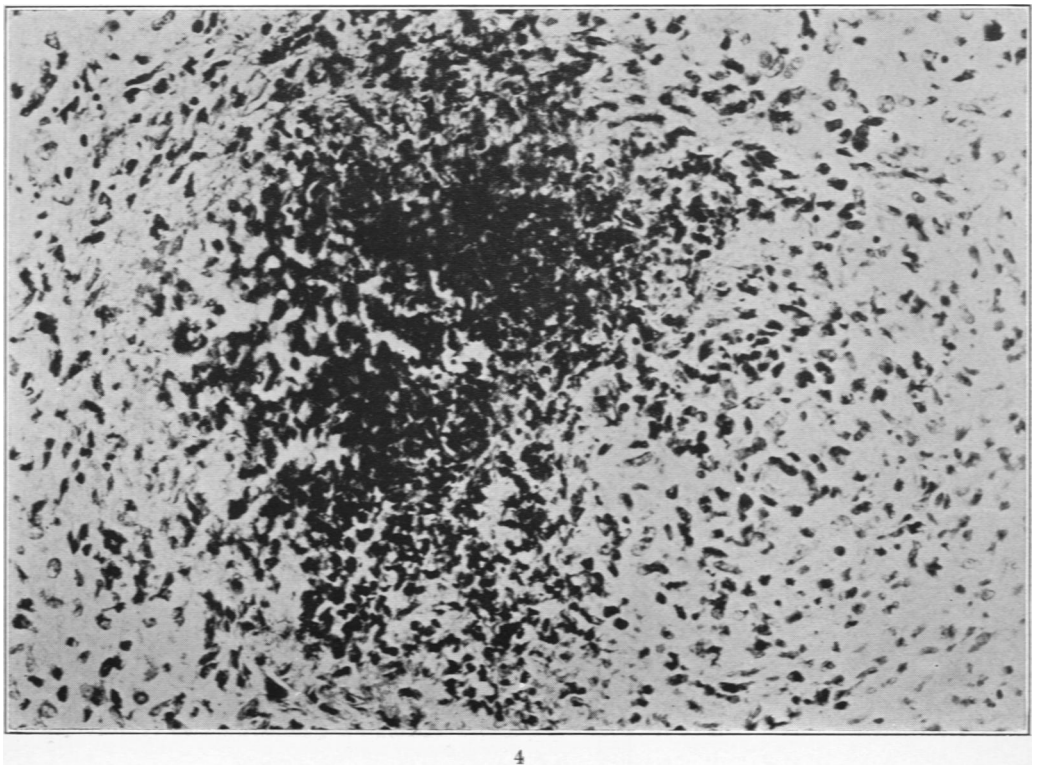

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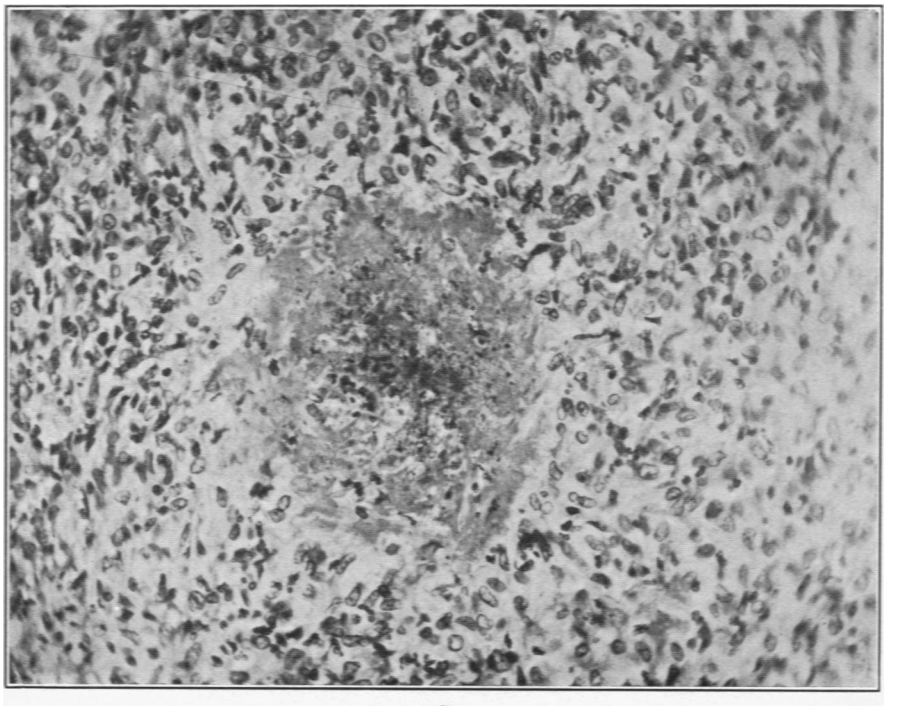
Medlar Caseation in Tuberculosis



