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Histopathology on non specific sinusitis

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THE HISTOPATHOLOGY OF NON-SPECIFIC SINUSITIS.

A THESIS WRITTEN IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE DOCTOR OF MEDICINE, TO BE GRANTED BY THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE.

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APRIL 26, 1935.
I wish to take this opportunity to thank all those who have helped me with this paper. I especially wish to thank Dr. W. P. Wherry, who gave me his very valuable assistance unselfishly. I also wish to thank the library staff of the University of Nebraska College of Medicine for their efforts in providing me with reference material and helpful suggestions. —— the author.
In writing upon the subject of histopathology of the paranasal sinuses one is faced with a wide range of rapidly accumulating literature of which only the more recent has laid any stress upon the microscopic pathology. It is quite difficult in any of this literature to find an adequate description of normal histological features of these accessory nasal structures. Excuse of course, may be made for the workers in this type of research when it is realized that the epithelium, and to a second degree, the underlying connective tissue of a sinus mucous membrane, is subject to tremendous environmental change. This is true to such an extent that it is very difficult to establish a normal criteria of the histology of the paranasal sinuses.

By way of limitation of the subject matter of this paper I choose to make some statement concerning the normal histology of the paranasal sinuses as they are now regarded. I next purpose to portray some deviations from the normal as produced both by bacterial and sterile irritants. I am making no attempt to record any work done before the middle of the last decade because such work as was done in this particular subject is largely of no value.

It is my purpose to consider the sinuses from the viewpoint of what is happening in the cells of the mucous membrane rather than to arbitrarily divide them into acute and chronic sinusitis phases and to attempt to lay down a specific picture in each case. Sinusitis, for the most part,
does not follow any specific pattern but tends to be subject to all the laws of heredity, environment, resistance, and virulence.

The mucosa varies also in different individuals of the same species even under the same conditions of environment. Nevertheless, a comparison of the mucosa of different patients and different bits of mucosa of the same patient show many points of similarity.

In a broad general way the mucosa of the sinuses is similar to that of the nasal region proper but differs in that it is thinner, less vascular, contains fewer glands, and does not have erectile and muscular tissue in the tunica propria.

I will now consider the four layers that make up the mucosa, giving the outstanding points of histology as interpreted by LeRoy Schall (1932), and Latta and Schall (1934).

The first layer is made up of columnar epithelium of a simple type (as defined by Latta and Schall and at variance with most investigators who have considered it to be stratified or pseudo stratified columnar epithelium), which is ciliated throughout the mucosal lining of the sinuses. The epithelium is replaced here and there by single goblet cells which are noted in various stages of change and which are thought by Latta to possibly be the earliest manifestation of a deviation from the normal. The most interesting feature of this layer is the cilia which are kept in constant motion and are covered with a thin layer of mucus which is kept in motion by a steady wavelike motion of the cilia.
The second layer is the basement membrane which is a thin band of unstained or faintly stained tissue, collagenous in character, on which the epithelial cells rest. It is of uncertain origin but is thought to be of connective tissue derivation due to its faculty of taking the connective tissue stain. It varies in thickness and may appear to be absent because of its delicate character. It reaches the greatest thickness in chronic infections. It is cribiform allowing processes of the underlying connective tissue of the tunical propria to extend into the epithelium and in this way permit the passage of cells to the surface of the epithelium.

The third part of the mucous membrane is the tunica propria or the structural connective tissue framework. This tissue consists of a fibro-elastic connective tissue network, serving to attach the membrane to the underlying structures. This tissue is superficially rich in cells and loose in type. In the deeper layers the stroma is compact and condensed with the progressive appearance of elastic fibers. The cellular elements consist of fibroblasts, occasional lymphocytes, ameboid wandering cells and possibly histiocytes in as near normal membrane as has been seen. The blood supply is obtained through vessels entering deep in the stroma. These vessels branch through the tunica propria to form a dense capillary network beneath the epithelium, and around the neighboring glands. The venous return is by way of superficial blood spaces leading to deeper venus plexuses. The glands encountered are of varying type and may be simple straight tubules lined with goblet cells or may become tubo-alveolar in type.
The fourth layer of the mucous membrane is a very dense
layer of the tunica propria just described. It is firmly
attached to the bone and is known as the pseudoperiosteum
and contains a scanty, thin network of slender bloodvessels.

