THE HISTO-PATHOLOGY OF SINUSITIS*

By H. A. LUCAS (London)

THE causes of sinusitis are complex so that some consideration must first be given to nasal physiology. Little is known of the function of the nasal sinuses, but the nasal sinuses and the nasal cavity form a functional unit, and what affects the one reacts on the other.

The nose is the natural portal of entry to the respiratory tract, and one of its chief functions is to prepare the inspired air for the delicate respiratory endothelium of the lungs. Adequate temperature and humidity are essential for rapid gaseous exchange in the lungs. The temperature of the inspired air is raised, by increasing the blood flow to the erectile tissue. This acts as a radiator, and heating is augmented by the warm air expired through the nose.

Humidification is effected by evaporation from the surface of the mucosa which is kept moist by the mucous glands, whose activity depends on the blood flow.

Gross filtration is done by the vibrissae at the nasal vestibules, but the cleansing is mainly carried out by the action of the cilia, which keep a continuous stream of mucus, moving in waves over the surface of the mucosa. This mucus blanket, acts as a conveyor belt carrying all particulate matter deposited on it to the nasopharynx and pharynx where it is swallowed. This mucus blanket is the most important factor in the defence mechanism of the nasal mucosa, it depends on two things, the action of the cilia and a continuous out-pouring of mucus of the correct viscosity.

Alteration of the pH, lowering of the temperature or increased viscosity of the mucus slows down the action of the cilia. Trauma, increased air currents, especially dry cold air, or obstruction, rapidly causes drying of the mucosa, with death of the cilia and metaplasia of the epithelium to a squamous type. The nose is unable to cleanse itself by muscular movement, hence the importance of this clearing mechanism.

The vascular system in the nose is composed of arteries emerging from the bony walls which terminate in capillary networks in the sub-epithelial layers of the mucous membrane. These capillaries connect with veins which in the deeper parts of the mucosa form plexuses, the so-called erectile tissue, this differs from true erectile tissue in that there is no arteriovenous anastomosis. The walls of these venous plexuses

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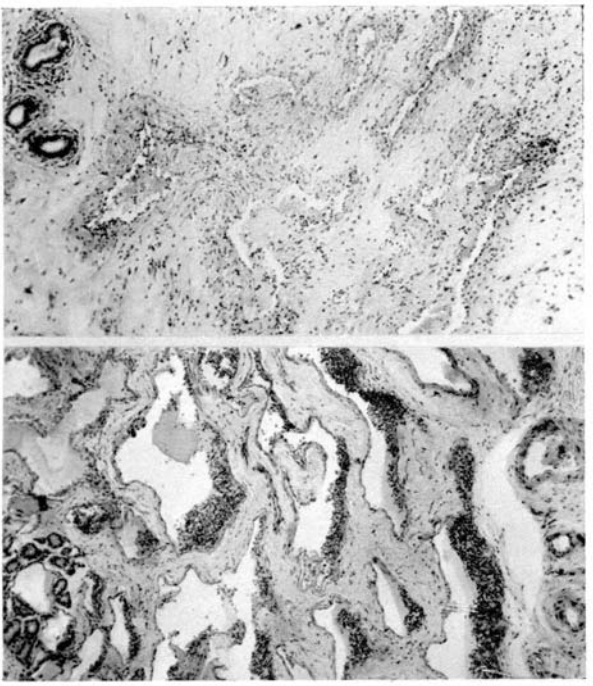


FIG. 1.
The Erectile Tissue × 54.
The top figure shows the muscular walls of the sinus when contracted. The lower figure shows the sinuses dilated.

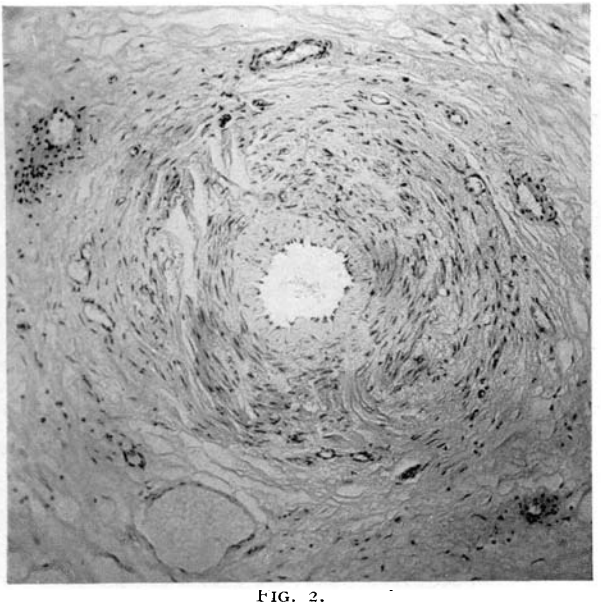


FIG. 2.
The Sphincter Musculature × 110.