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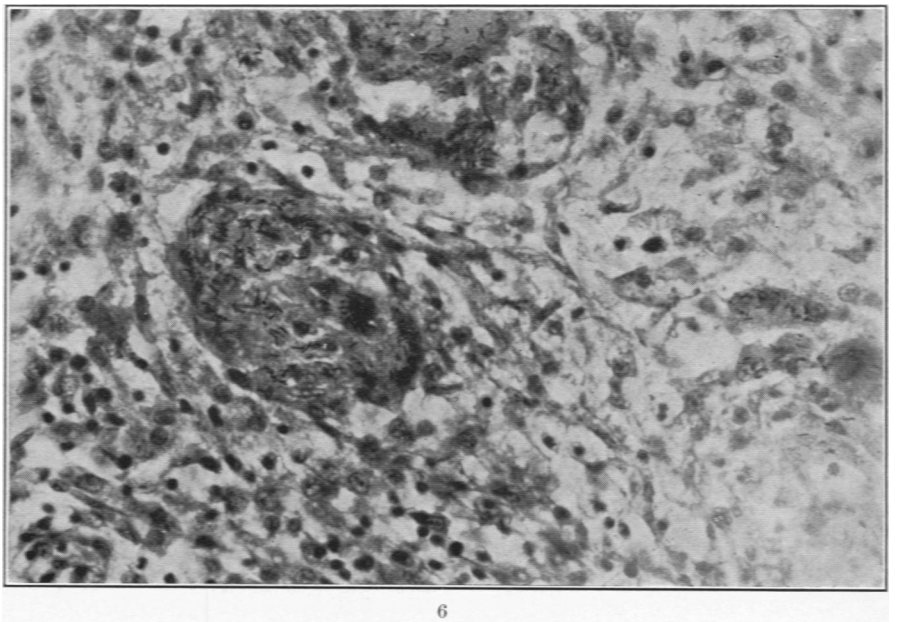

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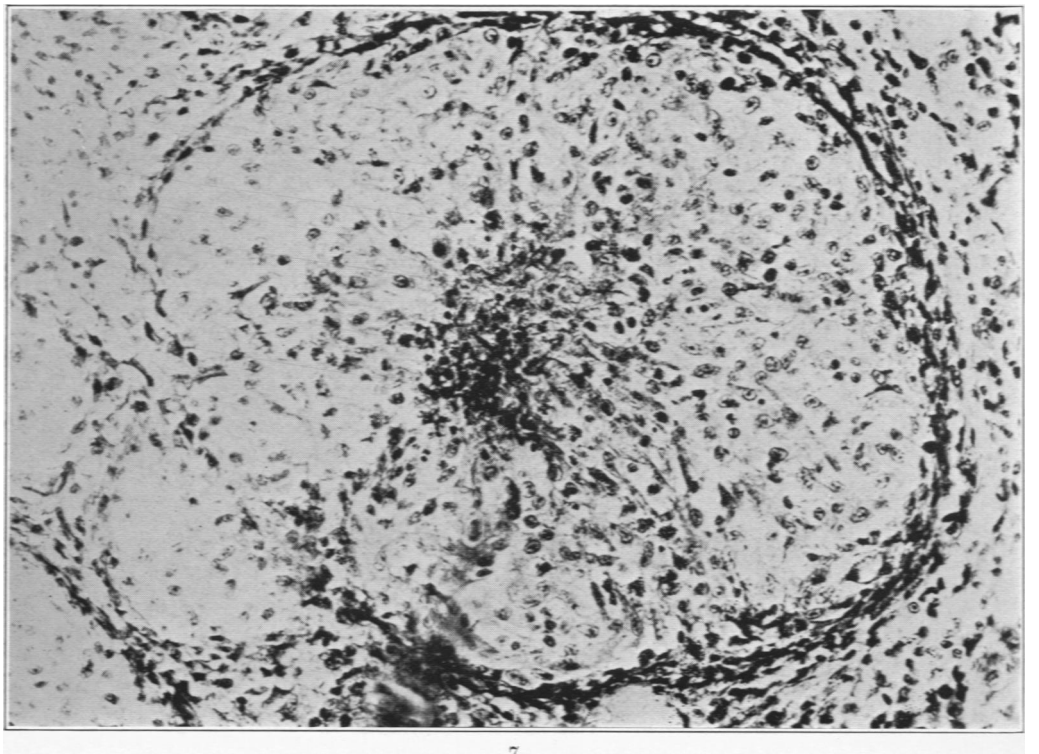

