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EXPERIMENTAL ORO-PARANASAL COMMUNICATIONS

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Following an experimental oro-paranasal communication, the mucous membrane revealed extensive cellular reactions in the different cell layers of the nasolacrimal duct. These cellular reactions as observed histologically were mainly limited to the injured area. However, increased epithelial cell proliferation extended to other areas of the mucosal membrane as revealed by the autoradiographic observations. Fibrosis of the submucosa was a pronounced phenomenon.

The stratified columnar epithelium in an area restricted to the traumatic communication revealed pronounced metaplasia into a non keratinized squamous epithelium.

Due to the limited experimental period (6 hours—14 days) no conclusions were drawn as to the problem if the cellular reactions are reversible or not.

The establishment of an oro-antral communication represents a common complication to the oral surgeon when performing surgery in the maxilla. Clinical experience indicates that small communications established through a normal maxillary sinus epithelium may heal uneventfully. However, the knowledge regarding the cellular reactions to oro-antral communications is limited. Furthermore, the oral surgeon is familiar with the complications which may occur with development of an empyema of the maxillary sinus, chronic sinusitis and oro-antral fistulas.

Most investigations related to the oro-antral communications have been limited to clinical examinations (*Semenov*, 1938; *Bauer*, 1943; *Mårtensson*, 1952; *Hargrove*, 1955; *Lehnert & Lehmann*, 1967; *Killey & Kay*, 1964, 1969). *Ryzhkov & Makhrakova* (1967) studied the radiographic and morphological changes of the mucous membrane of the maxillary sinus following perforations of its floor. The increase of fibrous tissue with a reduction of the

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vascularity in the subepithelial layer, metaplasia towards cuboidal and squamous epithelium and subsequent degeneration of the respiratory epithelium was striking if the communication had not been closed within the first days. Similar observations have been done by *Haanæs* (1970).

Apparently, no experimental investigations dealing with this particular problem have been presented. According to a review of the literatur, earlier investigations have been limited to different types of traumas, mainly to tracheal and nasal mucous membranes (*Hilding*, 1933 a, b; *Boling*, 1935, *Wilhelm*, 1953; *Sanderud*, 1958; *Burian*, 1960; *Hilding & Hilding*, 1962).

Knoluton & Mc Gregor (1928) using dogs, observed regeneration of the maxillary sinus mucosa within two months following total resection of mucosa and completely regeneration of the glands after five months. *Gorham & Bacher* (1930) similarly claimed that the mucous membrane of maxillary sinus returned to normal in humans within the same period. The works of *Semenov & Kistner* (1930), *Wright* (1930), *Mc Gregor* (1931), *Kistner* (1931), *Latta & Schall* (1934), *Semenov* (1938) and *Eggston & Wolff* (1947) indicate that the regeneration of the maxillary sinus epithelium after total removal is variable concerning both ciliar and gland restitution. The prognosis to a great extent appear to depend on the infection remaining in the nasal and paranasal cavities.

Since earlier investigations have dealt with extensive traumas to the respiratory mucosa, it appears to be of particular interest to study the tissue reactions following a limited trauma to a paranasal epithelium. The present study was therefore designed as an experimental approach to evaluate tissue reactions to oro-paranasal communications. Particular attention will be focused on the tissue reactions within the paranasal mucosa following a limited oro-paranasal communication. For this reason autoradiography using tritiated thymidine (H3TDR) has been added to the ordinary light microscopic examinations. This particular technique has proved to be a valuable tool in the study of cell dynamics following trauma (*Quastler & Sherman*, 1959; *Bullough & Laurence*, 1961, *Tonna & Cronkite*, 1962). Particular attention will be focused on:

the tissue reactions within the paranasal mucosa following a limited oro-paranasal communication,
metaplasia of the stratified columnar epithelium and
the reversibility of the tissue reactions observed.

MATERIAL AND METHODS

Anatomical remarks. The maxillary sinus in the guinea pig represents shallow lateral extensions of the nasal cavity between the turbinal bones. The lumen of the »sinus» is almost filled with these bones. The fact that the maxilla in the guinea pig is narrow, as seen in a caudal view of a cranium (Fig. 5), leaves no space for a maxillary sinus. In macrosmatic animals (i.e. animals with an acute sence of smell) the turbinal structure are exceedingly complicated and scrolls forming labyrinths occupying the greater part of the nasal cavity.

