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REPAIR OF THE OLFACTORY MUCOSA

WITH SPECIAL REFERENCE TO REGENERATION OF OLFACTORY CELLS (SENSORY NEURONS)

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Although the normal structure of the epithelium of the olfactory mucosa has been known for many years, little has been reported on its repair. There are at least two reasons why the possible mechanism of repair of this structure should be of interest: (1) It is a surface structure in which nerve cell bodies ("olfactory cells") or a primitive type of neuron lies in a peripheral tissue. (2) The mucosa in which these cell bodies lie is not separated from the lamina propria by a basement membrane, but rests directly upon a structure of some complexity, from which different elements could participate in the repair.

The present studies are an outgrowth of early work on chemical prophylaxis of experimental poliomyelitis in monkeys.[1,2] They were prompted by observations showing that the resistance afforded by an intranasal irrigation with zinc sulfate solution a day or two prior to intranasal inoculation with a given neuronotropic strain of poliomyelitis virus (MV strain) was usually followed in 3 or 4 months by resusceptibility to intranasal inoculation. The initial resistance induced could be explained by extensive destruction of the olfactory epithelium, thus interrupting the nervous pathway by which this strain could reach the central nervous system. It was not possible, however, for us to explain the ultimate return of susceptibility except on the possibility that some measure of restoration of the nervous pathway occurred in time. These observations, therefore, directed our attention to the possible mechanism

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underlying the return of susceptibility, and particularly to the possibility that this might be related to a restoration of olfactory sensory neurons (olfactory cells). A preliminary paper on our observations was published in 1941,[1] and enlarged on to some extent in 1942.[2] Further observations have been made from time to time since then, and it is the purpose of the present paper to summarize these.

Gross and Microscopic Structure of the Olfactory Region

The gross anatomy of the nasal passages in the rhesus monkey has been described by Geist.[3] Certain qualifications of his description are required, however, on the basis of our own observations. He stated that in the rhesus monkey, "there is nothing comparable to the human superior concha, this part of the wall being smooth and not appreciably elevated." He therefore recognized in the gross only the two lower conchas, which he designated superior and inferior. While it is true that there is little if any bony ledge in evidence where the superior concha should be, there is a clearly defined, tongue-like fold of soft tissue demonstrable on low power microscopic examination of sections made through the coronal plane. This tongue-like fold begins 4 or 5 mm. below the top of the nasal vault and is 1 or 2 mm. in length. The olfactory mucosa extends from the top of the nasal vault around the fold and down the lateral wall to a little below the level of the end of the fold. This is near the upper surface of what is designated by Geist as the superior concha, but which actually corresponds to the usual location of the middle concha, the upper portion of which in man also marks the lowermost limit of the olfactory mucosa. On the medial side, the olfactory mucosa extends down to about the same level as on the lateral side. Most of the mucosa lines a cleft which in the monkey measures about 1 cm. in depth, 1.5 cm. in length, and 1 mm. in width. The narrow width of the space covered by most of the mucosa is probably a factor of importance in the effect produced by chemical agents, since, in addition to its inherent susceptibility to a given chemical agent, such a narrow cleftlike space would tend to retain the agent and prolong its action.

Information on the microscopic structure of the olfactory mucosa can be found in any histology textbook. The illustrations, however, are likely to be in the form of schematic sketches, and not photomicrographs, as presented in this paper. The literature prior to about 1925 relating to the structure of the olfactory mucosa has been reviewed by Schaeffer,[4] Parker[5] and Hopkins.[6] Little relating to its normal structure has been added since. An extensive bibliography on the anatomy, physiology, and pathology of the olfactory system in vertebrates and invertebrates has recently been published by Airkem, Inc.[7]

Material and Methods

All of the observations were made on monkeys. One per cent solutions of zinc sulfate (C.P. or U.S.P.) in distilled water were employed for the intranasal treatments. These were applied by irrigation of the nasal passages while the animals were under ether anesthesia and suspended in a fully inverted position in a specially designed rack. The irrigations were carried out with a 50 cc. Luer syringe to which a short (12 cm.) rubber tube was attached. The latter carried a small bulb at its terminal end which was fitted snugly into the external nares. The fluid was put through the nasal passage gently while the animal's mouth was held open and the tongue pulled forward with forceps to avoid inhalation of the solution. After one nasal passage had been irrigated, the other was similarly treated. The animals were kept in the inverted position until they began to rouse from the anesthetic.

The procedure employed in harvesting the tissues was as follows: The animals were exsanguinated by cutting the neck vessels with a sharp razor, immediately after which the tissues were fixed *in situ* by gentle perfusion with the fixative. About 20 cc. of the fixative was first introduced via one carotid, and then a similar amount via the other, using a 20 cc. Luer syringe with a 22 gauge needle. Of a number of fixatives initially tried, the one which proved most satisfactory with the staining procedures employed was Bouin's solution. It was found that the perfusion must be carried out gently enough not to separate the olfactory mucosa artificially from the lamina propria or to otherwise disrupt the tissue. Preliminary perfusion with saline solution was not found to improve the fixation or the staining results, and, if anything, impaired the results. Its use was therefore abandoned early in the work.

After the perfusion, the soft tissues from both sides of the nasal vault were removed as one connected mass, usually with the olfactory nerve fila and olfactory bulbs included. To accomplish this satisfactorily required practice. The first step consisted of carefully breaking away small portions of the frontal and nasal bones with a bone forceps of suitable size. After the area had been adequately exposed, it was a relatively simple matter to detach the lamina propria from its bony attachments and to extract the mucosa *in toto* from both sides, along with the olfactory nerve fila and olfactory bulbs. To accomplish removal of the latter two as part of the interconnected mass, it was necessary to remove the bony spicules carefully within the olfactory foramen, the homologue of the cribiform plate in man.

After its removal, the tissue mass was reoriented on a glass slide to bring the parts back as nearly as possible into their normal relationships.