The histopathology of the paranasal sinus mucosa can
very naturally be classified on the basis of whether it is
a chemical or a bacterial irritant that is causing the
variance from normal. In recent years a great deal of work
has been done in determination of the response of body tissue
to irritants but it was not until very recently that this
type of study was made with any degree of success on the
paranasal sinuses. We are indebted to such men as Mosher,
McGregor, Fenton, Larsell, Dean, Proetz, MacMahon, LeRoy
Schall, Ross, and Hilding, and more recently we might add
the names of Latta and Schall for their contributions on the
study of sinus epithelium.

Until comparatively recent time very little was known
concerning the cilia of the mucosal epithelium beyond their
actual existence. The paranasal cilia are the first line of
defense of the whole mucous membrane. The cilia are much
more active than first supposed and resistant to a much larger
degree than would seem compatible with their construction.

The ciliated epithelium of the sinus mucosa tends to
regenerate almost completely if conditions are right and
even though conditions are somewhat unfavorable, the process
is attempted with a dogged indifference to the contradicting
and antagonistic factors. Vascular granulation is necessary
for the regeneration of cilia.
In portions of the sinus which are poorly or incompletely vascularized fibrous tissue formation is rapid and banding or scarring or diaphragm formation takes place without regrowth of ciliated epithelium. Experimentally it is found that sinus mucosa which is laid bare and exposed to open air loses its power to regenerate its normal ciliated epithelial cells and forms in their place cuboidal or squamous epithelial cells which are of course, not ciliated. It is further found that if a nostril is plugged, allowing the entrance of no air, that the ciliated epithelial cells are soon replaced largely by goblet cells in a much thinner epithelial layer. In this condition there is also a great formation of mucin. ( Hilding 1933).

There has been in recent years, in common with work of this type done in other body tissue, a very interesting bit of work in connection with the mineral element of the sinus epithelial cells. Wenner and Nemours, in a series of experiments with the maxillary sinus epithelium of rabbits, show the necessity of ionized calcium for ciliary motion. These workers followed the thought expressed by an earlier investigator ( Pantin 1926 ) that calcium is the one of four cations in sea water necessary for movement.

The investigators excised strips of epithelium of the maxillary sinus of rabbits and showed the ciliary motion came to a complete halt thirty seconds after application of 0.3% sodium alizarin sulphonate and four minutes after the application of 1% potassium oxalate, both substances having the power to precipitate calcium ions. In the former, recovery took place after return to a physiological solution of sodium chloride and evidently depends on reestablishment of
an equilibrium between free calcium ions and the reserve supply of unionized calcium in the cells. Wenner further shows that irrigating the sinus mucosa with calcium precipitants produces definite histological changes. The results obtained are a disappearance of cilia from the columnar epithelium and a marked infiltration of eosinophiles into the basement membrane. By decrease of the blood pH produced by intravenous administration of ammonium chloride, calcium precipitant reaction was hindered preventing the destruction of cilia and eosinophilic infiltration. Increase of pH on the other hand produced by intravenous injection of sodium bicarbonate caused loss of cilia and eosinophilic infiltration of the basement membrane. Sodium and potassium ions produced no constant changes in the presence of an altered pH.

Further work has been done in relation to other factors influencing ciliae structure of the epithelium. Fenton and Larsell (1933) performed a series of experiments in which they attempted to determine the results obtained with various diets, irradiation, calcium therapy, injected irradiated oil and the use of intradermal vaccines.

Diet variation was found to have little effect of any kind on the cilia or the rest of the mucosa. The diets used consisted of both acid and alkaline diets; also diets involving various combinations of minerals and vitamins. (I was unable to find mention of changes in pH or heat potential which it would seem would obviously affect the reading of results.)
Irradiation was found to cause damage to the ciliated epithelium but regeneration took place and in the later cases, showed a normal ciliated columnar epithelium. Irradiation has the effect of causing destruction of lymphocytes and their conversion to fibrous tissue. It next affects the blood vessel wall causing thrombosis of the capillaries and also the arterioles thus minimizing the blood supply to the irradiated area. The regeneration takes place if the lymphocytes are not too thoroughly killed. At times the columnar epithelium changes to squamous type. (Mosher 1934).

