THE PATHOLOGY OF GRANULOMA VENEREUM *

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Granuloma venereum, a disease widespread in tropical and subtropical countries, is best defined as an infectious granuloma of the pudenda. The question whether it is transmitted by sexual contact and should be considered a venereal disease is still undecided, but the experimental work of DeMonbreun and Goodpasture makes its traditional venereal nature appear at least doubtful.

In a previous study we discussed the incidence of granuloma venereum in various parts of the United States and, to some extent, were able to confirm Harris' statement that the disease seems to travel from the large seaports toward the inland sections along the great waterways. Supplementing Fox's report, we have collected 251 cases of granuloma venereum from the literature. This figure, however, is certainly not indicative of the true incidence of the infection in the United States, nor is our recent report of 294 cases observed over a period of 5 years in New Orleans a true gauge of the incidence of the disease in that community. Lack of cooperation on the part of afflicted patients, who generally belong to the lowest social strata, prevents exact diagnosis in many instances.

During studies of the various manifestations of the disease we have had occasion to examine not only surgically removed specimens and material from autopsied cases, but also, through the cooperation of the hospital staff, numerous biopsy specimens. It is the histopathological findings in this material that we wish to discuss in this commentation.

PATHOLOGICAL ANATOMY

The numerous classifications of the various lesions of granuloma venereum are based principally on their morphological character without consideration of their underlying pathogenesis. In our clinical study we have adopted, in a somewhat modified form, the purely descriptive terms applied to the lesions by Halty and have classified these as nodular, serpiginous, necrotic, hyper-

* Received for publication July 26, 1937.

trophic and cicatricial. From the standpoint of their pathological variations, however, we differentiate three groups of lesions: (1) those caused primarily by the infectious agent; (2) those caused principally as a result of a peculiar tissue reaction of the host to the infection; and (3) those caused by complications following the infection.

The nodular and serpiginous types of lesions, which were observed in 157 or 53.4 per cent of our cases, belong to the first pathological group. The nodular lesions are usually only the beginning stage of infection and undergo further changes which lead to development of the serpiginous ulcer, the most common and most typical manifestation of the disease. The lesion is characterized by a soft, easily bleeding granulation tissue which breaks through the epithelial lining of the skin and mucous membrane and shows a remarkable tendency towards superficial spread along the moist folds of the inguinal and pudendal regions (Manson). These lesions are only a few mm. deep and usually show very little suppuration. The exudate is serosanguineous, contains the infectious agent and spreads the disease by auto-inoculation. The rapidity with which the infection spreads varies considerably and healing may be observed in some portions of the lesion while other parts show continuous encroachment upon sound tissue. During the course of the disease considerable areas of the skin and mucous membranes are usually covered with these ulcerative lesions, with resultant severe anatomical mutilation of the genitalia and the perineum. The healing process is slow and the scars produced are atrophic with partial depigmentation of the skin and permanent loss of pubic hair.

The second group of pathological manifestations is the result of a peculiar host reaction to the infectious agent leading to hypertrophic and keloid-like lesions. These were present in 82 or 27.9 per cent of our cases. The surfaces of the hypertrophic lesions may be compared to the relief map of a mountainous country, with depressions between areas of piled up "mountains of tissue" (Harris). In consistence the lesions are firm and rather elastic, the overlying skin usually showing scars of previous ulcerations. There is often very little difference between this type of lesion and the true cicatricial or keloid-like lesion. In the latter there is an apparent overproduction of firm indolent tissue which replaces the

ulcerations. Our attention was first called to this type of lesion by complaints of patients that the scars from previous ulcerations were inclined to spread with gradual involvement of healthy parts in the keloid-like process. There is a distinct difference between this "spreading" type of scar and the usual atrophic and shrunken scar seen following ulcerative lesions. Our suspicion that we were dealing not with a healed stage of the disease but with a progressive lesion was further confirmed by the fact that histological examination showed the presence of Donovan bodies in the small nests of inflammatory cells embedded in the dense collagenous fibrous tissue obtained from such scars. Both the hypertrophic and the cicatricial (keloid-like) lesions show an excessive fibroblastic response of the host to the infection, usually developing rather early and inclined to progression. We believe that this lesion, observed rather commonly in the negro race, is due to an unexplainable constitutional peculiarity of the patient and not to chronic lymphatic obstruction, as claimed by Daniels. A further difference between the hypertrophic and keloid-like variety of granuloma venereum is found in the amount of intercellular collagenous substance present. In the hypertrophic form the amount is relatively small as compared to the mass of newly formed fibrocytes, while in the cicatricial lesion it is abundant.