A well defined paranasal structure in the guinea pig is represented by the nasolacrimal duct (Figs. 1, 2). In the 8 weeks old guinea pig this duct is approximately 15 mm long from the lacrimal sac to the anterior nasal floor (Fig. 2). By instilling a dye (Methylen blue) in the conjunctiva the position and length of the nasolacrimal duct was visualized and facilitated dissection of the region before starting the experimental series.

The nasolacrimal duct is slightly flattened and the diameter enlarges posteriorly. The duct is composed of a stratified columnar non-ciliated epithelium with goblet cells and one or two layers of flattened epithelial cells beyond the columnar surface cells (Fig. 4). The submucous tissue is mainly constituted by a loose connective tissue. Several vessels are running, chiefly longitudinally, i.e. parallel to the duct, especially along the caudal aspect. Lymph follicles are often found cranially and caudally to the duct (Fig. 1). Numerous elastic fibrils and a few minute nerve branches extending longitudinally are also found.

Experimental procedures. A total of 26 albino guinea pigs were used in the present investigation. The animals were approximately 8 weeks of age at the start of the experimental period and their average weight was 480 g. The animals were caged individually for 7 days prior to the experimental period. They were fed with guinea pig pellets (Felleskjöpet, Oslo) and were given drinking water ad libitum to which was added ascorbic acid 25 mg/100 ml.

Under intraperitoneal Nembumal anestesia (3 mg Nembumal pr. 100 g of body weight) the following procedure was performed in 18 animals:

An incision lateral to the incisive papilla and parallel to the midline was carried through the mucosa and the periosteum (Fig. 3). A nr. 2 round bur in a dental handpiece was used to drill through the lateral maxillary wall into the right nasolacrimal duct (Figs. 5, 6). Great care was taken to avoid damage to the dental papillae of the right upper incisor tooth (Fig. 1). The establishment of an oro-paranasal communication was verified by the appearance of saline water in the right nostrile following injection through the bur lesion.

Legends to Illustrations:

Fig. 1. Frontal section through head of guinea pig at level of incisive papilla.
SC: cartilaginous nasal septum.
SB: nasal bony septum.
N: nasolacrimal duct.
I: maxillary incisor.
P: incisive papilla.
Arrow: lymph follicle.

Fig. 2. Sagittal section through head of guinea pig. Metal probe (P) is passed through the entire length of the nasolacrimal duct after the removal of the thin cortical plate separating the nasolacrimal duct from the nasal cavity.
MA: maxilla.
R: root of the maxillary molars.
NF-arrow: nasal floor.
T: tongue.

Fig. 3. Soft tissue incision lateral, slightly posterior to incisival papilla exposing the bony surface of maxilla (arrow). Bur lesion was performed in this area.
M: 1. right maxillary molar.
T: tongue.

Fig. 4. Stratified columnar epithelium from the nasolacrimal duct (E).

Fig. 5. Cranium. Dry specimen. Caudal view.
I: maxillary incisors.
PM: premaxilla.
FI: incisive foramen.
S: suture between maxilla and premaxilla.
M: maxilla.
Z: zygomatic arch.
Arrow: area where bur lesion was performed.

Fig. 6. Lateral view of a cranium. Dry specimen. Bony lesion (arrow) illustrating oro-paranasal communication.
A: alveoli of maxillary molars.
I: maxillary incisor.
S: suture between maxilla and premaxilla.
Z: zygomatic arch.
Legends to Figs. 7—18.
General terms:
L: Lumen of the nasolacrimal duct.
E: Wall of the nasolacrimal duct.
T: Injured area of the epithelial wall.

Fig. 7. From specimen after 6 hours observation period. Damaged epithelium (T). Arrow shows the peripheri of the epithelial lesion. In area E the epithelium reveals an almost normal configuration.

