# THE HISTOPATHOLOGY OF ACUTE MUMPS ORCHITIS *

EDWARD A. GALL, M.D.
*(From Bethesda Hospital, Cincinnati 6, Ohio)*

Orchitis developing in association with mumps is universally recognized as a prevalent concomitant of this disease.[1] Frequency of occurrence varies with age and with each epidemic. With the exception of encephalomyelitis,[2] it is probably the most serious complication of the mumps syndrome. The possibility of residual atrophy with sterility lends particular interest to the malady.[1]

Despite the interest and attention which have been directed to the disease, there is comparatively little knowledge regarding the underlying pathologic lesion or its mode of development. This is not surprising in view of the low mortality rate, the self-limited character of the process, and the infrequency with which surgical therapy has been invoked. Stolz,[3] Reuscher,[4] Hall,[5] and Malassez [6] have described the late lesions appearing in chronic orchitis. Only in the case described by Manca [7] and in the two cases recorded by Smith [8] is there information pertaining to acute mumps orchitis in the human being. Findlay and Clarke [9] observed the testicular lesions in monkeys with experimental mumps.

In the course of a previously reported epidemic of mumps among military personnel,[10] the procedure of orchidotomy as suggested by Wesselhoeft and Vose [11] was carried out by surgeons upon approximately 85 patients with orchitis. The proponents of the method believed that incision through the tunica albuginea testis would serve to relieve intratesticular tension and thus avoid the sequelae of necrosis and atrophy. In carrying out this procedure it was noted that parenchymatous substance immediately bulged through the incised capsule. Accordingly, minute fragments were removed for histologic study.

Seventy-five such fragments, none of which exceeded 0.4 cm. in diameter, were found to be suitable for histologic study. Since this form of therapy was considered to be indicated only early in the course of the disease, none of the material received represented the lesion beyond the fifth day. The majority of the patients were orchidotomized within 48 hours of the onset of symptoms. One additional patient with mumps complicated by bilateral orchitis and femoral thrombophlebitis succumbed to massive pulmonary embolism 11 days after the onset of orchitis. Material from both testes obtained at autopsy in this case

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and the 75 specimens obtained for biopsy serve as the basis for this report.

In most of the fragments studied, a strip of tunica albuginea was included with the parenchymatous tissue. In 18 instances there were portions of extratesticular and extra-epididymal appendages included. With one fragment accidentally, and in the testes from the necropsied case, there were portions of the epididymis available for study. Zenker's fluid was utilized as a fixative for the autopsy material and 10 per cent formalin for the biopsy tissue. Sections were cut in paraffin and stained with hematoxylin and eosin. Connective tissue stains and examination for bacteria and inclusion bodies served no additional purpose.

## Histologic Observations

Despite the fact that all but one of the specimens were obtained within 5 days of the onset, there was nevertheless a wide variation in the extent and intensity of involvement. In view of the rapidity with which the disease reached its peak of clinical intensity, this variation appears understandable. The telescoping of range of transition within a brief period would naturally permit a rapid change in the nature of the lesion. Under such circumstances it was impossible to establish a consistent correlation between clinical duration and the character of the lesion. In part, this was due to the variation in intensity of the disease in different patients. Moreover, it seemed evident also that scrotal pain was not an infallible criterion of the onset of orchitis, for in certain instances it resulted from epididymitis or inflammation of extratesticular appendages. Such a condition, masking or mimicking orchitis as it might, precludes the acceptance of pain as an index of either duration or intensity.

On histologic grounds, however, there seemed reasonable evidence of a divisible developmental trend. Consistent microscopic features appeared to justify the assumption that the acute lesion in the testis was susceptible to subdivision into four fairly distinctive phases.

### *Testis*

In 6 specimens of testis it was impossible to detect any abnormality whatever (Fig. 1). There was normal structural arrangement and no evidence of either inflammation or edema. In each of these patients symptoms had been present for 24 hours or less, and it is presumed that they may have arisen either from involvement of the extratesticular appendages or from intratesticular foci not included in the sections.

The earliest abnormality recognized in 31 preparations was interstitial edema. This was manifested in the tunica albuginea by separa-

tion of connective tissue fibers and in the parenchyma by broadened interstices, fraying and floating of connective tissue elements, precipitated fluid, and separation of seminiferous tubules (Fig. 2).