The third group of pathological manifestations of granuloma inguinale consists of the lesions that occur as complications of the primary infection. The most frequent of such is secondary infection with an aerobic or anaerobic pyogenic or saprophytic genus. The onset of a virulent secondary infection is usually characterized by the appearance of toxic constitutional symptoms which are completely absent in the uncomplicated forms of granuloma venereum and by progression of the ulcerative process with the production of deep severe necrosis of soft tissues and even bone. During this stage Donovan bodies are generally not demonstrable, but there is an abundant mixed flora of secondary bacterial invaders. Here, the healing process results in severe mutilation of the genitalia with usual permanent impairment of their function. Fifty-five cases or 18.7 per cent of our series showed such deep ulcerations with necrosis and phlegmonous extension into the surrounding tissue. Two presented extragenital lesions, 1 case showing deep necrosis of the mouth and the structures of the neck with

secondary bronchopneumonia, the other a phlegmon of the gluteal region.

Histopathology

Fifty-six biopsies and 3 autopsies furnished the material for histopathological studies. In 3 cases a series of biopsies was obtained, enabling study of the evolution of the disease. Tissues were fixed in formalin, embedded in paraffin, sectioned and stained with hematoxylin-eosin, Wright's Gram's, and Giemsa's stains, and also by Mallory's aniline blue collagen stain.

In the very early or nodular type of granuloma venereum the epithelial lining of the skin does not appear to be interrupted, but there is distinct hypertrophy of the epithelium with offshoots from the papillae into the subcutaneous tissue (Gage). There is some edema in the papillary layers and infiltration of the corium of the skin, with polymorphonuclear leukocytes, eosinophiles and large monocytes (endothelial cells); these show no characteristic arrangement but seem embedded in a rather edematous matrix. With bacteria-revealing stains, numerous intracellular inclusion bodies — the so-called Donovan bodies — can be noted in the plasma of the large endothelial cells. On account of the pressure caused by infiltration the epithelium of the affected areas becomes thinned out and atrophic, exudate seeping through before the epithelial continuity is actually interrupted. Rapid proliferation of capillaries in the area of infiltration marks the beginning of the development of granulation tissue, which soon breaks through the epithelial lining of the skin to form the typical serpiginous lesions. Plasma cells, diffuse and in small groups, become increasingly prominent with progression of the lesion, and the leukocytes, which previously seemed to be the most important primary cellular response, are now found only at the surface. Large endothelial cells with numerous intracellular Donovan organisms are profuse between the capillary loops of the granulation tissue and are probably identical with the large foam cells described by Goldzieher and Peck as characteristic of this stage of the disease.

As the healing progresses, fibrocytes, which primarily were only sparsely scattered between the capillaries of the granulation tissue, become more abundant and, from the epithelial islands which have remained intact during the process of granulation tissue formation,

re-epithelialization of the surface begins. The scar tissue that repairs the serpiginous ulcer of granuloma inguinale usually shows a narrow epithelial lining with loss of all special structures of the skin and a moderate degree of subepithelial fibrosis. In the deep ulcerative processes, extensive necrosis with suppuration and phlegmonous extension may be noted. At the bottom of the necrotic areas there is sometimes fibrosis with interspersed nests of plasma cells and monocytes containing Donovan bodies. Bacterial stains reveal an abundant flora including *Borrelia vincenti* and fungi. Histological examination of the hypertrophic and the keloid-like lesions reveals marked fibrosis with numerous small nests of plasma cells and endothelial cells. The epithelium appears normal in thickness or shows slight hyperplasia. The walls of the larger vessels are thickened and their lumens narrowed. The lymph vessels are sometimes slightly dilated, but they are never the site of inflammatory changes as seen in elephantiasis caused by lymphogranuloma inguinale. The collagenous substance is extremely abundant in the hypertrophic cicatricial lesions. In the small collections of inflammatory cells Donovan bodies can be found, thus giving evidence of the activity of the lesion.