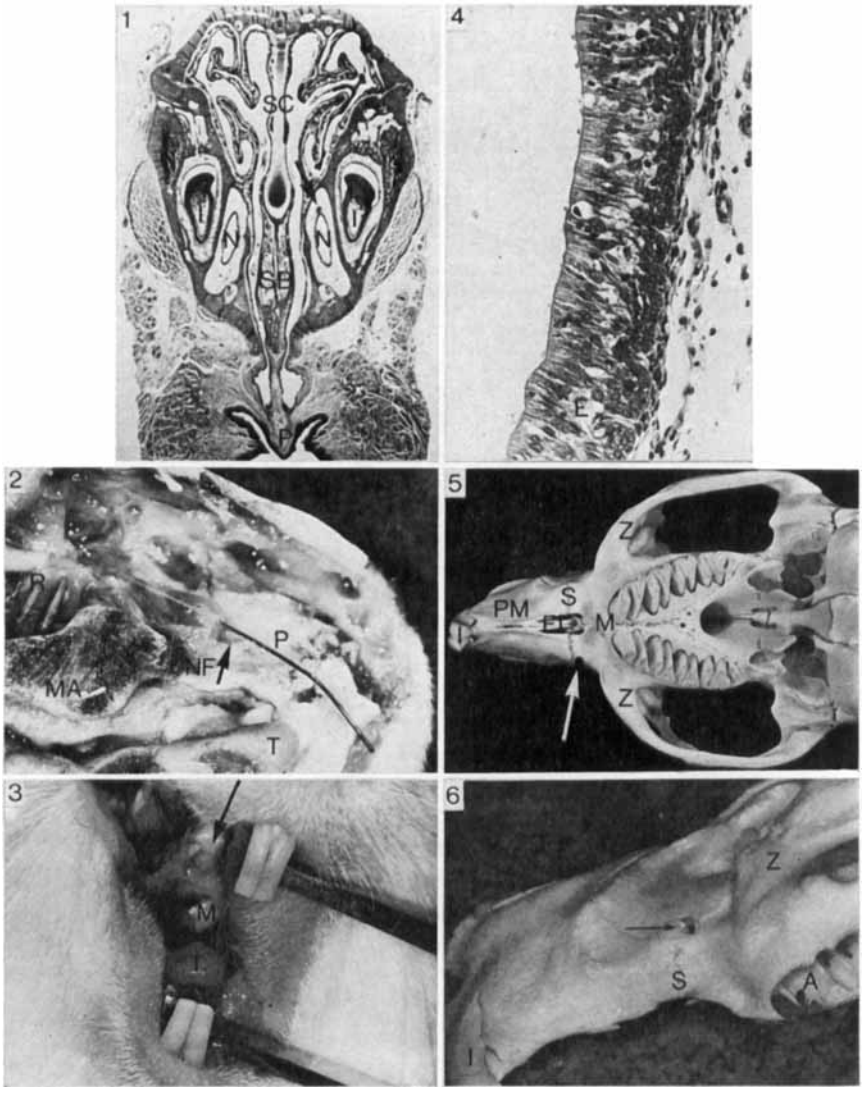
Fig. 8. 24 hours after experimental injury. Regeneration with a slight invagination in the subepithelial layer (R) close to the perforation (T). The epithelium reveals a squamous configuration in this area.

Fig. 9. 48 hours after experimental injury. Invagination of epithelial cells from the ductal wall into the subepithelial layer (arrow).

Fig. 10. Same animal as Fig. 9.
Lesion of the ductal epithelium in the cranial portion of the duct, demonstrating downgrowth into subepithelial connective tissue with metaplasia of the ancestral epithelium (arrow).

Fig. 11. Specimen 72 hours observation period. Downgrowth into the subepithelial layer of damaged area (I).