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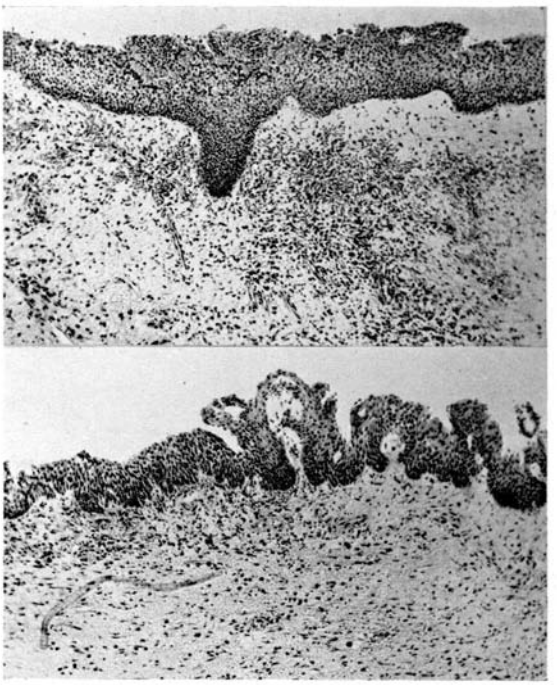


FIG. 3.
Squamous Metaplasia × 75.
Various degrees of change are shown in different areas.

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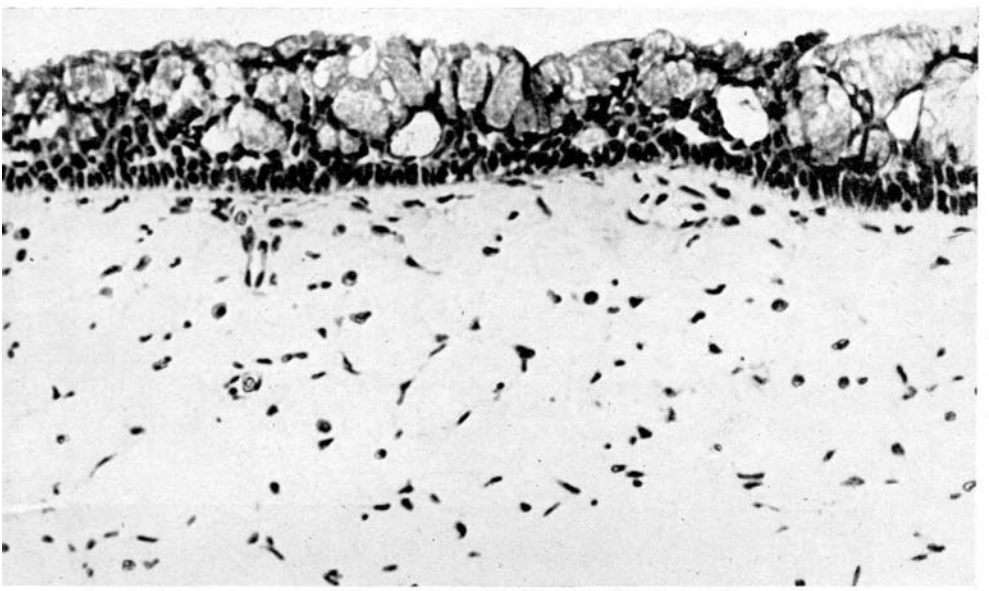


FIG. 4.
Mucosa of Polyp × 280.
From a large polyp which caused unilateral nasal obstruction.