Calcium therapy by topical application seemed to cause minor damage to the epithelium of the sinuses of such a character as to be subject to repair.

Injected irradiated oil was found to damage the epithelium by means of clogging of the cilia and obstruction of the mucous flow.

Vaccine therapy seemed to have no effect on the epithelium of diseased sinuses and no very great effect on the underlying tunica propria.

I now wish to briefly mention the effect of several common sinus therapy medicaments on the pathology of the sinus mucous membrane. Silver or one of its colloidal proteins has been one of the most commonly used medicaments. It is true that silver has an astringent action and there has been considerable said of its antiseptic properties but, on the other hand, silver is capable of protein coagulation and therefore destruction of ciliary motion. Silver proteins were
devised in an attempt to decrease the irritation of the silver by combination of ions; however, if applied to a surface the silver protein gradually liberates some silver ions. The silver ions become very irritating to the cilia but this preparation is more satisfactory than inorganic silver preparations.

Mercurial germicides of the past have produced precipitation of proteins with marked mucous membrane irritation. More recently there have been more refined mercurial germicides produced such as merthiolate, metaphen, etc., for which is claimed a high germicidal value and which apparently do not precipitate proteins. There has been little work done to prove that these antiseptics are any different or any better than those of earlier date. Most other antiseptics as phenol, chlorine, zinc, mercurochrome, the dyes, boric acid, etc., are commonly used but are mostly harmful to the mucous membrane. (Although such has appeared in the literature about various antiseptics in the mucous membrane, the fact remains that it is very difficult to change the bacterial flora of the sinuses through topical application). (Wherry 1935.).

Ephedrine solutions may be used in the sinuses without injury to the ciliated epithelium if kept within the threshold of tolerance and used over specific time limits. (Carmack 1933).

The epithelium cells present a very interesting picture in acute inflammation. The cells are more closely packed together brought about by hyperplasia and thickening. The goblet cells are not greatly increased in number but the superficial cells appear to be more heavily ciliated. In a condition
of this kind there is an accompanying inflammatory process in
the underlying connective tissue of the tunica propria. The
process may go on to such an extent that the epithelial cells
lose their strictly columnar appearance and the epithelium be-
comes stratified columnar in type.

In conditions of chronicity larger numbers of goblet
cells are found in the epithelial layer. In some cases, the
ciliated cells are greatly compressed but tend to spread out
to cover a greater area with cilia. In the more advanced de-
generative cases the whole surface may be covered with goblet
cells with absence of ciliated cells. The origin of these gob-
let cells seems to be the basal layer of epithelial cells but
there is some appearance to indicate that they may originate
from the ciliated cells. The goblet cell represents a de-
generating type of cell whose life of usefulness is over, upon
pouring out of its secretion. Regeneration of epithelium
apparently occurs from the irregular cuboidal cells of the
indifferentiated basal layer which are not involved in any
degenerative sloughing process unless the conditions of the
environment are very severe and then only part of them are
affected. These cells are believed to possess the potentiality
of forming either ciliated or goblet cells, depending upon the
environmental stimulus present while they are differentiating.
( Latta and Schall 1934 ).