Fixation in Bouin's solution was continued for one or more days, following which the tissue was put in 35 per cent alcohol, and from there carried through graded alcohols. The tissues were finally blocked in paraffin. Sections were cut as thinly as possible (5 μ or less) through the coronal plane of the normally oriented tissue, and mounts were made from different levels through all or most of each mucosa. This orientation made

TABLE I

SPECIMENS OF NASAL MUCOSA

Stage of repair	Mucosal specimens examined (no.)	Stage of repair	Mucosal specimens examined (no.)	Stage of repair	Mucosal specimens examined (no.)
Controls*	48	14 days	3	29 days	3
1 day†	13	15 days	4	30 days	7
2 days	11	16 days	3	31–40 days	10
3 days	11	17 days	4	41–50 days	7
4 days	9	18 days	2	51–60 days	10
5 days	6	19 days	2	61–70 days	5
6 days	3	20 days	4	71–80 days	7
7 days	4	21 days	7	81–90 days	4
8 days	5	22 days	3	3–4 months	25
9 days	6	24 days	2	4–5 months	27
10 days	9	25 days	5	5–6 months	4
11 days	4	26 days	5	6–7 months	11
12 days	1	27 days	1	7–8 months	11
13 days	10	28 days	5	12 months	1

* Control animals were untreated.

† "Days" indicate interval following intranasal irrigation with zinc sulfate solution.

possible observations on all 4 surfaces of the mucosa, at different levels, with portions of the respiratory mucosa often included. Generally included also in the sections were olfactory nerve fila, olfactory bulbs, adjacent meninges, and a small portion of the frontal lobe of the brain.

The staining procedure found most satisfactory and used almost exclusively was that described by Bodian [8,9] for staining nerve fibers. Although various modifications were tried during the early period of these studies, we did not find any of these superior. An essential ingredient in the reagents employed was "Protargol," supplied at that time by the

Winthrop Chemical Company for "tissue staining only," a product which we understand is no longer available. We have since tried protargols provided by the same company for medicinal use without obtaining successful results. With careful observation of the details of the procedure, the Bodian method with the protargol above referred to yielded excellent results on Bouin's fixed material. However, inadvertent overfixation with Bouin's solution at one time caused the loss of a large amount of valuable material.

The total number of specimens of olfactory mucosa from normal and treated monkeys that were successfully processed and studied cannot be stated definitely, but can be said to exceed 300 in number, which, with at least 10 sections per specimen, would mean at least 3,000 sections. Actually, the number of slides examined, usually with 4 or 5 sections per slide, greatly exceeded this figure, since an average of considerably more than 10 slides with "repeats" for better staining results, was the rule. A partial list of the total number of specimens examined and their distribution from the standpoint of the stages of repair represented is given in Table I. As indicated, 48 of the specimens came from untreated, normal monkeys; 68 from animals treated with zinc sulfate solution less than 10 days previously; 84 from animals treated 10 to 30 days previously; 27 treated from 31 to 60 days previously; 16 treated from 61 to 90 days previously, and 79 treated from 3 months to one year previously. The greatest attention was given to mucosa treated 3 months or more previously, after which time animals had shown themselves resusceptible to the neuronotropic virus employed.

Observations

Since the structure of the normal olfactory mucosa is not the primary theme of this report, this will be dealt with only insofar as certain facts relating to it have a bearing on this study. The epithelium is a fairly thick structure composed of olfactory cells (sensory neurons), of columnar shaped sustentacular or supporting cells, and of basal cells, usually rather squat, the whole presenting the appearance of a pseudostratified epithelium (Figs. 1 to 4). This structure, it is important to note, rests directly on the lamina propria, and is not separated from it by a basement membrane. In the lamina propria are found the glands of Bowman, ducts from which open at the surface of the mucosa, providing a serous secretion. Also found are bundles of axons from the olfactory cells which, soon after emergence from the epithelium, become ensheathed by Schwann cells; these constitute unmyelinated nerve (Fig. 1).

Normally, the bodies of the olfactory cells lie mostly in the midzone of the epithelium, but may at times be seen either near its base or near

its surface. The axons of the olfactory cells occur as fine, threadlike processes of uniform diameter which course between the cells of the mucosa in a winding or undulating manner to reach the lamina propria. Here they become grouped into bundles of increasing size which become ensheathed by Schwann cells soon after reaching the lamina propria. The dendritic process is usually thicker and more variable in form than the axon. It may be bayonet-like, its point surmounted by a short, delicate hair (olfactory cilium); it may be in the form of a thick process, solidly stained or lacy, in either case with bulbous or fingerlike terminals surmounted by one or more olfactory hairs, or may show other variations in form (Figs. 2 to 4). It has been postulated that differences in odor perception might be related to differences in function of the individual sensory elements. Should this be true, and differences in function be associated with differences in structure as well, these could be accounted for, to some extent, by the differences in form we have observed. The ends of the dendrites come close to the surface of the mucosa, while the olfactory cilia extend slightly beyond the surface, where, as has been stated, they are bathed by serous secretions from the glands of Bowman.

In the absence of either a dendritic or axonal process, there is relatively little to enable one to differentiate olfactory cells definitely from sustentacular cells by the staining method we employed. While certain differences in the nuclei and cytoplasm, and in staining properties, may be observed, we have felt unwilling to identify cells as olfactory cells definitely unless either an axon or dendrite was seen to be associated with it, or to identify a group of cells as containing olfactory cells unless dendrites or axons were associated with the group. Undoubtedly, many incompletely differentiated olfactory cells were observed during the course of these studies, but we preferred to limit ourselves to criteria of which we could be certain.

This report deals exclusively with the repair of the olfactory epithelium in monkeys, following its destruction by zinc sulfate. Thoroughly applied, a one per cent solution of this agent causes coagulation necrosis involving the full depth of the epithelium down to the lamina propria, and usually most or all of its entire area. Small areas may be missed at times, but these can be easily identified by their normal structure. The respiratory epithelium is little affected.