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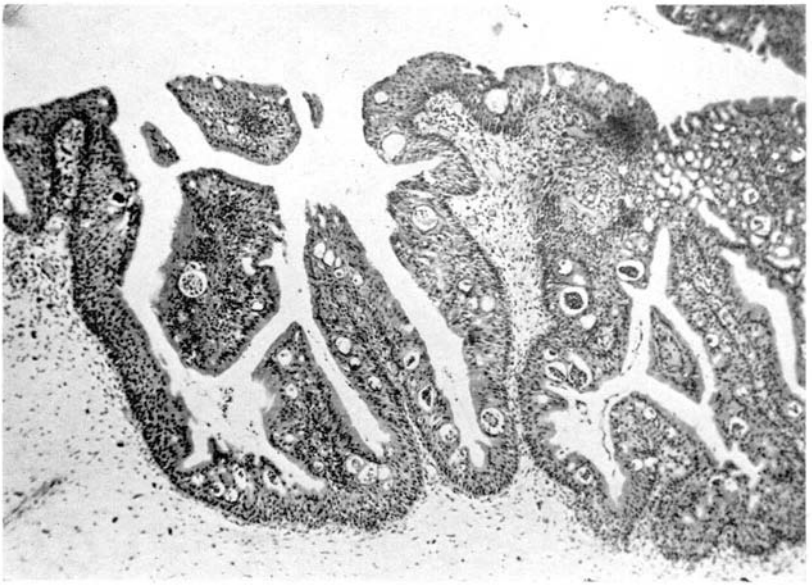


FIG. 5.

Antral Mucosa × 75.

From a case of bilateral polyposis eight months, with epistaxis. The effect of drying on the mucosa is shown and the small intra-epithelial abscesses.

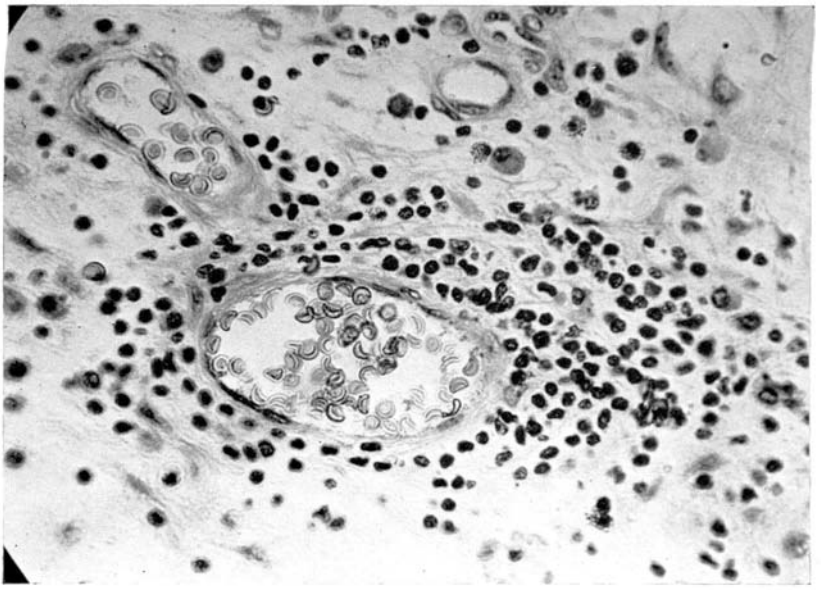


FIG. 6.

Allergic Polyp × 550.

Early reticulo-endothelial proliferation around a capillary vessel. Plasma cells can be seen towards the periphery of the field.

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contain smooth muscle arranged in a spiral manner around them and the system is closed by sphincter muscles which lie deep, close down to the bone (Figs. 1 and 2).

Some descriptions of the erectile tissue in man omit any reference to these sphincter muscles, but their importance, I think, is obvious.

This muscular vascular system is controlled by the autonomic system. This is shown by the action of drugs introduced into the nose, or if stimulation in the form of heat is applied to the superior cervical ganglion, a severely occluded nose can be rapidly cleared so that there is a free airway. It is difficult to see how this sudden clearance could occur except by the relaxation of these sphincter muscles. This system is also acted upon by hormones. The best clinical example is the rhinitis and sinusitis which occurs at the menopause, and the changes observed in the nose during pregnancy.

This vascular system is the means whereby the normal nose reacts to all environmental changes. The absence of this function is well seen in atrophic conditions, and congestion of the erectile tissue is present in all cases of " Stuffy Nose ".