The studies of Mosher, confirmed by Proetz (1931 ), who
made studies of the living cells of the mucosa of the sinuses
by use of teased tissue in saline solution on a warm, cupped
slide, are very interesting. He found that the living cells
under oil immersion were two to three times larger than in
the corresponding hardened prepared section. He observed that Brownian movement was constant and that the white blood cell moves slowly while the red blood cell moves quite rapidly. His observations on ciliary motion are illuminating, more so than any previous work on the nasal cilia. He found that the cilia move very energetically and seem to possess a strength beyond that of their size. Observation showed them to be strong enough to toss a wandering blood corpuscle in the air like a football. Mosher suggests that their action reminded him of a man shoveling coal. The cilia seemed to be fully as long as a blood vessel is wide. The author also proved that, contrary to the existing belief, cilia are not injured by infection because he found live cilia in forty cases of infected sinuses, Knowlton (1938) made a study of the regeneration of sinus mucosa in which he used three dogs in each of which he curetted out the antral mucosa. He then posted the dogs at varying intervals of time and examined the mucosa to determine the amount of regeneration obtained. The dog posted at the end of one month showed the epithelium to be bridging across an engorgement of organized red cells in a single basement layer with beginning formation of a true epithelium with goblet cells and cilia before even the fibroblastic tissue could replace the initial granulation tissue. After three months a second dog was posted with the finding of much more mature fibroblastic tissue and a more secure epithelium with particularly large goblet cells. After five months the third dog was posted and at this time the epithelium had assumed a near normal appearance with fewer glands.
The basement membrane layer of the sinuses is rather an inconsistent structure according to LeRoy Schall (1932). Its origin is uncertain though there is some belief that it is a derivation of connective tissue because of its faculty of staining with connective tissue stain. It varies in thickness and may be so delicate as to appear absent. It usually shows thickening in conditions of chronicity. It is cribiform allowing processes of the underlying connective tissue to extend into the epithelium and permitting passage of cells to the surface.

In discussing the pathology of the tunica propria these changes may be divided into those produced as a result of alteration of the blood stream and those due to variation of the cellular content.

As conceived by most pathologists the alteration in the blood stream is first a temporary constriction of the vessel with an acceleration of the blood stream. This is followed by a dilatation of the vessel and a slowing of the blood current.

Examination of the blood flowing through the blood vessel shows a normal central axial zone which contains the blood corpuscles and a peripheral zone which contains the blood plasma. With dilatation of the blood vessel wall the current is slowed and consequently the lighter cells of the central zone appear in the peripheral zone. This causes the leukocytes to lag along the blood vessel wall and adhere. Finally by diapedesis they pass through the wall into the surrounding tissue and migrate toward the point of injury. The fixed tissues migrate toward the point of injury as fixed tissue cells.
12.

In mucous membranes such as the sinus mucosa there is a dense capillary network immediately below the basement membrane and it appears reasonable that the most marked change should occur mostly in this region. In acute inflammation there is a dilatation of the tissue spaces just beneath the epithelium with an increase of the cellular elements. As the infection passes from the acute to the chronic stage the polymorphonuclears vanish and the cellular element of most prominence is the small lymphocyte.

One might therefore say that the response to chronic inflammation is a thickening of the blood vessel wall and an increase of the cellular elements of the tissue. In most infectious processes the cellular elements consist of lymphocytes, plasma cells, connective tissue cells, and endothelial cells. In some conditions as asthma and other allergic manifestations the eosinophiles may show a marked increase.

Chronic inflammation may take on any of the following types as classified by LeRoy A. Schall:

1. Edematous
2. Infiltrative
3. Fibrotic
4. Cystic
5. Degenerative

The edematous type is characterized mainly by edema in the superficial stroma in the dense capillary bed beneath the epithelium. In this type cellular elements are not prominent, but the vessel walls are thickened and there is dilation of the glands.

The infiltrative type of chronic inflammation has a cellular predominence, largely of lymphocytes. Infiltration
is seen throughout the stroma but is more predominant around
the glands, and beneath the basement membrane. In certain
areas the infiltration may reach such an intensity that the
clumps of lymphocytes may resemble lymph-nodules.

In this variety of inflammation as well as all other
types of chronic inflammation the glands are exceedingly
numerous. It is not definitely known whether this is an
actual increase in the number of glands or whether the glands
seen are normally present and seem more numerous because they
are more easily viewed in their dilated and engorged state.
The blood vessels are likewise more easily seen and have a
more thickened wall.

In the fibrotic type of inflammatory reaction the predom-
inating feature is fibrosis. There is a marked increase of the
fibrous tissue, constriction of the glands, and a marked
degree of the cellular elements even over those normally
present.

The most prominent feature in the cystic type is many
cysts. The cause of the cysts is debatable. One theory is
that the cystic changes are due to blocking of the ducts
of the gland by occlusion of the lumen. Another theory is
that the lumen is choked by periglandular infiltration.
Either theory may be right and the prominent feature in micro-
scopic section is that of multiple cysts.