The extent of the damage inflicted became evident on histologic examination 1, 2, or 3 days after application of the solution, during which time the necrotic epithelium was found in the process of peeling from the lamina propria. It usually came off *en masse* as a coherent membrane, often with many nuclei preserved by the fixative action of the solution (Figs. 5 to 8), the lamina propria being spared. Separation generally

took place first at the arch of the nasal vault, where it was most easily observed in sections cut in the coronal plane, but could be observed to take place also from other locations in suitable sections. It is important to add that its separation was usually so sharply defined and complete as to be comparable to a neat dissection. This has an important bearing in considering the repair that followed. Beginning separation at the top of the nasal vault could be observed in about 24 hours and was usually completed everywhere in 3 or 4 days. However, delayed separation in some places was observed in exceptional cases as long as 8 days after treatment.

As the separation proceeded from the vault downward, a single layer of new flat cells followed closely (Figs. 6 to 8). These cells increased rapidly in number so that by the third or fourth day the thickness of the new epithelium equaled or exceeded that of the normal. The cells making up this epithelium were derived largely if not entirely from the lamina propria, and with the possible exception of those portions bordering on the respiratory mucosa, did not arise from the latter, as reported by Smith [10] in rats. In other words, the new epithelium, with minor exceptions only, was not ciliated. In its early development, it resembled an atypical pseudostratified epithelium, with cells piled up in considerable disarray (Fig. 9). The thick new epithelium was often associated with marked proliferative activity in the lamina propria as well, evidenced by cords of cells extending from the new epithelium into the lamina propria (Fig. 9). At least part of the new cells were derived from duct cells of the glands of Bowman, some possibly from the sheath cells of Schwann, and some possibly from other elements in the lamina propria. The distinctive character of the new epithelium tended to be retained for some time, but there was also a well defined tendency for the cells to orient themselves gradually as in the normal olfactory epithelium. In some areas the new epithelium might not attain more than 1, 2, or 3 cells in depth and was either ciliated or nonciliated. Such areas, however, were usually comparatively small and few in number.

Prior to the tenth day there was relatively little to suggest that olfactory cells would be restored, although abnormal looking cells with processes, along with what appeared to be degenerated nerve fibers, were found at times during this early period of repair. Such findings were usually interpreted as residua of damaged neurons carried upward by proliferating cells. However, soon after the tenth day, normal-appearing cells with dendritic processes could generally be found in the new epithelium. The dendritic process seemed to be the first of the two processes to form and, from the first, was distinctive enough to be easily identified. The incidence of cells with processes increased sufficiently so that by

the 20th day they were numerous in most areas. While such cells might remain relatively few in number in some portions, their number, after several months, approached those of a normal epithelium in most regions. In certain mucosal fragments, removed 6 months to a year after zinc sulfate treatment, the general structure of the epithelium in most portions of the olfactory area was essentially normal. In certain of these late specimens, the epithelium appeared thicker than normal with a seemingly higher incidence of olfactory cells per unit area. Indeed, were it not for the extent of such portions, compared with the usual extent of the initial damage, it would have been easy to underestimate the probable extent of the initial damage or degree of restoration.

As stated earlier, patches of epithelium sometimes escaped the action of the zinc sulfate solution, presumably because the solution was shunted around the areas in question. These areas, however, were generally easily identified as "missed" and were usually not a problem in observations on the early stages of repair. In the later stages, they were less easily differentiated so that the average state of a given mucosal specimen had to serve as a measure of the probable extent of the repair. It should be added here that even in the late stage of repair, not all of a given mucosa was likely to show a restoration approaching the normal. In some of the later specimens there were one or more areas, usually relatively small, in which the cells were only one or two deep, with few or no olfactory cells included, or with the lamina propria covered by ciliated respiratory epithelium. Explanation of these exceptions was not considered within the scope of an investigation limited to the question of whether or not olfactory cells are restored.

Because space would not allow this, the observations made on the progress of the repair cannot be presented on either a case-by-case or a fixed-time-interval basis. It must therefore suffice to summarize the kinds of observations made which were held to indicate that in the repair, sensory elements (olfactory cells) were also restored. The evidence of this was based on a combination of the following kinds of observation: (a) the character and extent of the initial damage induced by zinc sulfate solution—this constituting a base line for observations on subsequent events; (b) the mode of separation of the necrotic epithelium from the lamina propria, seemingly leaving the surface of the latter free of residual olfactory cells (Figs. 5 to 8); (c) the character of the immediate re-epithelization of the denuded lamina propria with cells predominantly derived from it rather than from the adjacent respiratory epithelium (Fig. 9); (d) the appearance of distinctive individual cells or of compact nests of cells, associated or not with nerve fibers, in the new epithelium (Figs. 10 to 22); (e) the increased incidence of cells with dendritic

processes after the third or fourth week of repair; (f) the exceptional location of individual olfactory cells in newly formed epithelium, such as cells found close to the surface of a new epithelium (Figs. 10, 11, 17); (g) abnormalities in the orientation, grouping and general distribution of olfactory cells in late epithelium retaining some of the earmarks of having regenerated; (h) the extent to which an essentially normal epithelial structure was found after several months (Figs. 23 and 24); and (i) the resusceptibility of monkeys to intranasal inoculation with a neuronotropic strain of poliomyelitis virus 3 or 4 months after intranasal treatment with zinc sulfate solution. As reported by Schultz and Gebhardt,[2] this resusceptibility was associated with anatomic evidence of axonal regeneration and with the usual lymphocytic infiltration accompanying neuronal transmission of the virus.