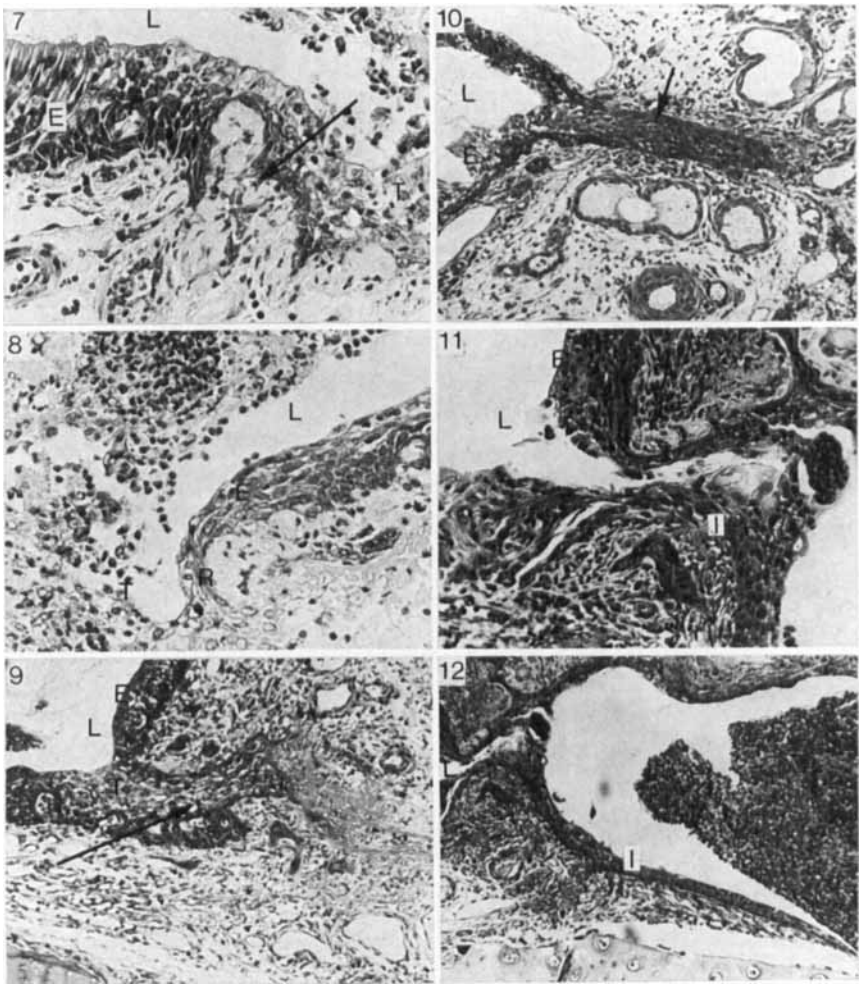
Fig. 12. Same specimen as Fig. 11 demonstrating marked epithelial downgrowth (I). Note the great number of inflammatory cells.



In 4 animals a sham-operation procedure was performed, in these cases only a soft tissue dissection through the periosteum was performed. The remaining animals were left untreated and served as controls.

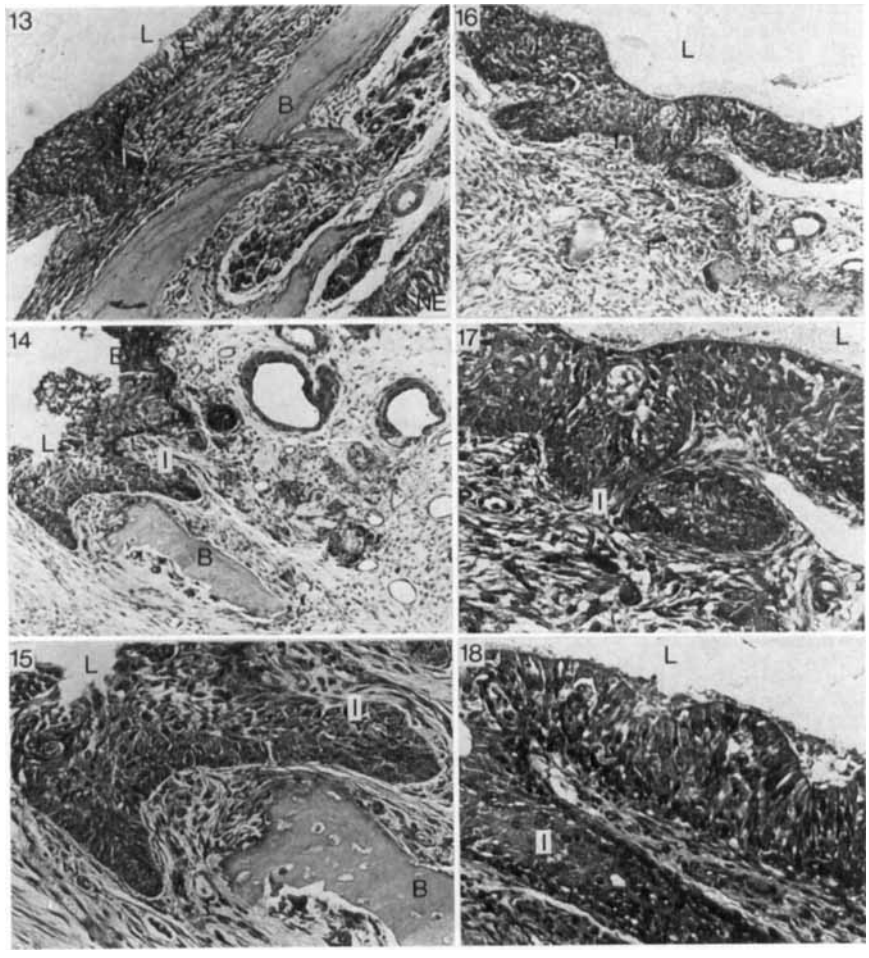
The animals tolerated the surgical procedure well. All animals gained weight at a rate parallel to that observed in the normal guinea pigs in a previous investigation (*Gilhuus-Moe* 1969).