Changes Due to Drying and Mucus Stagnation

It is well known that the anterior ends of the middle turbinates are frequently covered with squamous instead of normal respiratory epithelium. The same occurs in other parts of the nasal cavity or sinuses if they are exposed to direct air currents and to drying. Mucus cells disappear, the cells become taller, crowded, and cylindrical shaped ; if continued the cells become squamous, the epithelium becomes hypertrophied and even papillary. All stages may be seen to a greater or lesser degree in different areas (Fig. 3).

If the nose is occluded as was done by Hilding (1932) in animals, the cilia disappear and the cells become distended with mucus globules, this may involve the glands which undergo cystic dilatation. Sternberg (1924) believes that the ciliated columnar cells can become mucus secreting cells when conditions demand it. Similar changes to these are seen in sinuses which are obstructed and in which the mucus is stagnant (Fig. 4).

These changes have been described in the literature as Chronic Atrophic, Cystic, Metaplastic, and Papillary Sinusitis: they are common to all forms of polyposis and sinusitis, irrespective of their ætiology, and are the direct results of drying, stagnation of the mucus, and obstruction (Fig. 5).

Dixon, Hoerr and McCall (1949) studied the nasal mucosa of cases after laryngectomy and took biopsies. The squamous areas even on the middle turbinate reverted to respiratory epithelium, the mucous glands became normal and the mucus blanket was restored. The nasal cavity

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free of air currents assumed a condition similar to what is seen in a normal sinus. This indicates that these changes are reversible. It is common knowledge that laryngectomized cases rarely contract colds or suffer from nasal catarrh.

Ætiological Factors

The initial change in any pathological state in the nose or sinuses is a breakdown in the normal protective mechanism. So long as this is intact invasion by bacteria does not occur, nor does the deposition of foreign material reach the subepithelial tissues. Bacteria and inhaled foreign matter are the two agents, with which we are chiefly concerned.

Infection with pyogenic organisms may be the sole cause, or infection may be superimposed on an existing pathological state. Cultures made from sinusitis cases of all types yield virulent organisms in 20-25 per cent. of cases. In 30-35 per cent. of cases the organisms are of low virulence, and are secondary invaders, in the remainder the cultures are sterile. Thus in 75 per cent. of cases infection is relatively unimportant and possibly not the primary cause.

The nose acts as a filter for particulate matter, suspended in the inhaled air. This is chiefly dust. Dust contains pollens of grasses, trees and flowers, the spores of moulds and fungi, and small particles of such things as hairs, animal dander, feathers, wool, and cotton fibres, and this does not complete the list. The small particles in dust contain protein and are therefore antigenic. The work of Rimington and Maunsell on dust allergy has shown that a carbohydrate linked to a polypeptide association of amino acids, obtained from dust contains an antigenic substance.

Antibodies have been studied mainly in relationship to infection. Immunologists now maintain that this method of neutralizing agents harmful to the tissues is by no means confined to infections, but is part of a much wider defence mechanism employed against any foreign substance which may gain entrance to the tissues, or be formed in them by the action of enzymes, or in pathological processes. Moreover, this mechanism is in constant action, and is not confined to one organ or tissue of the body. In our problem there are two sources of inhaled material which may invoke this reaction, bacteria, and particles of protein antigenic material. Non-antigenic material does not invoke a reaction.

Globulin may be said to be the raw material from which antibodies are manufactured. Immunological studies have shown that antibodies are contained in the globulin portion of the plasma. The globulin is increased in highly immunized animals. Antibodies cannot be detected by purely chemical methods, though it is known that the beta and gamma globulin contains most of the immune antibody globulin.

Antibody globulin is formed by the reticulo-endothelial system.

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This system includes the marrow, the spleen and the lymphatic system as well as the primitive mesenchymal cells, which are capable of multipotential development and which lie on the capillary blood vessels in the nasal submucosa and elsewhere. There is general agreement that lymphocytes, plasma cells, and the phagocytic histiocytes all play a part in this formation, and that they are developed from the reticulo-endothelial system. About the inter-relationship of these cells, and the part played by each in the formation of antibody, there is less agreement. Antibodies are not all of the same type and it is probable that they are not all formed in the same way.