Certain odd occurrences of olfactory cells were observed in specimens obtained from late stages of repair. Among these was the appearance of gland-like spaces lined in part by olfactory cells (Figs. 25 and 26), spaces seemingly formed by invaginations of portions of the olfactory mucosa (Fig. 27). In these the overlying surface epithelium consisted of either essentially normal olfactory epithelium, or of either ciliated or nonciliated cells, without the presence of olfactory cells. A similar occurrence was the presence of islets of compact olfactory cells below a surface epithelium, the latter being either of normal olfactory structure (Fig. 28) or not. How these might have arisen was not clear. They could have arisen from either a burial of surface cells during the rapidly proliferating stage of the repair, or developed from potential olfactory cells in the depth of the tissue.

Still another unexplained observation made on membranes in the late stages of repair was the occasional occurrence of short stretches of nonciliated epithelium made up of somewhat cuboidal cells one or two cells in depth, at times with an occasional squat olfactory cell included. It would be of interest to know why such highly abortive restorations occurred in the midst of more or less fully repaired olfactory epithelium. Without knowledge of the usual extent of the initial damage, one might conclude that these represented the full extent of the original damage, a conclusion that would be at variance with the many observations made on membranes early in repair.

Discussion

The observations reported here seem to justify the conclusion that in the repair of the olfactory mucosa following zinc sulfate-induced necrosis, sensory neurons (olfactory cells) are largely restored. The question posed in these studies was not whether complete restoration occurred,

but whether or not restoration occurred at all. There was a basic reason for asking this question. In the olfactory cell we have a primitive type of neuron represented whose regenerative capacity might differ from that of other neurons in vertebrates. Prior to our first reports,[1,2] no evidence had been recorded indicating that the loss of olfactory cells could be followed by restoration.

The fact that areas were found in membranes late in repair, in which the restoration of olfactory cells was either slight or absent, constitutes, we believe, a separate problem, one relating to the factors that restrict the extent of restoration. Another problem considered to lie outside the scope of the present paper was the precise origin of the olfactory cells. While this question was of interest, it was held for possible future studies.

In 1938, Smith,[10] on the basis of observations made on rats, following intranasal application of zinc sulfate solution, reported that the destroyed olfactory epithelium was replaced by ciliated respiratory type of epithelium only, and that specimens obtained up to two months after treatment failed to show a replacement of olfactory cells. In 1951, however, Smith[11] reported observations that led him to the conclusion that a regeneration of "sensory olfactory epithelium" did occur. The latter observations were made on adult frogs in which the olfactory epithelium had been either destroyed by zinc sulfate solution or removed by operation. However, it should be noted that in neither of the two above investigations did he use other than the hematoxylin and eosin stains in his sections. Success in demonstrating nerve fibers of olfactory cells by simple staining methods is at variance with our own early experience, and if this were possible, would have saved us an enormous amount of technical work. On the contrary, it has been our experience that the fibers of olfactory cells are more fastidious, if anything, in their reception of staining methods than are the nerve fibers in the olfactory bulbs, with which staining results could be compared in the same sections.

Undoubtedly, many olfactory or potential olfactory cells, still without fibers, were not identified or classified as such in the specimens examined, since we wished to keep on secure ground and consider only cells with definite nerve processes. Where dendrites were numerous in a given area, we could assume that nerve cell bodies also were numerous. The reverse, however, was not necessarily true, since some olfactory cell bodies might not yet have formed fibers.

Just how early in a regenerating mucosa recognizable olfactory cells appear, we cannot state definitely, but these were observed soon after the tenth day. It is also not possible to state how long the restoration may continue, but the impression gained is that it may continue over a period of several months. Although mitotic figures were observed in the

regenerating epithelium, these were not numerous and were not identified with distinctive cell nests. On the other hand, the appearence of distinctive paired cells, and of closely packed cells in cell nests suggested that amitotic division may occur commonly.

Summary

Observations are reported on the repair of the olfactory epithelium in rhesus monkeys following coagulation necrosis induced by zinc sulfate solution. These observations show that in the repair of the epithelium, olfactory cells (sensory neurons) are largely restored. The restoration of these cells is seemingly a gradual process, extending over a period of several months, but may end in a restitution of most of the epithelium to its normal state within 6 months to a year. There are unexplained exceptions in some areas.

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[Illustrations follow]

Legends for Figures

Except where otherwise stated all sections were stained by the Bodian method for nerve fibers. The words "after treatment" used in the descriptions below mean "after intranasal irrigation with zinc sulfate solution."

Fig. 1. General structure of the normal olfactory mucosa. Shown are the relative thickness of the olfactory epithelium and the content of the lamina propria, including glands of Bowman and an olfactory nerve bundle. × 135.

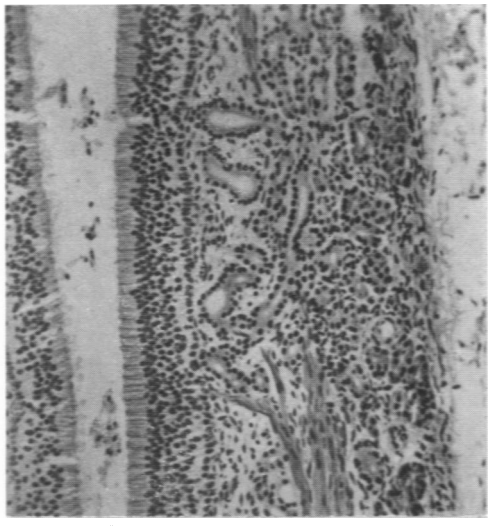
Fig. 2. Dendrites in a normal olfactory epithelium, showing a wavy course through the epithelium and bulbous terminations (olfactory vesicles). The latter end with fine olfactory hairs not clearly visible in the illustration. × 630.

Fig. 3. Dendrites in a normal olfactory epithelium, showing a wavy course through the epithelium, with fingerlike terminations of some and bulbous terminations of others. The former as well as the latter end with fine olfactory hairs. × 1250.

Fig. 4. Some of the variations in the form of dendrites in a normal olfactory epithelium. × 1250. (Reproduced from the *Journal of Infectious Diseases*,[3] with permission of the University of Chicago Press.)