The operated animals were sacrificed in pairs at intervals 6 hours, 24 hours,



48 hours, 72 hours, 7 days and 14 days after the surgical procedure. All animals in the experimental group received an injection of tritiated thymidine (H3TDR) 60 minutes prior to sacrifice. The dose given was 1 microcurie pr. g. of body weight. (Thymidine-methyl T, spec. activity 5.0 curies/mM. The Radiochemical center, Amersham.) The animals were sacrificed by sectioning of the neck veins under Nembumal anestesia. The head was immediately skinned and put in Lavdowsky's fixative. The specimens were demineralized in 20 per cent formic acid and Winn 3000 ®*: The demineralization was checked roentgenographically. Routine histologic sections cut in the frontal plane at 5 microms were prepared and stained in hematoxylin-eosin.

* Winthrop Laboratory, New York, N.Y.



Slides were prepared for autoradiography, using the dipping technique (*Joftes*, 1963) and exposed for 24 days in dry atmosphere. The autoradiogrammes were developed and then stained with hematoxylin.

RESULTS

Histological findings

The observations six hours postoperatively show a severe disarrangement of the epithelial cells of the nasolacrimal duct in the injured area (Fig. 7). In the subepithelial layer and the oral submucosa the whole extent of the injured

Fig. 13. Lesion on epithelium in the median bony wall (B) separating the nasolacrimal duct and the nasal cavity. Epithelial downgrowth in injured area (I). (E) normal epithelium. NE: nasal respiratory epithelium.

Fig. 14. From specimen after 7 days observation.
B: bone fragment in injured area with osteoclastic surface activity. I: epithelial metaplasia revealing squamous epithelium. Note the dilated vessels in subepithelial layer.

Fig. 15. Same specimen as Fig. 14. A metaplastic epithelium of injured area (I). B: bone fragment.

Fig. 16. Specimen of 7 days observation period demonstrating metaplastic epithelium of injured area. Fibrous reaction of subepithelial layer (F).

Fig. 17. Same specimen as Fig. 16. I: irregular epithelium in the wall of the nasolacrimal duct.

Fig. 18. Specimen from 14 days observation period. Metaplastic epithelium of injured area with distinct epithelial downgrowth (I).

Fig. 19 A—H:
Tracing of frontal sections through nasolacrimal duct (frontal view). At each observation both injured (left) and noninjured (control) (right) duct is visualized.
A: lower lateral quadrant.
B: upper lateral quadrant.
C: upper medial quadrant.
D: lower medial quadrant.
F: area of experimental trauma
index number indicate experimental animal.

The sequence of number and distribution of H3TDR labeled cells in the examined epithelial wall are plotted to these tracings.
. : 2 labeled cells.