Sabin (1939) observed how an azo-dye antigen was taken up by the phagocytes and that its disappearance from these cells coincided with antibody production. It was also observed that a portion of the cytoplasm was shed into the lymph and subsequently taken up by the lymphocytes, which in turn repeated the process in the blood stream. Trowell (1947) estimated that 200 million lymphocytes enter the blood stream hourly, replacing an equal number which are disposed of by the reticulo-endothelial system. There is some evidence that this release into the blood stream is increased by the action of pituitary, cortical-adrenal hormones.

Plasma Cells and Antibody Formation

The work of Fagraeus and others have traced the development of antibody in plasma cells. They conclude that antibody globulin produced by plasma cells occurs in the course of their development. Thorell and others have pointed out that the staining of the cytoplasm of plasma cells is due to the high content of ribo-nucleotides and this is evidence of protein synthesis. The work of Bing, Plum, Kagan and others showed that there is a definite relationship between plasmacytosis, antibody formation and increased globulin, and it has been demonstrated that nasal polypi rich in plasma cells contain more globulin than the patient's serum.

Both Fagraeus and Ehrlich and his colleagues regard plasma cells as playing a major part in antibody formation when the antigen is subcutaneously introduced. The same is true of antigens which gain entrance to the submucosa of the nose or sinuses. This is the method of immediate or local production of antibodies (see Figs. 6 and 7).

I have deviated some way into the field of immunology to show why these cells appear in sinusitis and rhinitis. Histology is the best illustration of any pathological lesion, but its interpretation in terms of function is more important than the identification of cells.

Lymphocytes and plasma cells, which are the ones most commonly met with in all cases of sinusitis, are derived from the reticulo-endothelial system and their function is to render innocuous foreign

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substances and bacteria which gain entrance to the tissues. They fulfil this function by the formation of antibody globulin.

So far only the general nature of these reactions have been dealt with. Consideration must now be given to particular types of reaction, and it will be convenient to consider allergic reactions first, but before doing so a brief consideration of the general nature of allergy will make the conception clearer.

Allergy

Allergy has been defined as " an altered reactivity ". By this is meant a hypersensitivity to substances which cause no such reaction in normal individuals. These substances are numerous and have no chemical, physical, or immunological relationship to one another. The seasonal sensitivity to pollens is a typical example. There has been reluctance in this country to accept allergy as an ætiological factor of importance in disease. It is much more widely accepted on the Continent and in America. Perhaps one reason for this is our inability to demonstrate by experimental methods, the presence of antibodies in all cases. Antibodies can be demonstrated in anaphylaxis, by which I mean, the induced phenomenon in experimental animals by the injection of protein substances. The work of Rimington and Maunsell showed that hypersensitivity could be demonstrated to a carbohydrate linked to a polypeptide association of amino acids. This substance did not give all the reactions of proteins, and it was shown that if the polypeptide chain is broken the substance becomes inert. This affords evidence that sensitivity can be induced by substances which are not complete proteins, and therefore the type of antibody may be different and its presence less easy to demonstrate by the usual methods. That antibody is present in the serum of allergic cases is shown by passive transfer tests.

This test is made by taking the serum from an allergic patient " A " and injecting it into the skin of a normal person " B ". After a latent period of four hours " B's." skin over the injected area can be shown by cutaneous tests to react to the substance to which " A " is sensitive. This is known as a passive transfer test or Prusnitz-Kustner reaction. It is the most accurate method of testing for sensitivity. It demonstrates that a reacting substance is present in the serum of allergics, and that these antibodies become attached to cells. It has been shown by Ballenger (1949) that cilia will continue to function in a solution which contains the sensitizing agent, it is therefore unlikely that these cells are affected. It is difficult to say to which cells the antibodies become attached, there are two possibilities, the capillary endothelium or the plain muscle cells. When such a highly complex body as a pollen granule enters the tissues it is broken down into simpler substances, and

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it is highly probable that it is one or more of these which are the sensitizing agents, or alternatively, some combination of these with substances in the tissues.

The predisposition to allergy is inherited in the majority of cases. Histamine is liberated as the result of the allergic reaction, and is the cause of some of its manifestations, but is not the ætiological factor.

All the most recent work shows that allergy is the result of an antigen-antibody reaction. Infection results in immunity which is specific but may not be of long duration. A similar mechanism, antigen antibody, renders foreign substances which gain entrance to the tissues inert.