The Causal Agent

Although granuloma venereum has been known for over half a century, its causal agent has not yet been definitely established. Formerly identified with lues (Maitland, MacLennan), rhinoscleroma (Goodman), tuberculosis (LeDantec), and various other infections, since 1904 granuloma venereum has been definitely linked with an organism described by Donovan as Piroplasma and considered by him protozoal in nature. Martini in 1913, and Aragao in 1917, cultivated this organism on Sabouraud's medium and Aragao gave it the name "Schizomycete kalymmatogranulomatis." Castellani and Mendelson succeeded in growing an encapsulated bacillus that showed a close morphological relation to the Donovan organism and which was identified culturally as belonging to the group of *Aerobacter aerogenes*, genus *Encapsulatus*, Castellani and Chalmers. However, they do not believe this to be the causal organism. Aragao denied the identity of any bacillus belonging to the group of *Klebsiella* with the *Calymmatobacterium*, believing that the latter has never been cultivated. Organisms not

definitely classified but showing characteristics similar to the ones obtained by Castellani were grown by Poindexter, and by Goldzieher and Peck. DeMonbreun and Goodpasture confirmed Castellani's findings by growing organisms belonging to the aerogenous group from human lesions. Although they produced the disease by injecting human material into monkeys, they failed to do so with cultures of organisms obtained from such material. Campbell, in criticising the work of McIntosh, states very emphatically that, to date, no lesions have been produced with organisms cultivated from venereal granuloma. In the past year, Menon and his co-workers have critically analyzed the bacterial flora present in venereal granuloma. In addition to the Donovan organism, they have noted in human cases various spirochetes and fusiform bacilli, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Corynebacterium diphtheriae* and numerous types of staphylococci. These Indian investigators have succeeded in isolating the Donovan organism in pure culture from 12 out of 14 cases, and believe it to be related to *A. aerogenes*. Its inoculation in young rats and mice resulted in the production of distinct pathological lesions. Although the majority of recent authors seem to agree that an organism belonging to the *Klebsiella* group can be recovered from a large percentage of lesions present in granuloma inguinale, its etiological significance is still debated.

We have been able to observe the Donovan organism in practically all tissue sections stained by Wright's method in 60 to 80 per cent of smears obtained from the lesion. The nucleus of the capsulated body resembles a small curved bacillus, shows one or two terminal swellings simulating polar bodies and may, therefore, readily appear as "diplococcoid bodies" (Randall, Small and Belk). In acute fulminating lesions the majority of the organisms are not encapsulated and can easily be recognized extra- and intracellularly. In the large mononuclear cells they may fill vacuolar spaces in small clumps or clusters, or may be present in such numbers as to obliterate completely the outline and structure of the cells. We have regularly found plastin bodies, as described by Goldzieher and Peck, and they have been of considerable help in diagnosis, although we do not understand their significance. Our attempts to cultivate an organism from the human lesions have been successful in 8 out of 11 cases. The organism, similar to that

isolated by DeMonbreun and Goodpasture, belongs to the aerogenes group, but we have failed, so far, to produce any pathological lesions in laboratory animals comparable with the human lesion.

Summary and Conclusions

1. The pathology of granuloma inguinale has been studied in a series of 294 cases observed over 5 years at the State Charity Hospital of Louisiana at New Orleans.

2. The typical manifestations of the disease embrace nodular lesions and serpiginous ulcerations, which have a tendency to spread along the moist folds of the pudendal region, healing with the formation of atrophic scars.

3. Atypical manifestations are produced by unexplained increased fibroblastic reaction of the host leading to hypertrophic and cicatricial (keloid-like) lesions, which must be considered active stages of the infection.

4. Secondary infection produces serious ulcerative necrotic lesions which may severely mutilate the infected parts and give rise to sepsis and toxemia.