Fig. 5. *En masse* separation of necrotic olfactory epithelium from the lamina propria; near the nasal vault; 28 hours after treatment. × 135.

Fig. 6. *En masse* separation of necrotic olfactory epithelium from the lamina propria; near the nasal vault; 2 days after treatment. A layer of new epithelial cells has begun to cover the denuded lamina propria. Hematoxylin and eosin stain. × 135.



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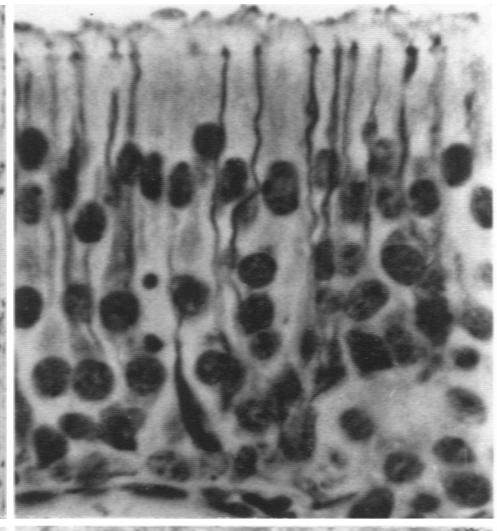

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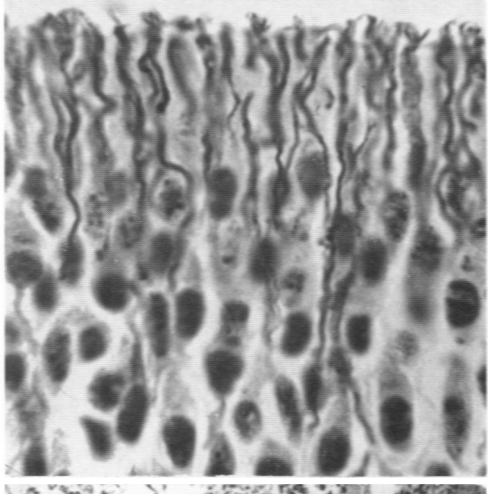

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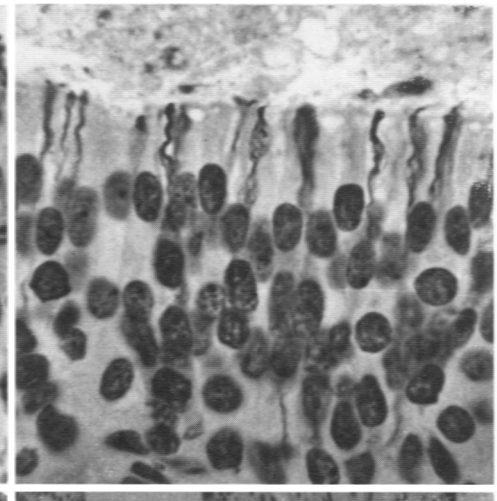

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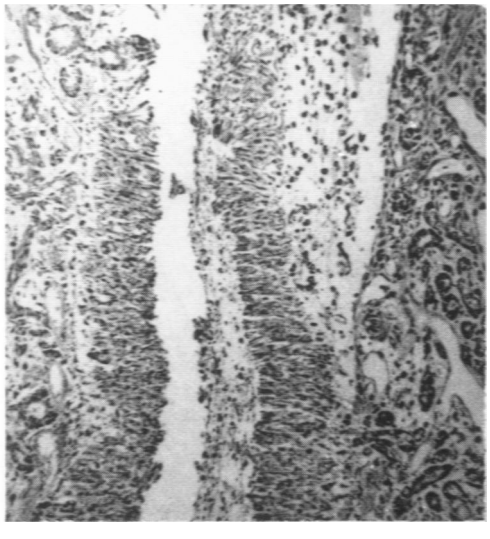

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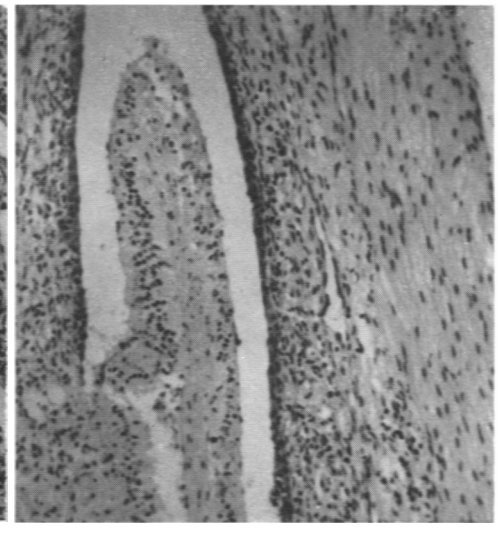

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FIG. 7. Separated necrotic olfactory epithelium lying free in the nasal meatus; near the nasal vault; 44 hours after treatment. A layer of new epithelial cells has formed to cover the denuded lamina propria. Hematoxylin and eosin stain. × 135. (Reproduced from the *Journal of Infectious Diseases*,[2] with permission of the University of Chicago Press.)

FIG. 8. A layer of new epithelial cells following closely on a separating necrotic epithelium; 44 hours after treatment. Hematoxylin and eosin stain. × 675. (Reproduced from the *Journal of Infectious Diseases*,[2] with permission of the University of Chicago Press.)

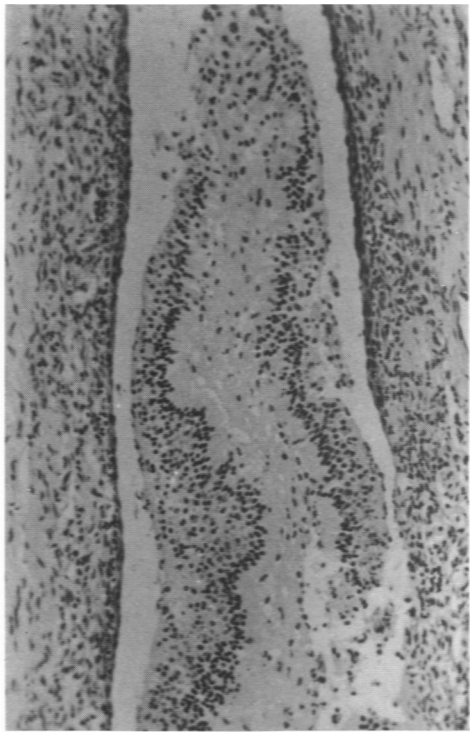
FIG. 9. New epithelium 5 days after treatment. A thick epithelium with fingerlike extensions into the lamina propria is manifest. There is no evidence of cells with fibers. × 225.