Allergy results in sensitivity, and may be regarded as a dysfunction of this antibody protective mechanism.

The Allergic Reaction, in the Nose and Sinuses

The wheal induced by the intracutaneous injection of an allergic substance is an area of œdema, with eosinophilic infiltration. An allergic mucus polyp, at its inception is an œdematous fold of the mucous membrane, which being in a rigid walled cavity can only expand in one direction and so becomes polypoid. When these are sectioned they show œdema and a variable eosinophilia. The conclusion is inescapable that they are examples of a similar allergic reaction to an induced wheal. The examination of a large number of undoubted allergic polyps shows that the number and distribution of eosinophils is very variable, sometimes they are scattered throughout the tissue, and in others their distribution is local. So far it has not been possible to correlate this variation with the clinical condition. Eosinophils also appear in the nasal mucus.

Plasma cells are always present in allergic polypi, and again in variable numbers. I have shown how they are produced locally and arise from the cells of the reticulo-endothelial system, and in these areas the cells can be seen at different stages of development (see Figs. 6 and 7).

Lately Berdal (1950) has investigated the antibody content of fluid taken from polypi of patients sensitive to inhalant and food allergens. The sensitivity was confirmed by passive transfer tests. These experiments demonstrated that specific antibodies were present in the polyp fluid to substances to which the patient was sensitive, in a concentration 100 times greater than in the blood plasma. It also shows that the œdema, the primary cause of polyp formation is due to an active process, allergy, and not to passive congestion.

Œdema and eosinophilia are characteristic of an allergic reaction and eosinophils appear in the nasal secretions (Fig. 8). Eosinophils are present in the stroma, with some plasma cells, very few other cells

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are present in the uncomplicated cases (Fig. 9). The developing plasma cells are responsible for the local production of antibody globulin (Figs. 6 and 7).

Infective Sinusitis

Acute Sinusitis is an inhaled infection in the majority of cases, infection *viâ* the teeth being a notable exception. It does not differ from an acute infection elsewhere and usually ends in resolution, leaving a variable amount of damage to the tissues, and showing the changes and complications common to any acute suppurative process.

Chronic Sinusitis; this either follows an acute attack or is a secondary infection superimposed on either structural defects, or some other pathological process. The polymorph is the predominant cell in an active pyogenic process, and the number present is a rough guide to the activity of the pyogenic process, if an active suppuration has previously occurred, areas of granulation tissue or fibrosis will be seen (Fig. 10). If of long duration a lymphocytic infiltration with some plasma cells is present. Evidence of stagnation effects as already described is common. If the damage is extensive the glands are destroyed and dense fibrous tissue covered with a variable type of epithelium is found.

Non-Suppurative Sinusitis

There is a group of clinical cases which have been well named non-suppurative sinusitis. These cases have pale œdematous mucous membranes, with nasal obstruction and thickening of the mucosa of the sinuses, with bilateral polyposis, and are usually long-standing cases. Jelly like globulin clots may be expelled from the nose, or washed out from the sinuses. Microscopically, there is an intense and widespread infiltration with lymphocytes and plasma cells. These two cells predominate in every field. Authorities differ as to whether there is any lymphoid tissue in the normal submucosa of the nasal cavity. If it exists, it is certainly present in very small amounts and is seldom seen in routine sections. In cases of non-suppurative sinusitis scattered lymphoid follicles can be seen in various stages of development. Eosinophils are present in some of these cases but not all, and are found in the subepithelial layers only, but are not numerous. Polymorphs are only present in small numbers in the subepithelial layers, the numbers do not indicate an active infection. The clots expelled are mainly globulin mixed with mucus and in these polymorphs are seen, they also appear in nasal smears made from these cases. The respiratory epithelium in these cases is mainly normal, except for changes characteristic of stagnation of the mucus blanket.

The interpretation of this reaction is difficult, the cases are not numerous, though they exist. A closer correlation, between the clinical

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data and the pathological changes in a series of cases is required for their full evaluation. Tentatively this may be said to be the result of a long continued immunological reaction, with little or no evidence to show by what substance it was invoked.