The term degenerative, is added to this list not because
it is very descriptive but to comment on the findings of a
number of investigators such as Mosher and Ross that there
really is no true degenerative inflammatory process in the
sinus mucosa. It has already been noted that Mosher found
living functioning cilia in more than forty cases of pus in
the maxillary sinus of long standing. (LeRoy Schall, 1932).

Before going into any further description of pathologi-
cal change in the mucous membrane of the paranasal sinuses it
would seem necessary to discuss briefly the method of study
which has been used in experimental work to determine the type
of cell found in the tunica propria layer of the mucosa. I
refer to the vital staining technic. This technic makes use
of the fact that on introduction of certain dye substances
into the living organism certain cells of the tissue being
studied will elect to take the dye and these cells may be
studied in the organism after death.

Fenton (1931) made use of vital staining for the first
time that it was ever used in sinus study. His method was
use of extreme dilutions of trypan blue. He used one drop of
1% trypan blue solution per 15 cc of physiological sodium
chloride solution for surface staining of human material in
the incubator and the repeated injection of a few minims of the
1% solution for selective staining of the tissues of the
living animals.

This investigator believes that it is necessary to
attach considerable importance to the histiocytes of the sinus
tissue because of their marked phagocytic power and because of
their earlier appearance than either the lymphocytic or
polymorphonuclear leucocytes. In consideration of the various
cellular elements of connective tissue it is well to present a
summary of these structures as presented by Maximow (1930);
In the main, three large groups of cells can be distinguished in connective tissue and in the blood: (1) Fixed highly differentiated elements, which, as fibroblasts produce collagen; as endothelium provide blood channels with their cellular lining; and as changed elements can be designated as fibroblasts or as fibrocytes; (2) fixed or free element which phagocytose, store dyes and various other colloidal substances, and play a part in the general metabolism and body defense. These are the histiocytes or resting wandering cells; (3) free cells which circulate in the blood or are scattered in the connective tissue; these are the hemocytes. Among them are to be distinguished: (a) undifferentiated cells, the hemocytoblasts, which serve as stem elements, as granulocytes, monocytes, erythrocytes, and megakaryocytes, which arise from the hemocytoblasts.

Inflamed connective tissue shows three main cell types: (1) the heterophil leucocyte which migrates from the blood vessel at the very beginning of the process and after playing its part degenerates in the tissue. (2) the fibroblast in which mitotic division takes place very rapidly under the stimulus of inflammation to form granulation tissue and later to elaborate the collagenous fibers of the scar. (3) The mononuclear exudate cell, an ameboid, phagocytic, nongranular cell of great diversity of appearance and capable of transformations from which comes their name polyblast.

In the course of inflammation, the fibroblasts proliferate but keep their original structure rather well intact. The author claims that they are never transformed into amboid
wandering cells or leukocytes as several investigators have claimed.

The polyblast cells referred to above are of several types. The one which has excited the most attention in the rhinology field is the histiocyte. The histiocytes form a portion of the polyblastic cells. These are, however, other cells which take a part in the polyblast formation and to a probable greater extent than the histiocytes. These cells are the lymphocytes and monocytes of the blood stream which migrate out into the tissue, undergo a rapid hypertrophy and are transformed into large polyblastic elements. Therefore we have polyblasts from two sources. The histiocytes of local origin and the mononuclear and lymphocyte cells from the blood stream.

In the later stages of inflammation when there is formation of scar tissue, the polyblasts remain scattered among the fibroblasts. They become nonmotile cells and may be transformed into fibroblasts. (Maximow, 1930).

See table on next page.
Fixed, undifferentiated, mesenchymal cell

- Chondrocyte
- Osteoblast

\[ \text{Endothelial cell} \quad \text{(in the embryo)} \]

- Granulocytes
  - (in the embryo and in ectopic myelopoiesis)
- Fat cell

- Histioocyte
  - (in inflammation and in tissue cultures)

- Active polyblast
- Monocytes
  - Histiocyte (in inflammation and in tissue cultures)

- Myelocytes
  - (3 types)
- Granulocytes
  - (3 types)

- Erythroblast → Normoblast → Erythrocyte

??Platelets??