FIG. 10. A lone olfactory cell with a dendrite near the surface of a portion of new epithelium; 17 days after treatment. × 675.

FIG. 11. An oval olfactory cell with a short dendrite near the surface of a new epithelium; 24 days after treatment. This cell is associated with dendritic processes from other olfactory cells. × 675.

FIG. 12. Scattered, darkly stained cells with fibers in a new epithelium; 22 days after treatment. × 675.

FIG. 13. A mixture of cells and fibers, and a mitotic figure, in a portion of new epithelium; 13 days after treatment. × 1215.



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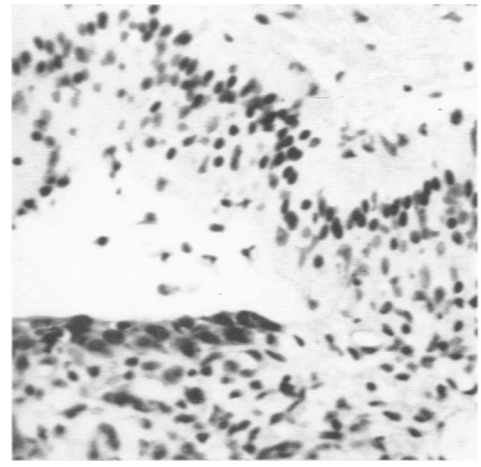

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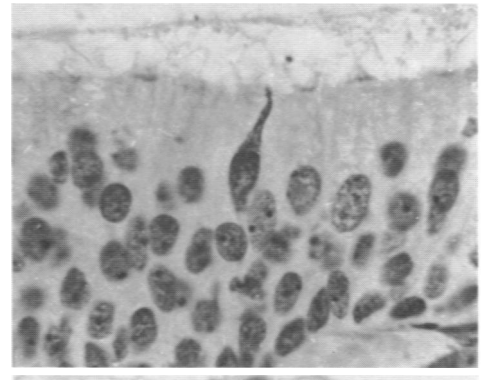

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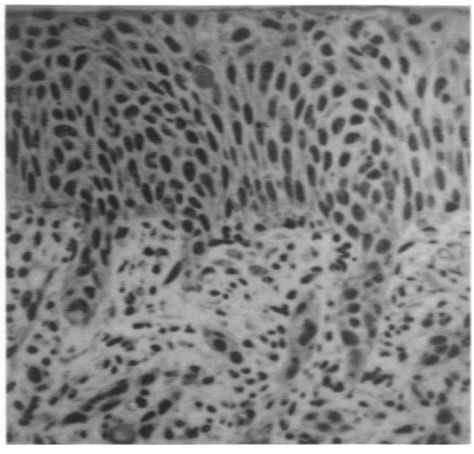

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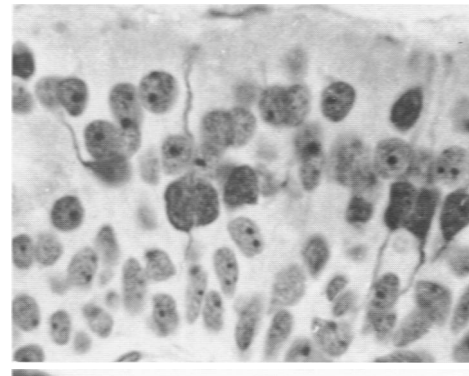

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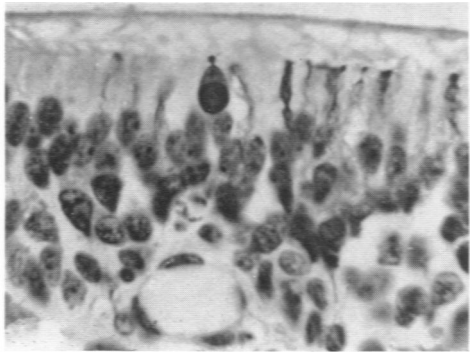

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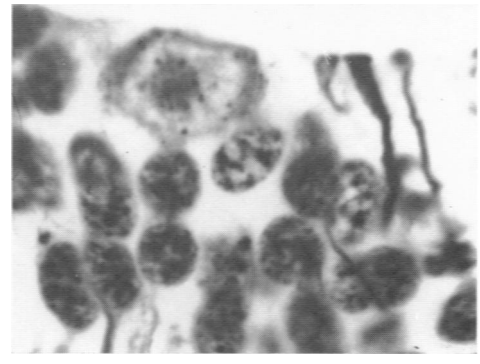

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FIG. 14. Darkly stained cells and cell masses, associated with dendrites of different form, in a portion of new epithelium; 28 days after treatment. × 1215.

FIG. 15. A nest of cells in new epithelium. A dendrite extends to the surface; 17 days after treatment. × 810.

FIG. 16. A nest of cells in new mucosa. Several dendrites and axons have emerged; 13 days after treatment. × 1215.

FIG. 17. A collection of well separated new olfactory cells with short, plump dendrites, mostly near the surface of the epithelium; 13 days after treatment. × 1215.

FIG. 18. Cell nests in a portion of new epithelium; 28 days after treatment. These nests are associated with dendritic processes. Some of the new epithelium is ciliated. × 200.

FIGS. 19 and 20. Portions of new epithelium, showing cell nests with dendritic processes; 28 days after treatment. Fig. 19: × 620. Fig. 20: × 1090.