Lymphoid follicles in different stages of development are more commonly met with in material from non-suppurative sinusitis cases than any other condition, but they also occur in chronic infective sinusitis. The chief difference in the histological picture between these two conditions is the absence of changes due to suppuration in the former (compare Figs. 10 and 11).

The histological reactions so far described are characteristic of, infection, allergy or non-suppurative sinusitis, but evidence of allergy, i.e. eosinophilia and œdema may be combined with either of the other conditions especially with a chronic infection. It is difficult to say how large a part allergy plays in these mixed types, it is probably a large one, as evidence is frequent in biopsy material from all sources. Allergy always produces bilateral changes, but it cannot be diagnosed by direct examination alone as the appearance can be imitated by other conditions. The use of nasal smears taken on cellophane handkerchiefs, and fixed on slides soon after taking are a useful diagnostic method, and can be repeated in doubtful cases. Allergy can be diagnosed or excluded by biopsy in nearly all cases. Biopsy is valuable in other cases if correlated with other clinical data. Investigation of the allergic state does not consist of doing a few cutaneous tests. It requires a careful evaluation of the history and habits of the patient by a worker with a knowledge of allergic literature. Cutaneous tests can then be made to confirm the clues obtained from the history. Hypersensitivity once established is liable to progress, so that long-standing cases are usually sensitive to several substances. The use of antihistaminic drugs or other palliatives does not prevent this progress in sensitivity, hence their prolonged or indiscriminate use is to be deplored.

There is a further problem which confronts us, and that is how far are these changes reversible or recoverable? Infection causes damage which heals by fibrosis and is not reversible, though there may be considerable functional recovery if the damage has not been too extensive. Allergy without infection is a reversible change, this can be seen by the normal appearance of the nasal mucosa in pollinosis cases in the non-seasonable periods and by the return to normal in allergic cases which have been desensitized. X-rays also confirms this in the sinuses. Where allergy and infection is present desensitization will produce improvement and if it is then followed by appropriate surgical methods to promote a free airway and drainage a satisfactory result can be obtained.

All the evidence tends to show that it is either trauma or infection which produces irreversible changes. The experimental work shows that

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the mucosa has considerable powers of recovery if a free airway and drainage are established, this recovery applies both to the epithelium and to the cellular infiltration in the submucosa.

The autonomic nervous system is fundamentally the means whereby the organism reacts to its environment. The stimuli may be external or internal, physical or emotional. Under normal conditions this system is in a state of balance; when this is disturbed we get a condition of sympathetic or adrenergic stimulation or alternatively, para-sympathetic or cholanergic stimulation. This balance is maintained by the action of hormones and enzymes, acting on the autonomic system. It is thus probable that an imbalance can account for certain of these cases, and it undoubtedly does so in what Duke (1925) has described as physical allergy. Clinically these cases are of the paroxysmal type. In these allergy plays no part, that is, there is no antigen antibody reaction. The imbalance is caused by external physical stimuli such as cold, increased humidity, or sunlight, etc.

This imbalance can be influenced both by vasodilator drugs and also those which stimulate the sympathetic system. Nicotinic acid acts as a vasodilator similar to histamine, and the success attending treatment with Ephedrine, Epinephrine or Amphetamine is well known. The action of the antihistaminic group of drugs is another way in which this imbalance may be corrected.

Changes in the autonomic system due to acidosis or alkalosis accounts for the success recorded in some cases by giving acid, and I have seen two cases of rhinitis due to over enthusiastic treatment with alkalis.

There is a relationship between some of the vitamins and hormone production, which is another way in which this imbalance may be corrected.

Crude Liver Extract has no side effects, its action is powerful, it also has the additional advantage of correcting minor degrees of anæmia and subnutritional effects which are frequently present. The varying success attained by these methods of treatment can all be attributed to their action direct or indirect on autonomic imbalance. Alone, these measures are successful in a few cases.

The ætiology of sinusitis is complex. The demonstrable changes arise from the reactivity of the reticulo-endothelial system, this is invoked by an antigen antibody response to infection and inhaled protein material which is antigenic. Allergy I regard as a dysfunction of this type of reaction, and from the nature of things is frequent. The cellular reaction seen in these cases is the result of this antigenic stimulation and these reactions are characteristic, though mixed types occur.