5. Histopathological study of biopsy material and tissue obtained at autopsy reveals that the stage of infiltration is quickly followed by the stage of granulation, during which the epithelial lining of the skin or mucous membrane is perforated by a vascular granulation tissue. Donovan organisms can be demonstrated in the infected tissue during all stages of the infection.

6. Search for a causal agent has resulted in the isolation of an organism belonging to the *Klebsiella* group. Inoculation of various laboratory animals with this organism has failed to incite lesions comparable to the disease in the human, although such lesions have been reported as produced by inoculation of material derived from human cases.

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DESCRIPTION OF PLATES

PLATE II

FIG. 1. Male negro, aged 25 years. Multiple nodular lesions of 3 weeks duration.

FIG. 2. Male negro, aged 32 years. Bilateral serpiginous ulcers of 4 months duration.

FIG. 3. Male negro, aged 37 years. Cicatricial lesion with progressive mutilation of penis and scrotum of 3 years duration.

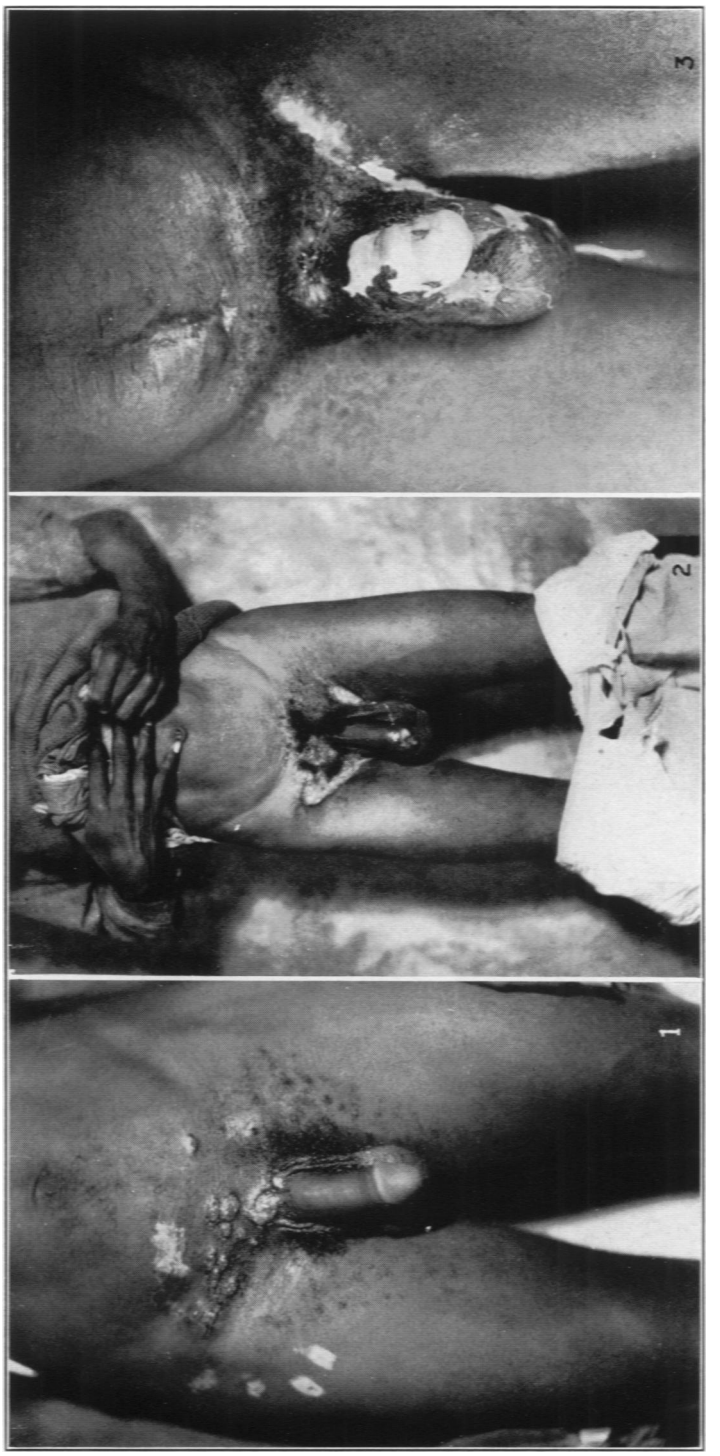

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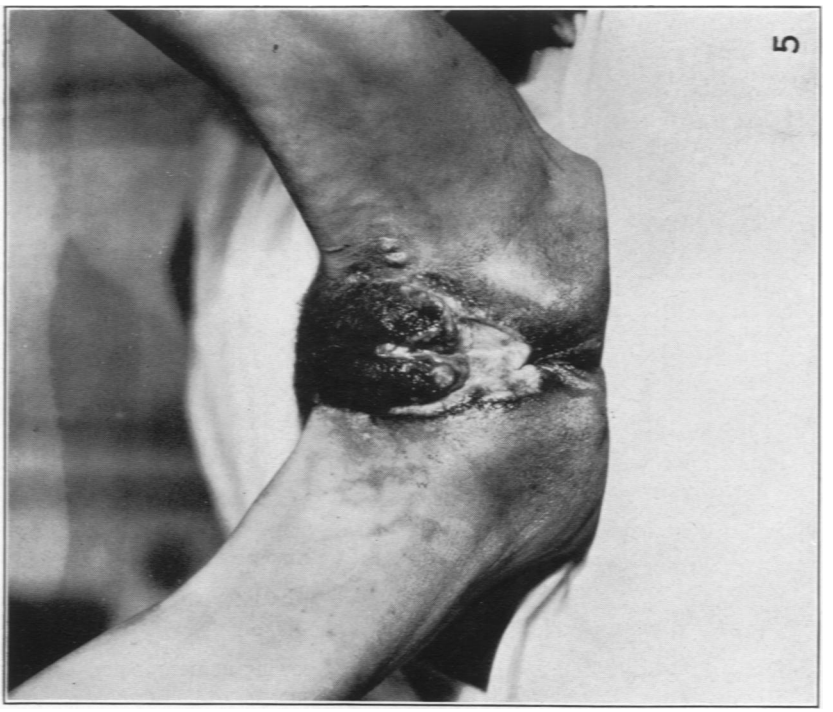
PLATE 12

FIG. 4. Negress, aged 28 years. Hypertrophic lesion involving labia and mons veneris of 1 years duration.

FIG. 5. Negress, aged 52 years. Deep ulceration with necrosis of entire perineum of 8 months duration.



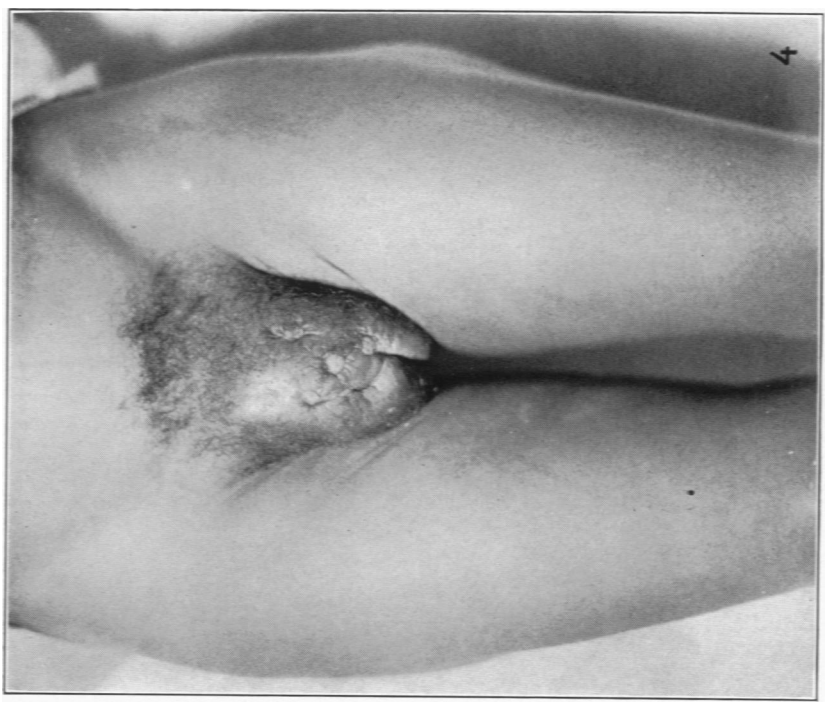


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PLATE 13

FIG. 6. Section through a nodular lesion showing initial proliferation of epithelium with subepithelial infiltration.