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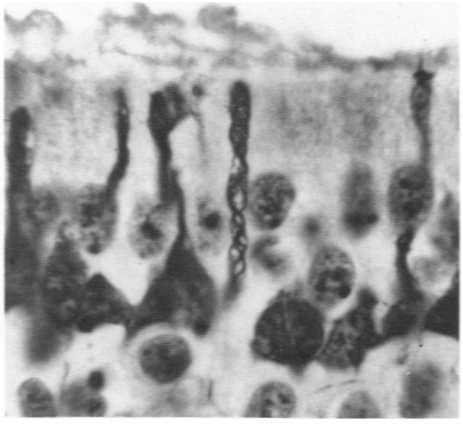

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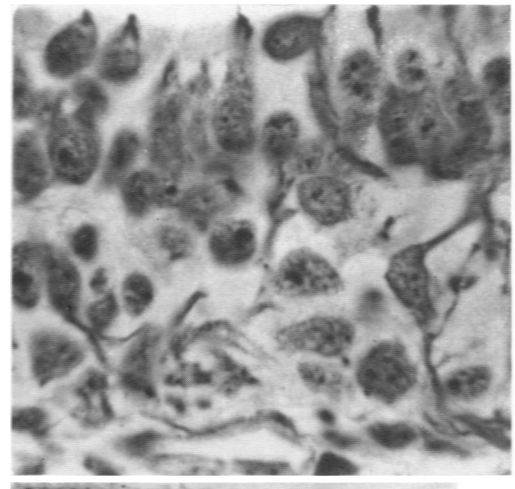

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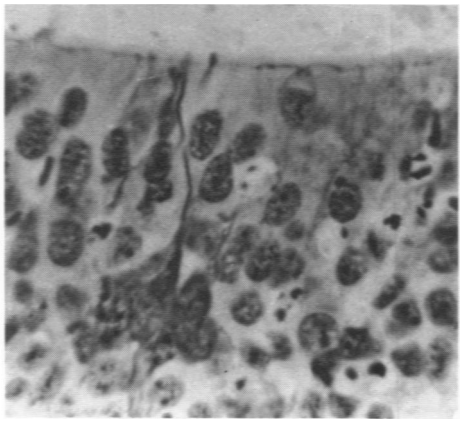

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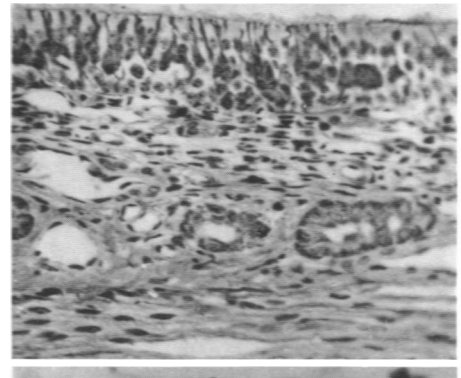

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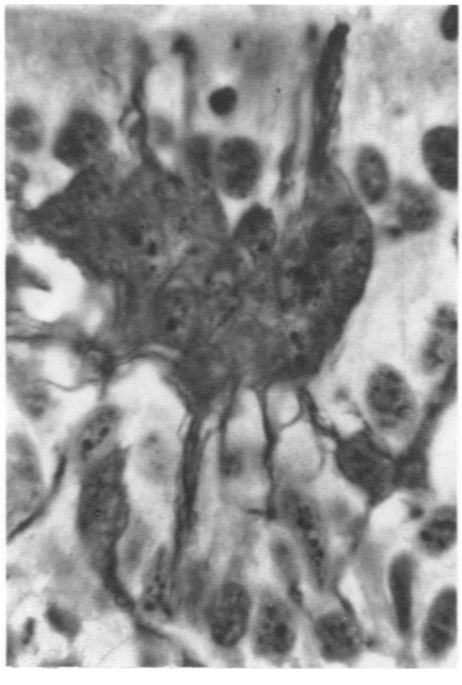

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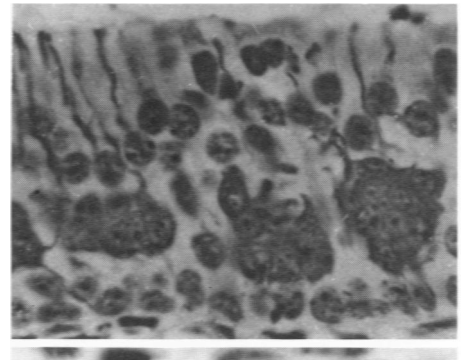

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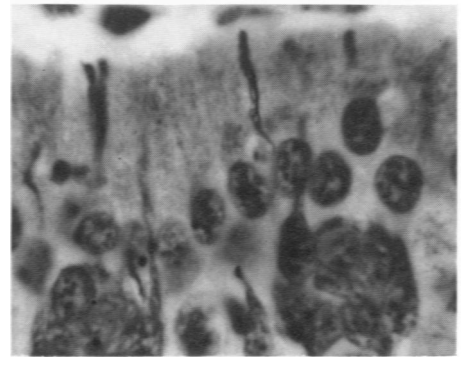


FIGS. 21 and 22. Portions of new olfactory epithelium, showing separated cells with dendritic processes; 20 and 21 days, respectively, after treatment. × 810.

FIG. 23. A portion of olfactory epithelium, representative of much of the olfactory area; 4¾ months after treatment. The epithelium is thick, normal in cell arrangement, with about the normal number of dendrites per unit area. × 270.