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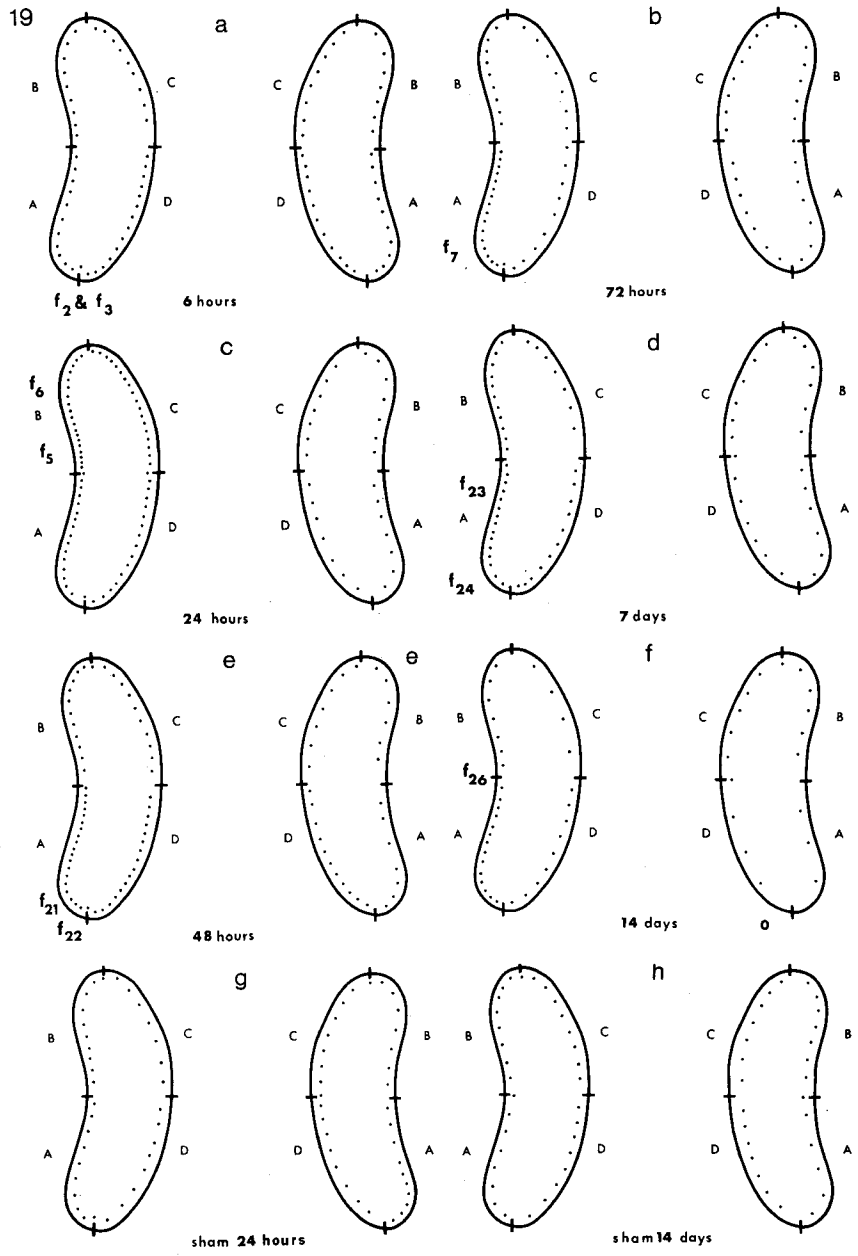
area reveals inflammatory edema. At this stage it is observed a flattening and migration of pseudostratified marginal cells. Further intraepithelial edema is discerned. In the lumen of the nasolacrimal duct neutrophilic cells, exudate and exfoliated epithelial cells are observed (Fig. 7). In one of the animals at this experimental period, the nasal cavity is partly filled with blood and inflammatory cells. The margins of the oral mucosal incision are separated due to edema and exudate.

At the 24 hours observation period regeneration of the epithelial lining may be observed (Fig. 8). The infiltration of inflammatory cells is prominent subepithelially close to the lumen of the duct. Dilated and congestioned vessels are distinct. The ductal epithelium at some distance from the lesion, however, reveals an almost normal configuration. A slight epithelial downgrowth is seen in specimens from 24 hours observations. Proliferative processes in a localized area in the median wall can also be observed.

At the 48 hours observation period the exudate in the nasal cavity appears to be reduced. In both animals sacrificed 48 hours following the injury, the damaged area of the duct demonstrates invagination of the epithelial tissue. These structures appear to be irregular (Fig. 9). The epithelial cells, similar


19
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f_2 & f_3
6 hours
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72 hours
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f_{24}
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sham 24 hours
sham 14 days

to the cells found at the 24 hours observation, show a flattened appearence close to the perforation of the duct. Through the entire lesion infiltration of inflammatory cells is observed, at this stage dominated by round cell or lymphocyts.