Germinal epithelium exhibited minor degenerative changes such as cytoplasmic swelling, increased depth of nuclear staining, and desquamation of surface epithelium into the lumen. Spermatogenesis, however, appeared to proceed in unimpeded fashion.

The next (second) phase, exemplified by 10 specimens, was characterized by definite, but relatively slight, reactive change. There was a considerable degree of vascular dilatation and engorgement, particularly in the deep portion of the tunica albuginea and in the loose fibrillar zone intermediate between capsule and parenchyma. Small numbers of lymphocytes were clustered about capsular blood vessels. Interstitial edema persisted in the parenchymatous region and, in addition, arterioles showed mural thickening. This was in part the result of swelling of smooth muscle components and in part due to proliferation as evidenced by increased numbers of smooth muscle nuclei. Here, as in the capsule, there was a scant, loose, perivascular aggregation of lymphocytes (Fig. 3). Germinal epithelium showed little additional degeneration, although many of the tubular lumina contained precipitated fluid in addition to desquamated elements.

Fifteen specimens showed progression to a more advanced (third) stage. Perivascular lymphocytic collars in the capsule were wider and more thickly populated and there was now a sprinkled infiltration of the edematous capsule as a whole by similar cells. As before, in the deep portion of the capsule and in immediate subcapsular stroma, the reaction was more pronounced. Not only were lymphocytes more numerous here, but there was also an irregular hemorrhagic extravasation. Many arterioles showed mural thickening (a single instance of arteritis with thrombosis was encountered), but as a rule evidence of unquestionable intrinsic vascular damage was lacking. There was no arterial necrosis. Polymorphonuclear leukocytes, though present, were sparse, but there was a rather pronounced membrane-like deposit of fibrin particularly evident in the immediate subcapsular region.

Within the parenchyma itself the lesion was distinctly spotty (Fig. 6). Many areas retained the appearance described in the earlier stages. Here and there the perivascular lymphocytic reaction was more intense and spread in an irregular manner within the intertubular tissues. Clusters of Leydig cells were not primarily affected but were often partially obscured by the advancing exudate. In some areas lymphocytes were so numerous that they completely filled, in a closely packed manner, the space intervening between tubules (Figs. 4 and 5).

Where the exudate was less pronounced, perivascular aggregations of lymphocytes attained considerable depth. There were an associated scanty fibrin deposit and comparatively few polymorphonuclear leukocytes, the latter exhibiting no focal concentration. There were also interstitial hemorrhages which, though usually small, were in some instances widespread and coalescent. In such circumstances encompassed tubules were sharply outlined by the brightly staining mass of erythrocytes. Neither thrombosis nor necrosis appeared in the interstitial tissues.

During this phase, for the first time, inflammatory elements were noted within the seminiferous tubules. This reaction was also focal and appeared but rarely in areas free from interstitial exudate. Its composition differed from that of the interstitial process in that the exudate was composed preponderantly of polymorphonuclear leukocytes. Among these cells were a few phagocytic macrophages. The germinal epithelium exhibited progressive degeneration with pyknosis and cytoplasmic fragmentation. Ultimately all of the epithelium in an affected tubule was dislodged from its mural attachment, spermatogenesis ceased, and an agglomeration of fragmented cells, débris, polymorphonuclear leukocytes, and phagocytes formed in the lumen. Only Sertoli cells remained attached to the lamina propria of the tubule. These cells, though frayed, did not at this time appear intrinsically damaged. These supporting elements seemed to coalesce and form a narrow tessellated syncytium lining the tubule. At the same time the lamina propria showed a segmental arcuate thickening which eventually involved the entire circumference. This apparently was initiated in those portions adjacent to interstitial blood vessels, the adventitia of which contained reactive exudates. The thickening seemed to result partially from fibroblastic proliferation, partly from infiltration by inflammatory exudate, and partly by apparent fibrosis of residual Sertoli elements (Fig. 5). The intramural exudate, comprised initially of lymphocytes, became polymorphonuclear in character as the intraluminal lesion progressed.

It could not be determined with certainty whether or not this change occurred along the entire longitudinal extent of a tubule. From the appearance of those sectioned sagittally and the larger sections available from the necropsy, it appeared that this was indeed the case. In other words, though focal and spotty with regard to the testis as a whole, individual tubules were involved throughout their entire extent.