- Megakaryocyte

(Unitarian theory of blood and connective tissue formation after Maximow.)
In the cat material used by Fenton and Larsell (1933), the histiocytes showed trypan blue granules on section due to the vital staining technic already described. All of the animals used were studied at intervals of forty-eight to seventy-two hours after injection of the 1% trypan blue subcutaneously.

The investigators tried by use of a number of substances to find out what types of irritants called forth a histiocyte response. Injection of castile soap caused the entire mucosa to be edematous, somewhat injected and filled with pus cells which had penetrated the epithelium until it was scarcely recognizable.

Thin glucose solution showed destruction of the epithelium, with a mucosa filled with pus cells, with but few histiocytes.

An emulsion of fifty percent coccanut oil with agar seemed to injure the free ends of the cilia, clogging of the cilia and considerable mucous secretion. The tunica propria was somewhat injected but otherwise quite normal. Histiocytes were present in normal numbers but the leukocytes were present in large numbers.

Jelly of chondrus crypus which contained salt caused uneven thickening and injection of the mucous membrane with a large number of leukocytes and few histiocytes.

Mucilage of tragacanth caused little injection or thickening of the mucosa but did cause considerable mucous secretion with enlargement of the goblet cells. Pus cells were frequent in the tunica migrating toward the epithelium.
Milk of magnesium produced large numbers of histiocytes but destroyed the epithelium to a tremendous extent.

Petrolagar with ten per cent glycerine left the epithelium intact and produced large numbers of histiocytes. The goblet cells were noted to be swollen and some lymph follicles were found under the epithelial layer.

Calcium hydroxide of five per cent strength, emulsified with one-half per cent agar, showed destruction of cilia, epithelial damage and marked migration of leukocytes through the epithelium. The tunica propria showed large numbers of polymorphonuclear cells, some lymphocytes and plasma cells with very large numbers of histiocytes which in common with most of these specimens of cellular migration showed the histiocytes to be migrating toward the epithelium.

Calcium lactate of one per cent strength caused bad epithelial destruction but caused a wonderful cellular response of all the defensive cells of inflammation, especially the histiocytes. In spots where the epithelium was nearly destroyed the histiocytes formed a quite continuous layer at the basement membrane of the epithelium.

Sodium phosphate one per cent with two per cent gelatin showed a rather normal mucosa somewhat swollen in spots. Histiocytes were present in somewhat more than normal numbers.

Scarlet red five per cent with oxyquinolone sulphate two per cent, as used for stimulation of skin grafts, caused mucosal edema and epithelial damage with loss of cilia in some areas. Leukocytic migration took place but there were very few histiocytes present.
Dichloramin two per cent in chloroform caused only unusually large goblet cells with the other findings being normal.

The investigators then tried a double antrum experiment. The right side of the animal was injected with a virulent hemolytic streptococci of a known variety affecting the upper respiratory passages. The injection was performed in semi-liquid gelatine culture. The left side of the animal was studied as a control. Two days after infection of the right antrum, a vaccine was made up of the same organism and one cc. was injected intradermally. Another injection of vaccine was given two days later and after two more days trypan blue was injected and the material fixed. The infected sinus showed slight hyperemia and in section the membrane was hyperemic and edematous, the epithelium tall, with many mucous cells. At some points there were numerous lymphocytes and leukocytes with great thickening of the mucosa. At such areas, the epithelial cells were elongated and the cilia along with their mucous coat absent. The investigators assume that it is at these latter points where infection finds its way into the deeper structure of the mucous membrane. Very interestingly the control (left) side was entirely normal aside from a definite increase in histiocytes and plasma cells.

From this series of experiments the conclusion drawn by Fenton and Larsell, is that the local use of solutions or suspensions of the alkaline-earth salts or hydroxides favors the mobilizing of histiocytes in acute inflammation.
The further conclusion is reached that oily and colloidal substances are destructive of epithelium, favor infection by interference with ciliary action and cause invasion of the subepithelial layer by polymorphonuclear leukocytes without any increase in the number of histiocytes. Chlorides were noted to favor edematous changes with marked increase of lymphocytes. Plasma cells seemed to be the invariable accompaniment of the prolonged fibrous changes. (Fenton and Larreil, 1932).