In specimens from a 48 hours animal it is observed lesions in the cranial portion of the epithelial lining of the nasolacrimal duct (Fig. 10). This lesion is performed by the canula used when proving the establishment of the oro-paranasal communication. Dilated and congestioned vessels are still to be seen in both the specimens from 48 hours observations (Figs. 9, 10).

In animals sacrificed at 24, 48 and 72 hours (especially those at 48 hours) the periosteum on both sides of the bur lesions reveals intense vascularization and cell infiltration. *At 72 hours, 7 and 14 days* a pronounced periostal bone formation is observed. This is also seen at some distance from the bone lesion. Periostal osteoclasts are observed frequently at 7 and 14 days observation time.

At the same observation periods macrophages containing hemosiderin are abundant in the injured areas. 72 hours after the experimental procedure intraepithelial edema in the epithelial lining of the duct still is observed. A distinct invagination of the epithelial cells into the clot and thickening of the squamous epithelium are also found (Figs. 11, 12). A laceration in the median wall of the duct, probably another canular lesion, can be demonstrated in Fig. 13.

At 7 and 14 days following the injury, epithelial metaplasia from columnar to squamous epithelium in the damaged area of the duct can easily be discerned (Figs. 14—18). Goblet cells are not found in the injured area at any observation time in this study.

At observations 7 and 14 days after the experimental procedure the subepithelial layer of the nasolacrimal duct demonstrates a pronounced increase in the number of fibrocytes (Fig. 16). This increase of fibrous tissue may be reversible, however, the significance of this feature needs longer observation periods in order to be assessed.

In the originally damaged area of the oral mucosa a gradual organization of the tissues operated upon is observed during the healing period. Immediately after the operation, formation of a blood clot initiates the healing process. The number of leucocytes in the area as well as in the neighbouring tissue is pronounced, especially during the first 2—3 days postoperatively. Formation of leucocytes in groups, like small abscesses in submucosa, are seen som places. However, at the late observation periods the epithelium have proliferated and the original incision is covered with regular oral epithelium.

Table I.

Mean number of labeled epithelial cells of nasolacrimal duct in 13 experimental animals

Experimental period	Number of labeled epithelial cells	
	Injured side	Noninjured side
6 hours	92.32	73.71
24 hours	143.00	58.83
48 hours	115.67	63.67
72 hours	84.33	59.00
7 days	88.50	49.67
14 days	70.67	34.00
sham 24 hours	71.67	67.33
sham 72 hours	70.00	65.67
sham 14 days	66.67	56.67

When examining the epithelial lining of the nasolacrimal duct in the non-operated side this does not appear to be influenced by the contralateral trauma.

Autoradiographic observations

The observations are based upon findings in the autoradiographs following H3TDR »flash» labeling and limited to the epithelial lining of the nasolacrimal duct.

The observations are restricted to the number of H3TDR labeled epithelial cells and their location in the ductal epithelium. Labeled epithelial cells were identified and counted within the 4 different quadrants of the nasolacrimal duct as they appear in frontal sections (Figs. 19 a—h). The distribution of labeled cells in the examined epithelial wall are plotted to these tracings. The sequence of number and distribution of H3TDR labeled cells in the above defined areas were counted in 3 specimens from each animal. The mean values of labeled cells of each observation period are recorded in Table I. The autoradiographic data demonstrate a rapid increase in the number of labeled cells. This rapid increase of proliferation is followed first by a distinct (48—72 hours), later by a mild (7—14 days) decrease in proliferative rate of the epithelial cells. The distribution of H3TDR labeled cells is semi-schematically demonstrated in Fig. 19 a—f. The tracings reveal that the experimental trauma leads to an increase in proliferative activity mainly

restricted to the injured quadrant. Furthermore, this increased number of H3TDR labeled cells is observed both proximal and distal to the perforation.

The sham operating procedure performed in 4 animals, sacrificed after 6, 24, 72 hours and 14 days, do not seem to affect neither the proliferative activity nor the histological features in the ductal epithelium on either the injured or non-injured side (Fig. 19 g—h) in any of the animals.