The most advanced acute lesion (fourth stage) in this study was observed in 13 specimens. Although focal distribution was maintained,

there was evidence of a tendency for the involvement to become diffuse with few of the parenchymatous structures remaining uninvolved (Fig. 7). Capsular changes had not progressed beyond those previously described. The interstitial tissue, however, was completely filled with densely packed lymphocytes, among which relatively small numbers of polymorphonuclear leukocytes and macrophages were evident. In some cases a thick intertubular fibrin deposit was noted and in others there were many foci of hemorrhage. The lumina of the tubules now contained no viable germinal epithelium, nor was the Sertoli cell syncytium apparent. Instead, the tubules were distended and plugged by dense masses of polymorphonuclear leukocytes which lay enmeshed within a delicate fibrin network (Fig. 8). Interspersed among these cells were fewer but variable numbers of macrophages, lymphocytes, and fragments of cellular débris. The lamina propria, though thickened and infiltrated by leukocytes, was intact and there was no evidence of destruction of sustentative elements. Despite the degree of damage, it would seem from the nature and extent of the changes that complete atrophy of the testis would be an unusual sequela. That permanent damage may result focally, however, was shown in the later stages observed in the patient who was studied by necropsy.

Material from both testes was examined in the fatal case. The lesions differed in several respects from those noted above, probably as the result of the duration of the process (11 days). They seemed to be more intense than in the surgically procured specimens. Interstitial tissue in all areas (the sections were sagittal and included the entire gonad) was markedly edematous and contained large foci of hemorrhage, a considerable fibrin deposit, and a heavy infiltration of lymphocytes and macrophages. Despite the intensity of this lesion, there were very few polymorphonuclear leukocytes. Many of the phagocytes contained vacuoles and hyperchromatic detritus. The capsular reaction was identical with that described above. Several large groups of tubules showed retention of normal epithelium which was proliferating actively (Fig. 9). The great majority, however, suffered from a variety of changes ranging from desquamation with heavy mural infiltration of lymphocytes and plasma cells to complete cessation of active inflammation with organization of the tubules. This was manifested by increased thickness of the lamina propria and collagenization of both the lamina and the Sertoli remnants attached to the wall. In tubules so affected, permanent atrophy undoubtedly resulted. Between the two extremes cited there were many tubules, the lumina of which were filled with coagulated débris and many lymphocytes and laden

phagocytes. It is interesting that in none of the tubules in this case were polymorphonuclear leukocytes so prominent a feature as in the earlier and more acute lesions described above.

### *Testicular and Epididymal Appendages*

Eighteen examples of testicular and epididymal appendages were studied. All showed some evidence of inflammatory infiltration which was not unlike that seen in the tunica albuginea of the testis. There were edema and congestion of variable degree. Some capillary channels were widely dilated and pool-like in appearance. There was a variable amount of perivascular lymphocytic aggregation which was spotty in distribution. In one case with a history of scrotal pain intermittent for months preceding the attack of mumps, a large number of eosinophils were found interspersed among the lymphocytes. This probably represented a mumps-induced exacerbation of a nonspecific epididymitis. It was the only instance in which granulocytes were found in the lesion of the appendage. Surface epithelial elements and those lining the pinched off downpouchings were wholly intact.

### *Epididymis*

Sections from three epididymides were available (two of these were obtained at autopsy). The appearance of the connective tissue was identical with that described in the testicular capsule and the appendages. In the main there was a focal lymphocytic exudate associated with relatively little fibrin deposit and a rather marked vascular engorgement. The infiltration about the ducts, however, was intense, consisting of closely packed lymphocytes clustered about the tubules and often completely filling the interductal spaces (Fig. 10). The epithelial cells lining the ducts were intact and apparently unaffected. The lumina were usually unremarkable, but in some instances contained masses of desquamated epithelium and débris and even a few small clumps of polymorphonuclear leukocytes. It is believed that these represented products of the orchitic process which had been swept up into the epididymis.