From all of these painstaking experiments it has been determined by Fenton and his coworkers that the histiocytes are the first line of defense of the tunica propria after the irritation has passed out of the control of the ciliated epithelium. As long as the epithelium is able to combat irritating substance, be what it may, the histiocytes do not come into play but as soon as the epithelium is broken through and providing that the substance causing the irritation is not destructive or inhibitory to histiocyte formation, these elements come into play.

Fenton (1932) set up the following tabulation of function of the various cellular elements of the mucosa. He considered that for the most part presence of the eosinophile denoted allergy. The lymphocyte was considered to be an indication of active reparative process. The polymorphonuclears were considered as being an early phagocytic agent and were not seen to have any value in the reparative process and to be nearly absent in the sections showing repair. The histiocyte play a defensive role in the mucosa not only by their power
to act as phagocytes but also from the standpoint of pure mechanical defense by laying down an actual layer under the epithelium at a point where infective agents try to break through.

Mullins and Ball (1928), previously to the work of Fenton and Larsell, set up a somewhat different classification of the histology of the sinus mucous membrane. Their classification consisted of four groups.

They first considered edema as a polypoid appearance with a serous clear fluid drip on cutting, which is not at all in contradiction of any other investigator's work.

Their second group consisted of fibrosis and their claim was that it was not always associated with a leucocytic reaction. As the studies of these investigators were taken from cases in their clinics it is quite conceivable that they examined many specimens of fibrotic material where they saw no leucocytes because that phase of the sinusitis was past and what they were seeing was sinus tissue healed by connective tissue fibrosis.

The Mullins and Ball third group is the leucocytic reaction group and they report that the monocyte is most frequently found. (A cell little mentioned by LeRoy Schall). These investigators also mention large numbers of lymphocytes and plasma cells which is compatible with the later work. They mention that polymorphonuclears are present in the mucosa of inflamed sinuses but not in the proportion of the rest of the body. I have not in my survey of the literature
found any comparison by other investigators of the relative proportions of these cells in relation to other body tissues undergoing inflammation.

The fourth group as classified by these investigators is the glandular hyperplasia and atrophy group, which according to them, consists of distension of the glands with mucoid material and very little other pathological change. This is not the thought expressed by other investigators mentioned who believe that gland hyperplasia is part of the picture of a quite massive change in the histology of the mucous membrane.

CONCLUSION.

In making a survey of the literature on this subject one is met with a large number of articles, many of which are accompanied by many microphotos. One point stands out on examination of these photos. Very few of them seem to resemble one another. There are many different reactions in the sinus mucosa and the same pathological picture is seldom obtained on repetition. There are, however, certain rather well defined reactions and postulates of the sinuses which are binding in any pathological process of the sinus mucosa and it is these reactions which I have attempted to discuss in this paper.

I have reached the following conclusions:

1. The nasal cilia and their enveloping coat of mucin are the primary defense mechanism for the sinus epithelium as well as the remainder of the sinus mucosa.
3. The epithelium, as normally found in the sinus mucosa, is the simplest variety of columnar ciliated epithelium.

3. The goblet cells found in the epithelium of the sinus mucosa are probably an early indication of later pathology. (There has been little work done on this subject which is deserving of more investigative effort).

4. The cilia of the sinuses tend to regenerate even though conditions are very much adverse. Similarly, in the presence of even severe infections the nasal cilia tend to keep in constant motion.

5. The presence of an intact epithelium is in itself a barrier to infection of the sinus mucosa underlying it.

6. The ability of the blood stream to bring cellular elements to the tunica propria layer of the mucosa as needed is a defense mechanism. The capillary bed of the tunica coat, directly beneath the basement membrane is a potent factor in the prevention of further spread of inflammation.

7. The number of polymorphonuclear cells present is an indication of the acuteness of the infection.

8. The histiocytes are the primary defensive mechanism of the tunica propria but are secondary in my opinion as a defensive mechanism for the mucous membrane as a whole. In defense of the mucous membrane as a whole I would place the histiocytes secondary to the ciliated columnar cells.

9. I am forced to consider the various diet and topical applications, as well as internal application of drugs, experiments as not conclusive until the conditions of pH, heat potential, and other physical factors are more adequately controlled.
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