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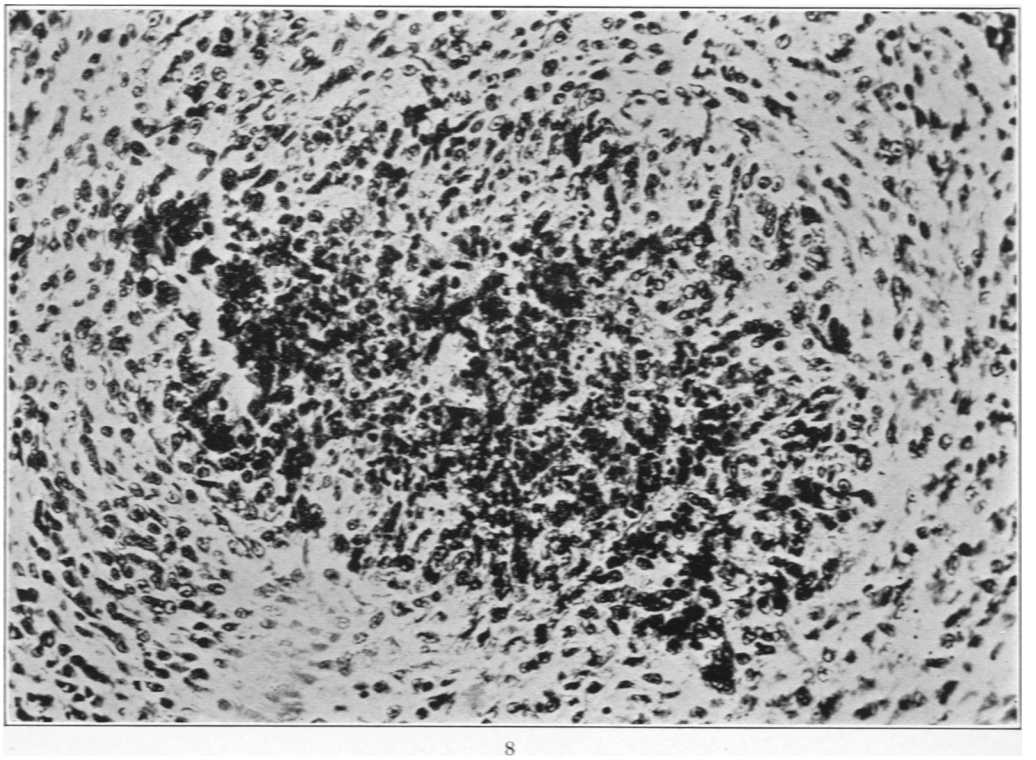