## Discussion

Both Wolbach (in Smith [8]) and Manca [7] described lesions which, with but little variation, resembled the process as it was manifested in the present series of cases. Wolbach noted the focal character of the exudate in the tunica albuginea, the edema, small hemorrhages, and perivascular exudates. He found, however, that the reactive cells were not lymphocytes but "endothelial leukocytes" and polymorphonuclear

leukocytes. This was also the case in the parenchymatous process. Here the contrast between intratubular and extratubular exudates was not as striking as in the acute cases in the present series. He found polymorphonuclear cells predominating in both regions. Manca examined both testes in a case which was autopsied several days after the onset of mumps orchitis. In his material, too, there was close similarity to the observations made in the present series. Lymphocytes appeared in great numbers in the interstitial area but polymorphonuclear leukocytes were increased in the more advanced foci. The fibrin deposit seemed to be greater than was apparent in the current group. The epididymitis was identical in appearance with that described above.

The pathogenesis of the lesion remains somewhat obscure. Inclusion bodies similar to those described by Johnson and Goodpasture [12] were not recognized in Giemsa-stained preparations of several of our specimens. It would seem that whatever the cause there was initially a mild but widely distributed vascular injury manifested by edema, congestion, and perivascular lymphocytic clustering. It is possible, as suggested by Wesselhoeft and Vose,[2,11] that with this as an initiating impetus and the limited expansibility of the tough tunica albuginea as a concomitant, the degenerative and suppurative changes were altogether secondary in nature. In other words, the lesion is presumed to represent a combination of mild inflammatory response to the mumps virus and pressure necrosis inherent upon the architecture of the testis. The specific necrotizing effect upon the germinal epithelium in contradistinction to the stimulating effect upon the supporting structures may be attributed to the more highly specialized development of the former elements. Epithelial cells would, under such conditions, be expected to exhibit less resistance to disturbance of nutrition than would sustentative tissues. Another factor which may in part explain the disproportionately greater amount of intratubular reaction is the failure of drainage from tubules plugged by fibrin and desquamated epithelium.

In the absence of evidence of widespread organization of the damaged testis it would not seem likely that persistent significant clinical stigmata might be anticipated. Certainly, complete atrophy should not be expected in the face of the spotty distribution of the lesion. It is probable that scattered tubules might fail to regenerate and, as noted in the fatal case, become hyalinized. It is not unusual to find islands of hyalinized tubules in otherwise normal testes examined incidentally at necropsy. In view of the collagenization observed at 11 days, it is reasonable to assume that these may represent in some instances the residua of previous attacks of mumps. In the unusual case of orchitis, in

which the disease is fulminating and diffuse, it is probable that complete atrophy and, in the event of bilateral involvement, sterility may result. Unfortunately, save for the rare case subjected to delayed surgical intervention or autopsy, interpretations of atrophy recorded in the literature are based upon conclusions reached by clinical examination. Since relative size and consistency of the gonads are used as criteria, interpretative accuracy must be considered equivocal.

## SUMMARY

Testicular and epididymal tissue obtained from 76 cases of acute mumps orchitis (75 for biopsy and one at autopsy) have served as the basis for this study. In all cases testicular tissue was available. In 18 cases there was material from the appendages and in 2 (3 specimens) from the epididymis. Material was obtained during the first 5 days of symptoms in all but one case (11 days).

Considerable variation was evident in the character and extent of the lesions in the testis but it seemed that a developmental trend could be detected. From early edema and a scant perivascular lymphocytic exudate the process progressed to a diffuse lymphocytic infiltration of the interstitial tissue with focal hemorrhage and pronounced destruction of germinal epithelium, with plugging of the tubules by epithelial débris, fibrin, and polymorphonuclear leukocytes. The intratubular lesion remained focal in most instances but in a few cases every tubule in a given section was involved. Evidence of collagenization was elicited only in the one late case.

Inflammation of the testicular appendages and the epididymis remained confined to the connective tissue elements and, with a single exception, was wholly lymphocytic in character. Epithelial elements were unaffected in these structures.

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[ *Illustrations follow* ]