FIG. 7. Section through the margin of a serpiginous ulceration showing atrophy of the epithelium with marked edema and exudation.

FIG. 8. Section through the same lesion 3 weeks later showing development of a marked vascular granulation tissue.

FIG. 9. Section through a cicatricial lesion showing numerous active foci of the infection embedded in collagenous tissue.

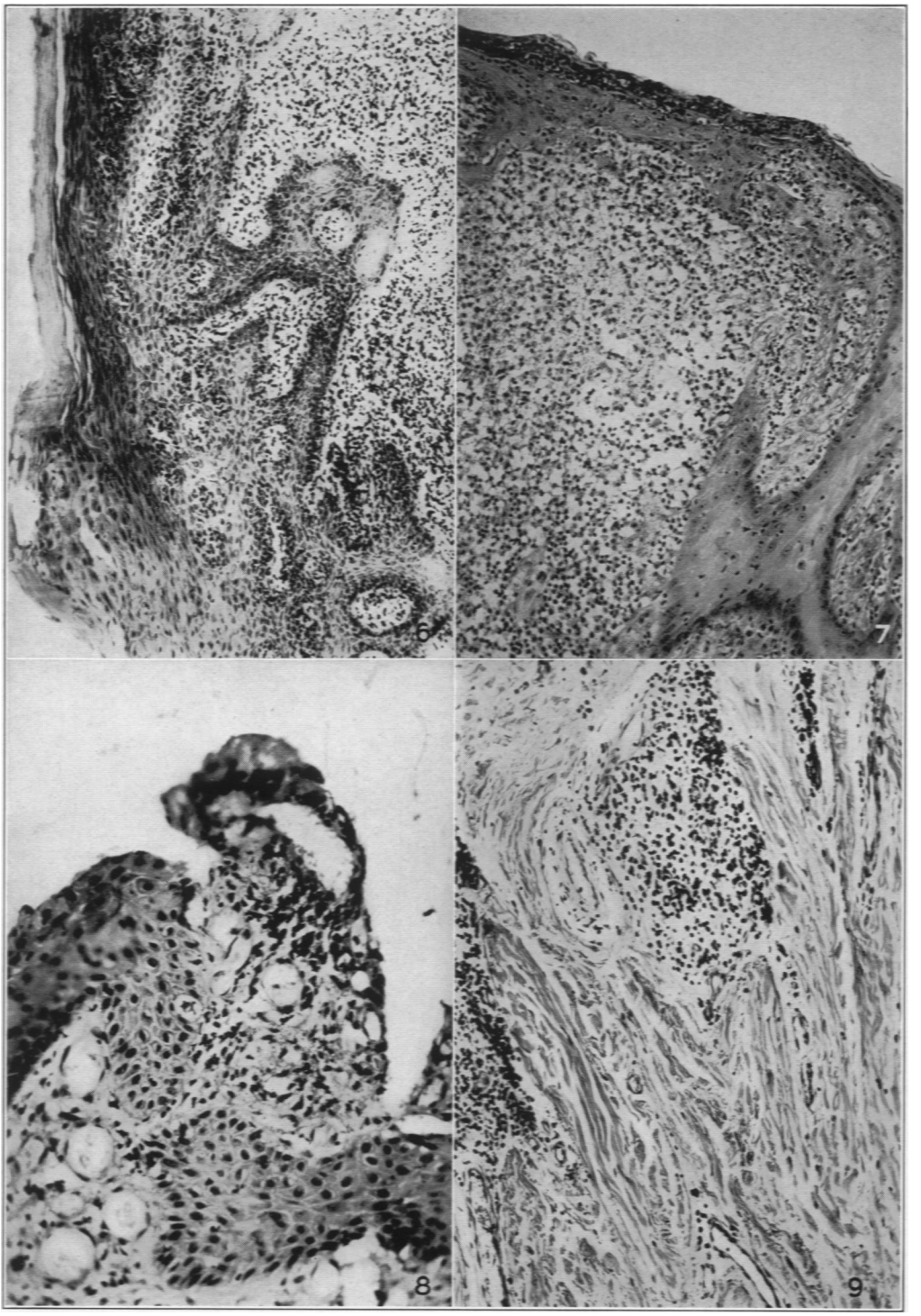

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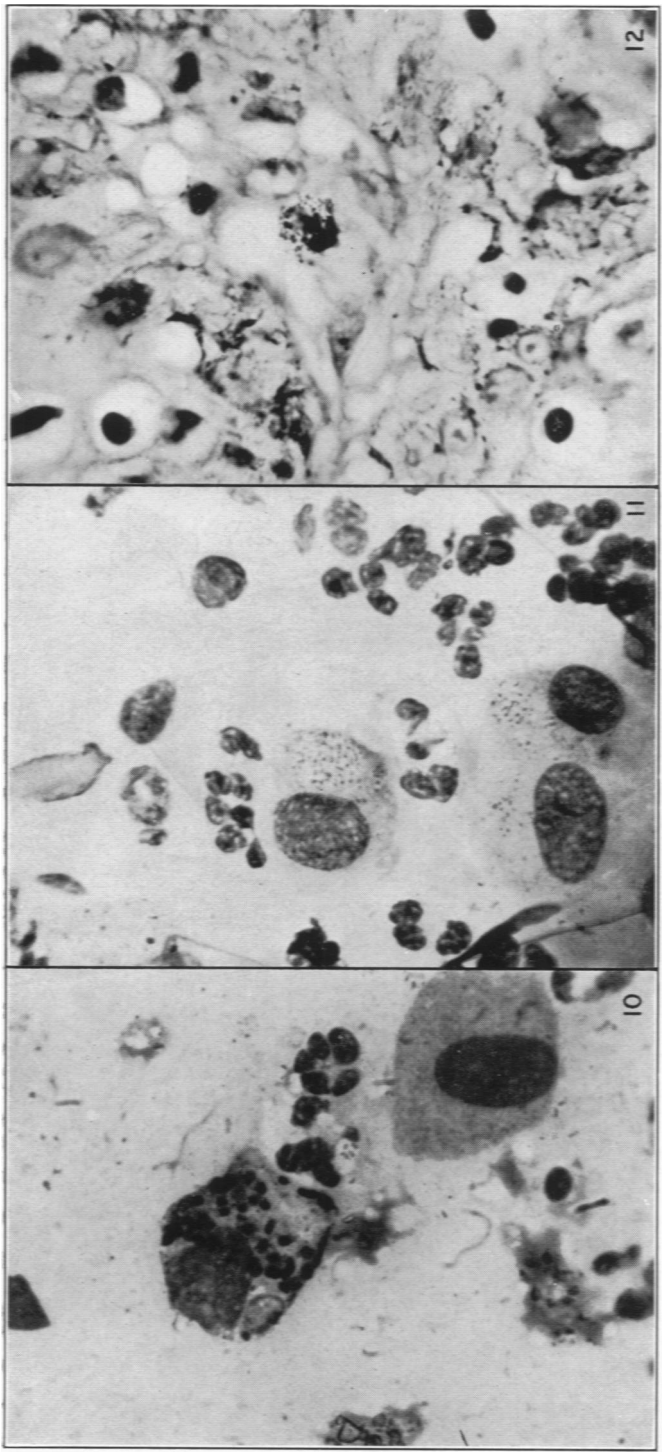
Plate 14

Fig. 10. Smear from a serpiginous ulcer stained with Wright's stain. Numerous Donovan bodies are present in the plasma of a large monocyte.

Fig. 11. Smear from an acute ulcerative lesion stained with Wright's stain showing numerous non-encapsulated organisms growing in the plasma of monocytes.

Fig. 12. Section through a cicatricial lesion stained with Wright's method demonstrating numerous encapsulated and non-capsulated organisms in the plasma of an endothelial cell.



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