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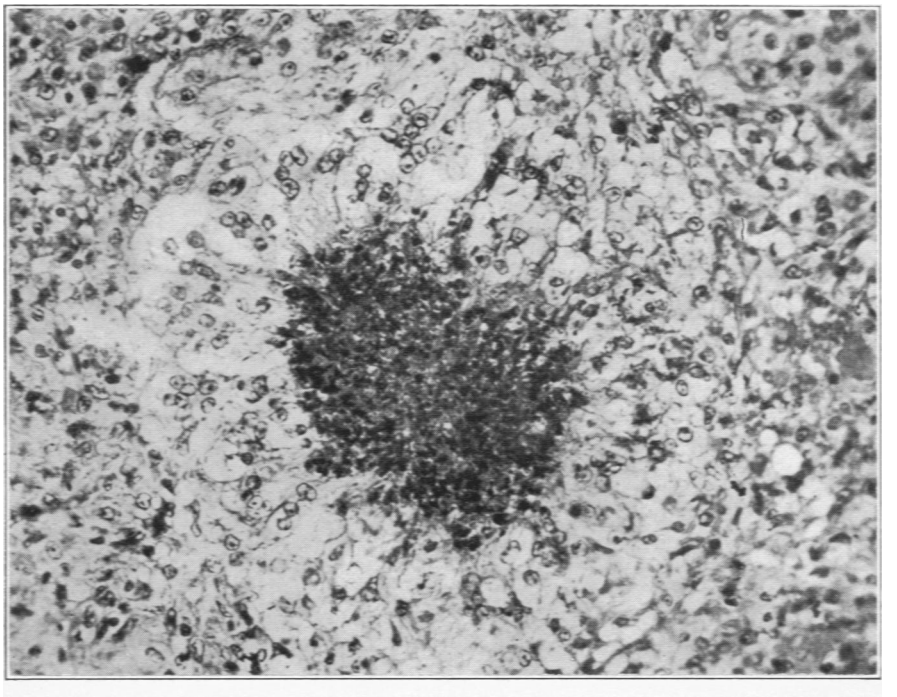
Medlar Caseation in Tuberculosis



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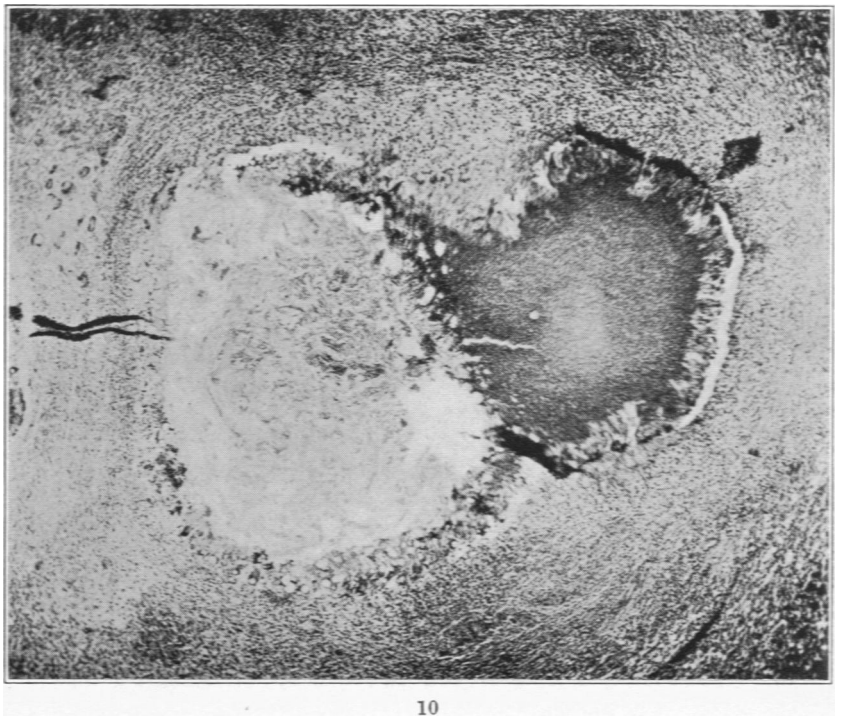