## DESCRIPTION OF PLATES

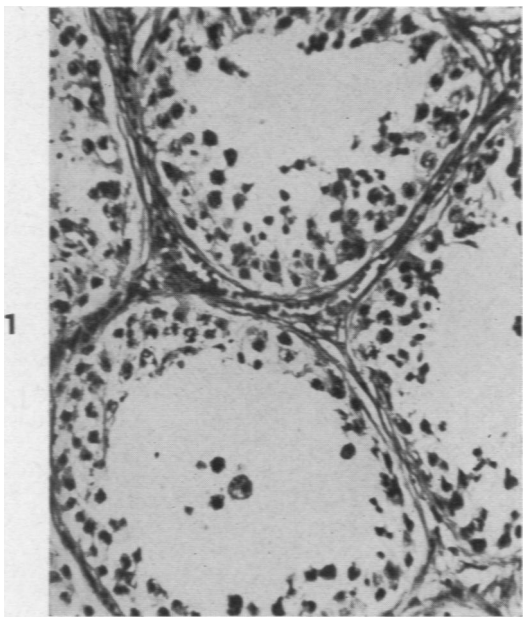
### PLATE 107

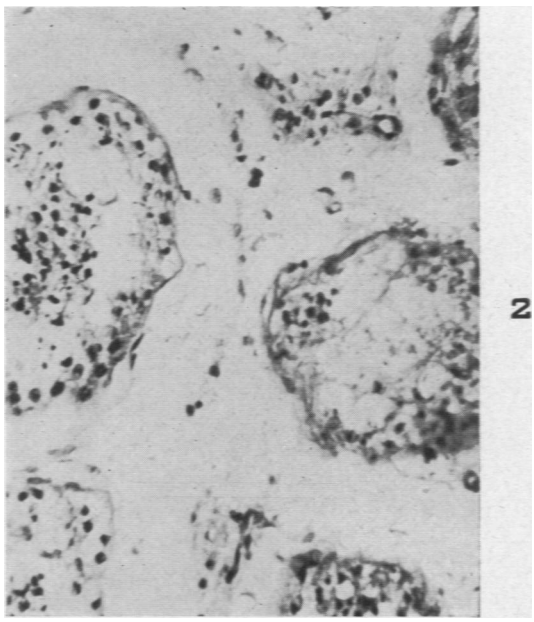
FIG. 1. Testicular parenchyma, as observed in 6 cases with scrotal pain and mumps. No abnormality is detected. Tubules show active spermatogenesis and are closely approximated with little intervening stroma. × 200.

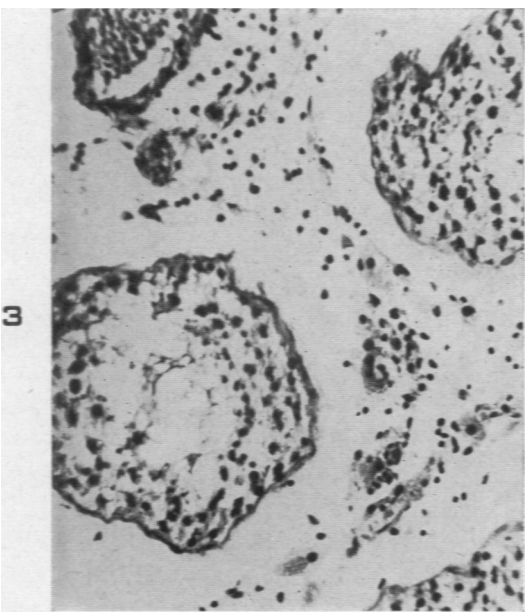
FIG. 2. The earliest perceptible change in mumps orchitis. There is pronounced interstitial edema with separation of tubules and little or no cellular exudate. Mild degenerative changes have occurred in the germinal epithelium. × 200.

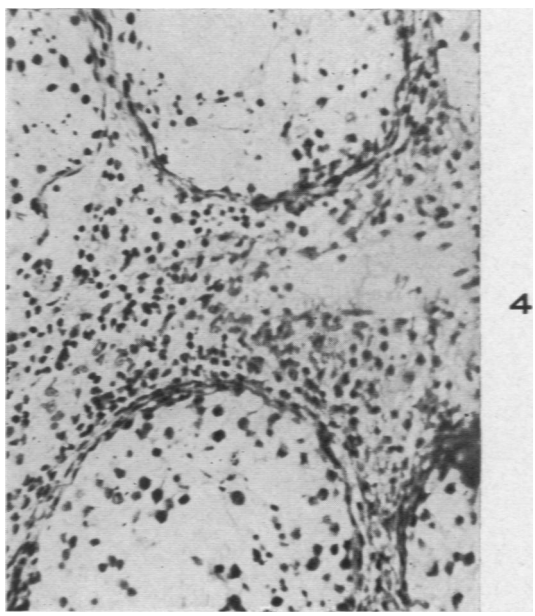
FIG. 3. A second phase of the lesion, showing in addition to interstitial edema a sprinkled infiltration of lymphocytes having predilection for a perivascular distribution. There is some increase in intratubular degenerative change. × 200.