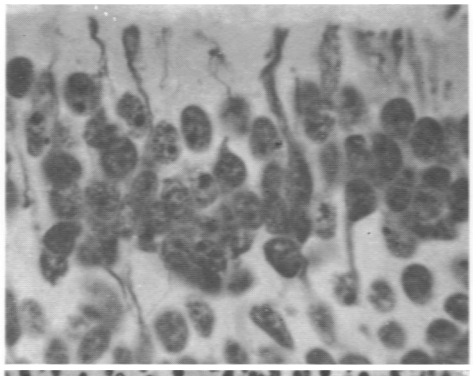
FIG. 24. A portion of olfactory epithelium, representative of much of the olfactory area, from an animal 7½ months after treatment. A thick, essentially normal olfactory epithelium is evident. Basal cells are columnar, instead of squat, as commonly observed in the normal state. × 270.

FIG. 25. A glandlike space, lined in part by olfactory cells, below a surface epithelium; 5 weeks after treatment. Some of the cells of the surface epithelium are ciliated, but none show dendrites. × 210.

FIG. 26. Glandlike spaces, lined in part by olfactory cells, lie below the surface epithelium; from an animal 3½ months after treatment. No olfactory cells are present in the surface epithelium. × 210.

FIG. 27. An invagination of new epithelium, showing how glandlike spaces lined in part by olfactory cells might be formed; from an animal 3½ months after treatment. Surface epithelium is not ciliated and shows no cells with dendrites. × 210.

FIG. 28. A rounded mass of olfactory cells below a surface olfactory epithelium that is essentially normal in structure; from an animal 4¾ months after treatment. × 270.



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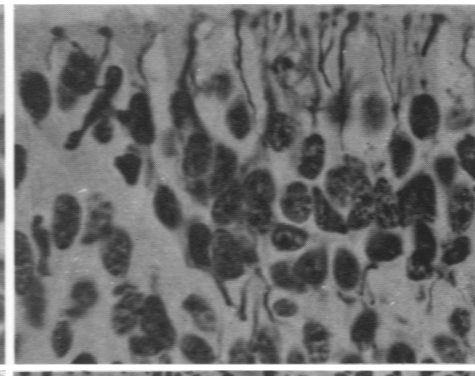

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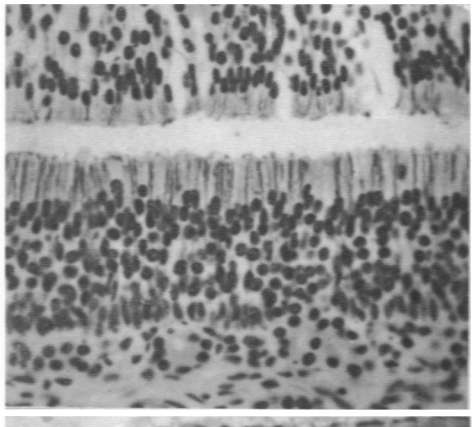

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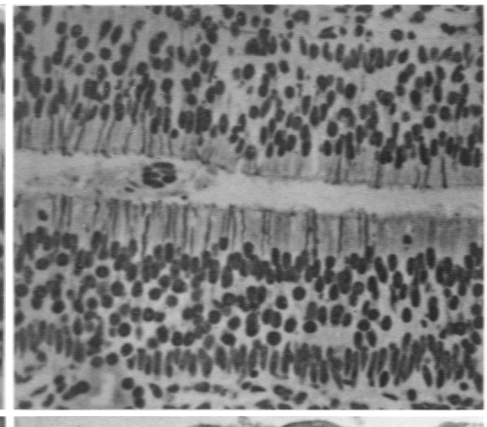

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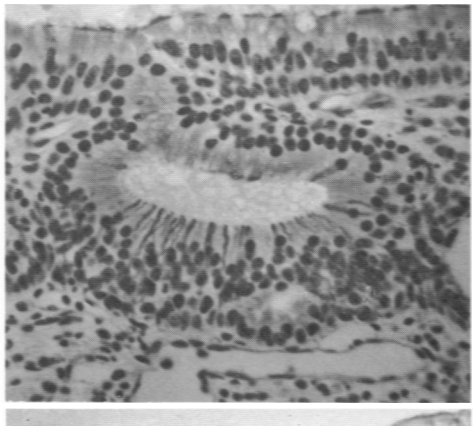

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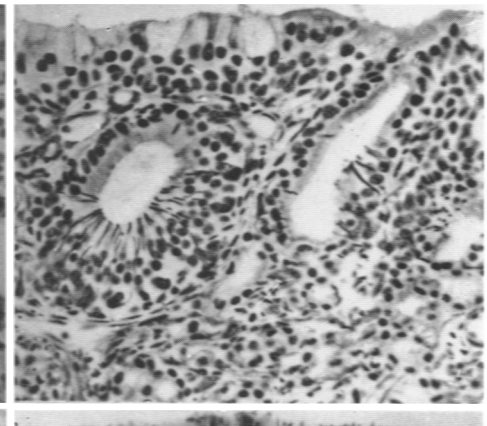

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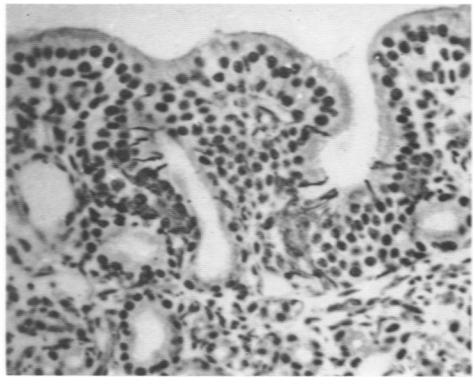

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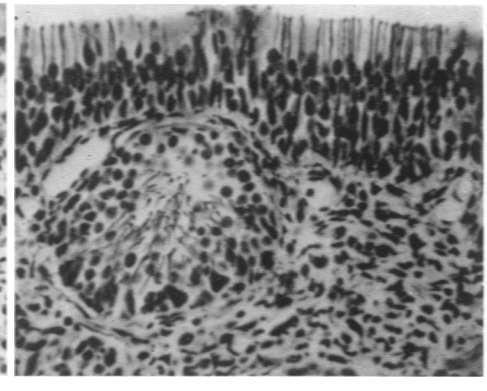

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