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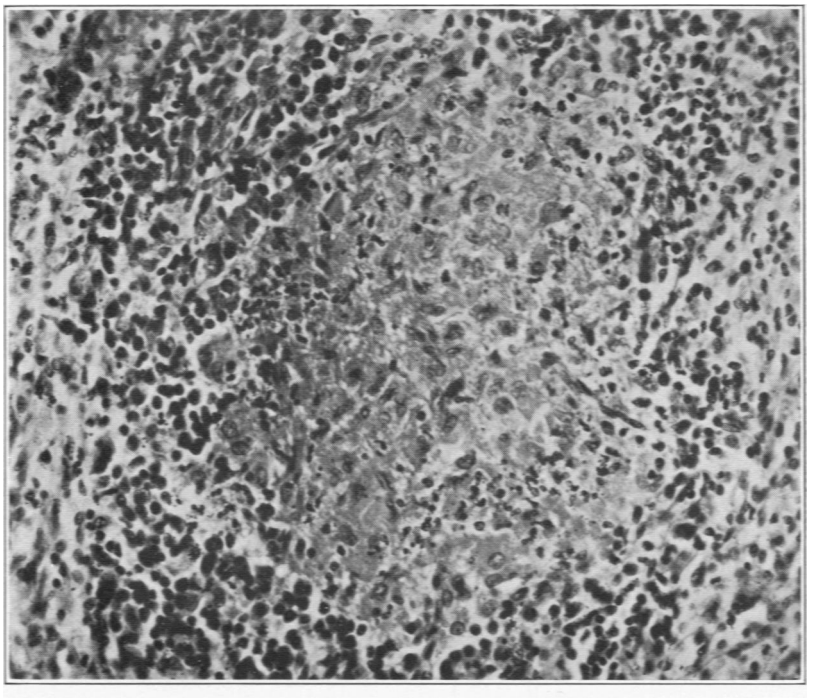
Medlar Caseation in Tuberculosis



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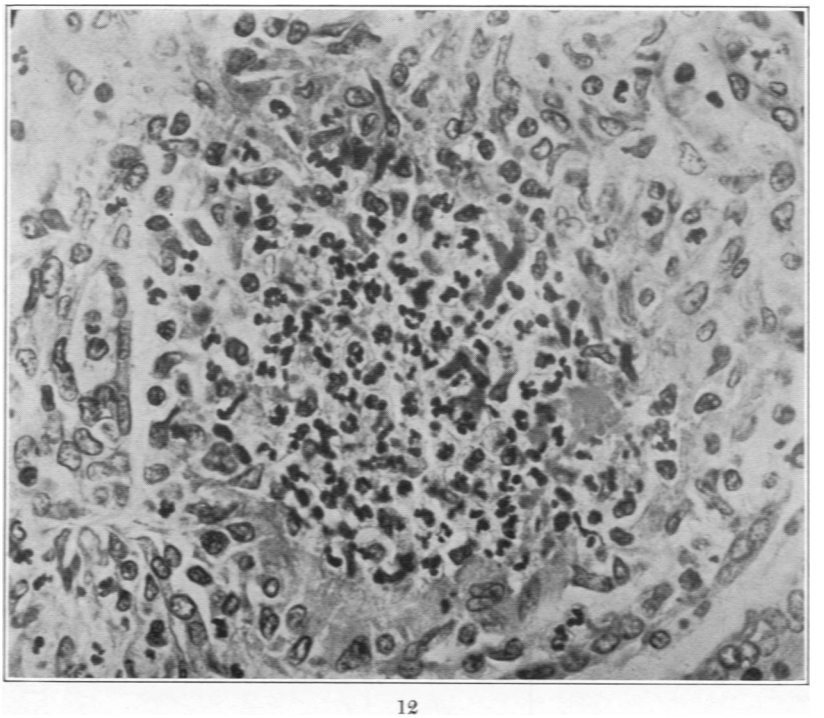
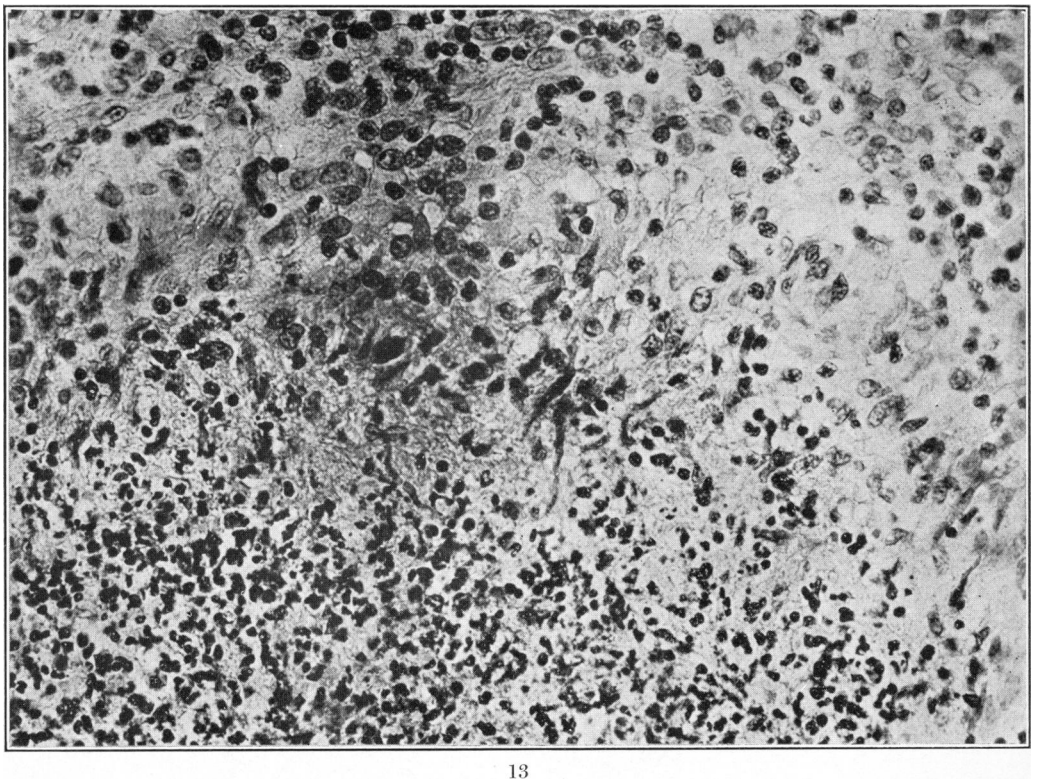