FIG. 4. The interstitial exudate has increased in intensity. It is almost wholly lymphocytic in character. Spermatogenesis has ceased and a scant intratubular exudate of polymorphonuclear leukocytes and macrophages has appeared. × 200.









Gall

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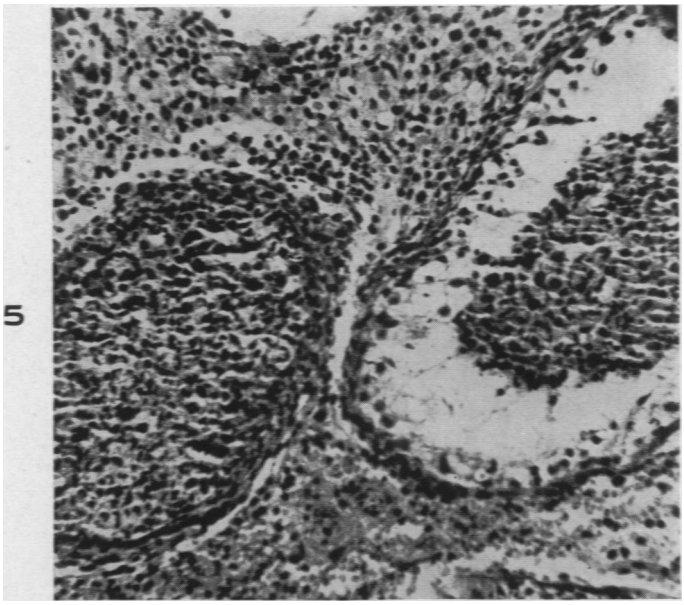
PLATE 108

FIG. 5. In addition to a lymphocytic exudate and hemorrhage in the interstitial tissue, there is now a rather dense polymorphonuclear exudate in the tubules. The lamina propria of the tubule appears thickened and Sertoli cell remnants have fused to form a frayed syncytium. × 200.

FIG. 6. The parenchymatous reaction is shown to be spotty. × 40.

FIG. 7. The process now appears more diffuse and there is suppuration within many tubules. × 40.

FIG. 8. Seminiferous tubules filled completely with a polymorphonuclear exudate. The sole residue of the pre-existing tubule is the moderately thickened lamina propria. Interstitial stroma shows edema, hemorrhage, and lymphocytic infiltration. × 200.



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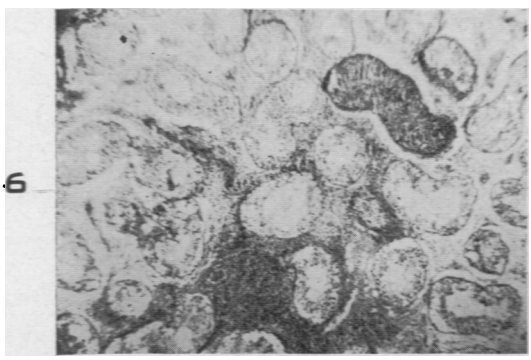

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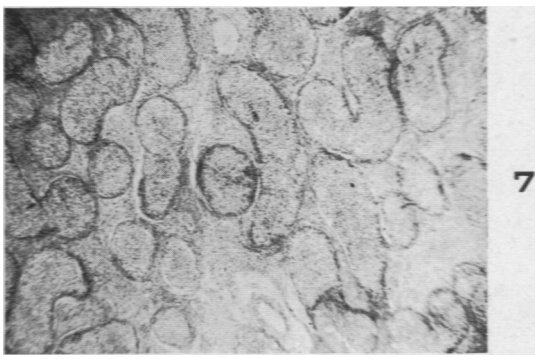