DISCUSSION

The anatomical features of the upper respiratory tract in the guinea pig are based upon observations by *Klein* (1881 a, b), *Alezais* (1899), *Dieulafe* (1906), *Negus* (1958) and by the present findings following dissections and histological examination of the region. *Alezais* (1899) stated that a maxillary sinus was absent in the guinea pig, a feature common for rodents (*Dieulafe*, 1909, *Negus*, 1958). A maxillary sinus is found in larger animals like dogs or monkeys, but the cost of the isotope made it prohibitive to use such animals.

Klein (1881) maintained that the columnar cells lining the nasolacrimal duct appeared covered with cilia on the surface. This observation has not been confirmed in this study.

In the present experimental study the cellular reactions occuring within the first two weeks postoperatively following an oro-paranasal communication were studied. Previous studies have indicated that ciliar restitution, if reappering at all, do so within 4—10 weeks following injury to a respiratory epithelium. (*Boling*, 1935; *Garschin*, 1936, *Wilhelm*, 1953; *Otto & Wagner*, 1956; *Sanderud*, 1958; *Burian*, 1960). For this reason, since the present examinations were limited to short observation times, the nonciliar nasolacrimal duct lining of guinea pig, served the purpose.

It was of particular interest to find that a localized lesion to the paranasal epithelium lead to extensive changes involving a major portion of the ipsilateral paranasal mucous membrane. This was demonstrated by the autoradiographic observations which further indicated that tissue damage initiated a rapid increase in the cellular proliferation. This was followed by a gradual decrease over a period of time 7—14 days after the injury to values as observed in noninjured ductal epithelium. In this way the differentiated epithelium reacted in the same way as any undifferentiated mesenchymal tissue in population (*Tonna & Cronkite*, 1962).

From the present findings it appears that metaplastic changes from a pseudo-stratified columnar epithelium to a non keratinized squamous epi-

thelium in the area of the bur lesion occurred within 24—48 hours following the trauma. These metaplastic features can even more clearly be demonstrated at longer observation periods. This observations are in conformity with those of *Boling* (1935), *Garschin* (1936) and *Sanderud* (1958). Furthermore it is of interest to observe that the effect of a limited and localized injury (canula lesions at 48 and 72 hours) rapidly induced metaplastic changes in a small area of respiratory epithelium. The downgrowth at 24 hours observation in the median wall may probably be a result of a complicating bur lesion diagonally to the planned lesion produced by the experimental procedure. The close relationsship of the bur lesion performed to the nasolacrimal duct and the maxillary incisor (Fig. 1), did only in one of the experimental animals result in a slip of the bur with a subsequent lesion to this portion of the tooth germ.

The findings in this study covering a 14 days observation period do not justify any discussion of whether the metaplasia of the ductal epithelium following traumatic and inflammatory injuries was reversible or not. *Knowlton & Mc Gregor* (1928), *Mc Gregor* (1931), *Sanderud* (1958), *Burian* (1960) have all demonstrated that metaplastic changes of respiratory epithelium may be reversible if the observation periods are prolonged, i.e. 2—8 weeks following the injury, depending on type of respiratory epithelium, animal species and experimental procedure.

The fibrous reaction of the subepithelial layer which occurred following a local injury to the epithelium has been emphasized by *Gorham & Bacher* (1930) and *Boling* (1935). The present observations were in harmony with these findings, clearly visualized by a pronounced posttraumatic fibrous reaction of the submucosa. The final result in this may obviously lead to the formation of scar tissue lacking the normal structure of the submucosa. The formation of this scar-tissue may be an important factor in the later phases of repair.

The importance of persistent oro-paranasal fistulas in the establishment of irreversible metaplasia of the paranasal epithelium cannot be evaluated from the observations of this study. This is due to the fact that closure of the communication with bony regeneration did occur in all experimental animals.

The degree of influence of oral infection to the injured tissues thus remain unsolved. However, the experimental technique performed, introducing oral infection to the paranasal mucosa, is not unlike that occurring in dento-alveolar surgery. According to the reversibility of the proliferative activity following the trauma in this study, infection does not appear to be a main factor in this particular type of injury. Finally, it should be stressed that the area of epi-

thelial metaplasia is limited, mainly restricted to the area of traumatization. In this way it may be assumed that the observed cellular reactions are mainly due to the experimental trauma and not a result of secondary wound infection.

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