12

Medlar Caseation in Tuberculosis



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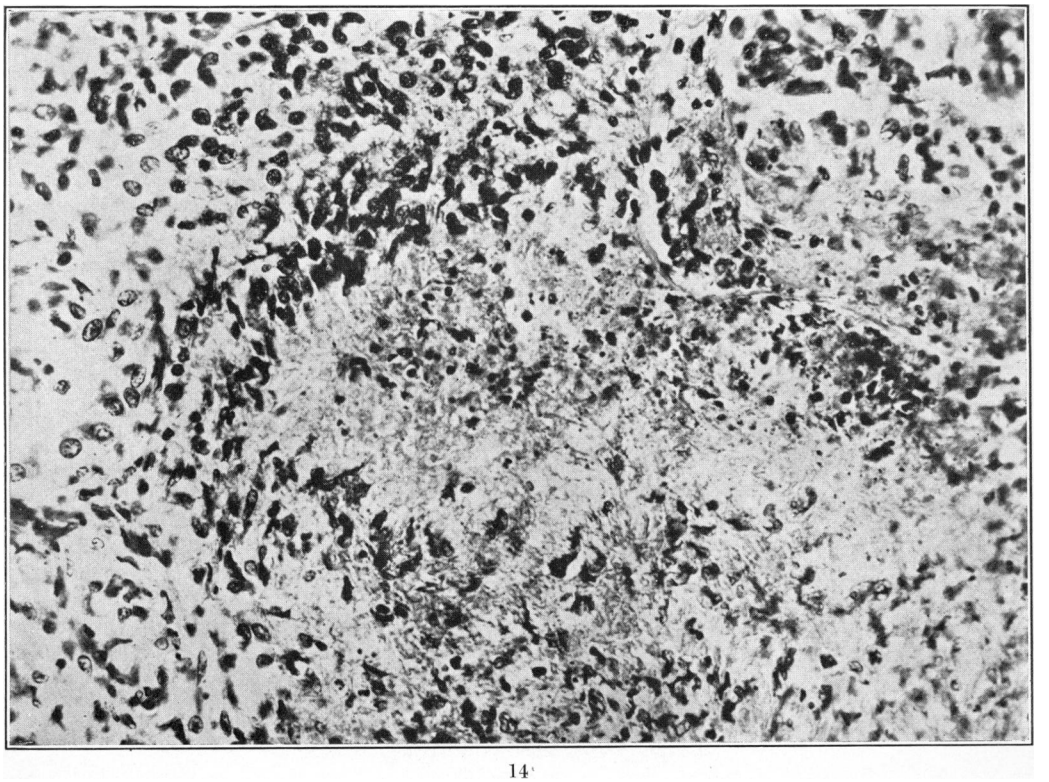

14

Medlar Caseation in Tuberculosis