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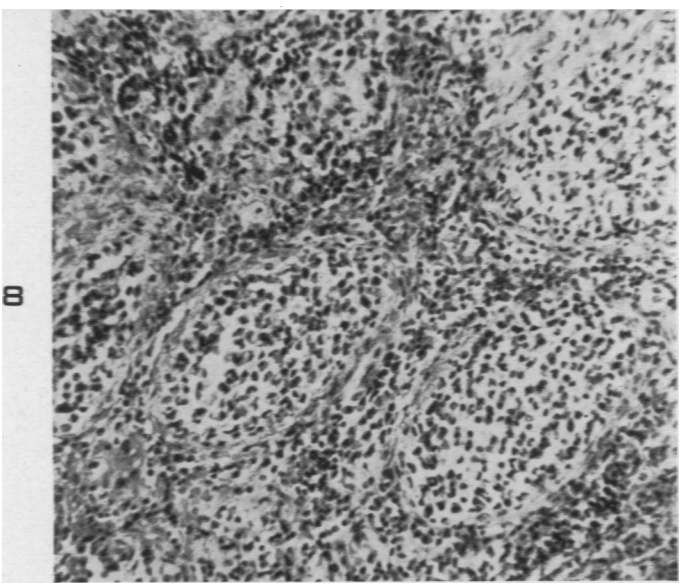

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Gall

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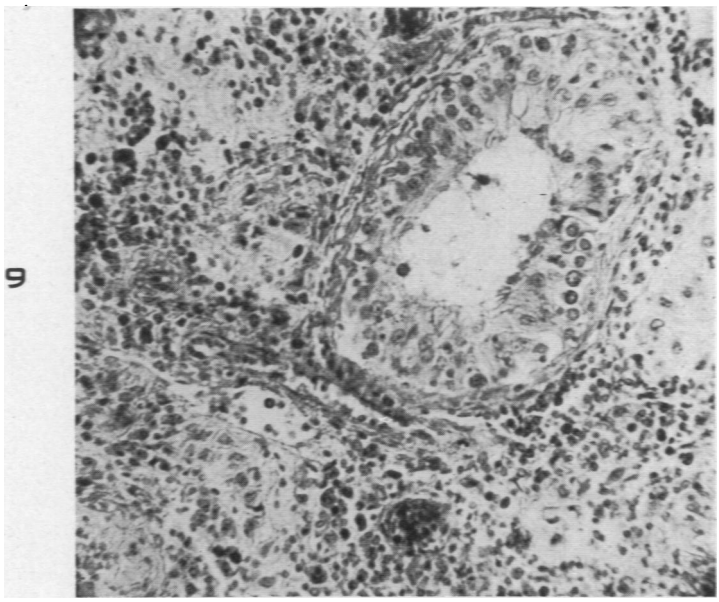
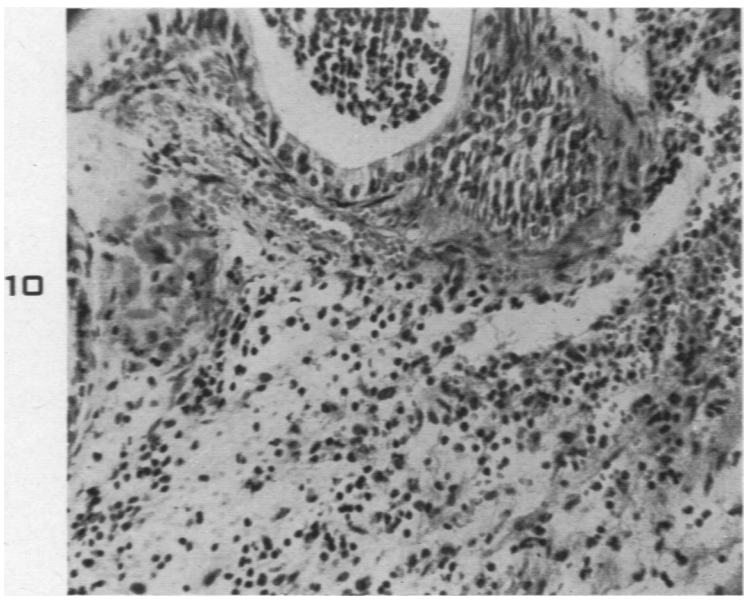
PLATE 109

FIG. 9. An area from a testis 11 days after the onset of mumps orchitis. An actively functioning seminiferous tubule contrasts with the surrounding intense inflammatory reaction. Adjacent tubules are the seat of severe degenerative and inflammatory changes. × 200.

FIG. 10. Epididymis in mumps orchitis. There is interstitial edema and a rather pronounced lymphocytic infiltrate. Tubular epithelium is preserved but the lumina contain an exudate presumably swept up from the severe orchitic process. × 200.

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