Coincident with this reaction is an autonomic imbalance of the erectile tissue. Immunologists regard this as the result of the antigen antibody response, some others regard it as an inherited condition which

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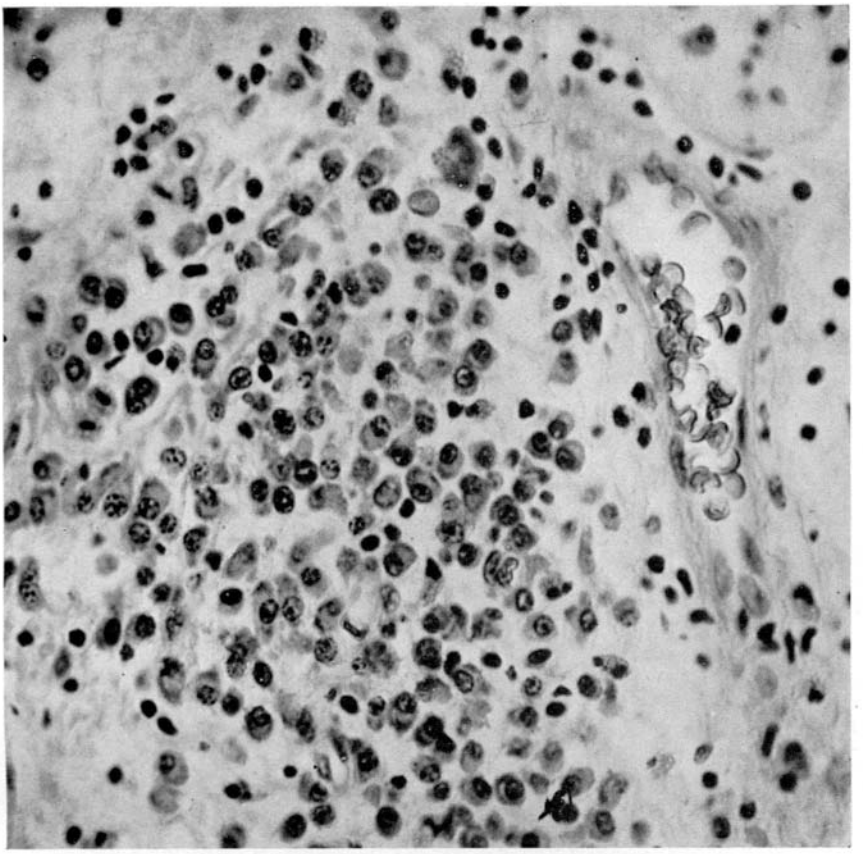


FIG. 7.

Allergic Nasal Polyp × 520.

A later stage of the process shown in Fig. 6. Plasma cells fully developed.

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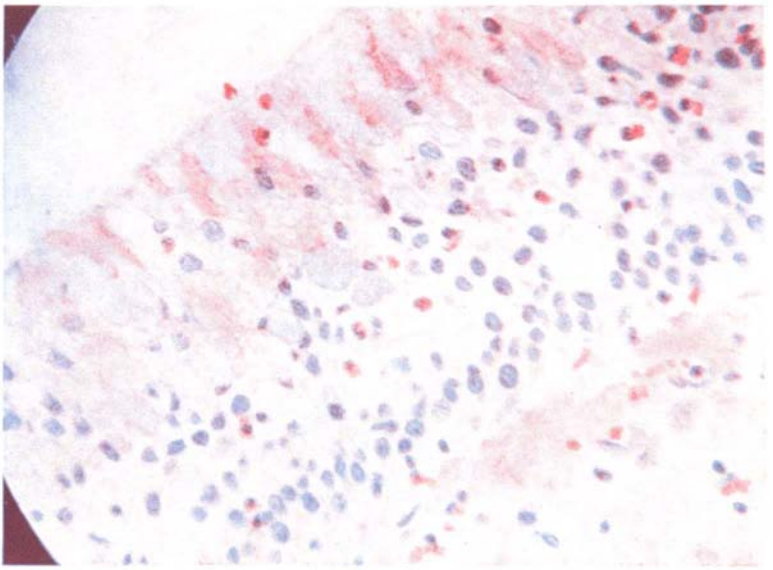


FIG. 8.

Mucosa of Allergic Polyp × 375.

The cells contain mucus globules, early stagnation changes. The eosinophils can be seen traversing through the mucosa into the nasal secretion.

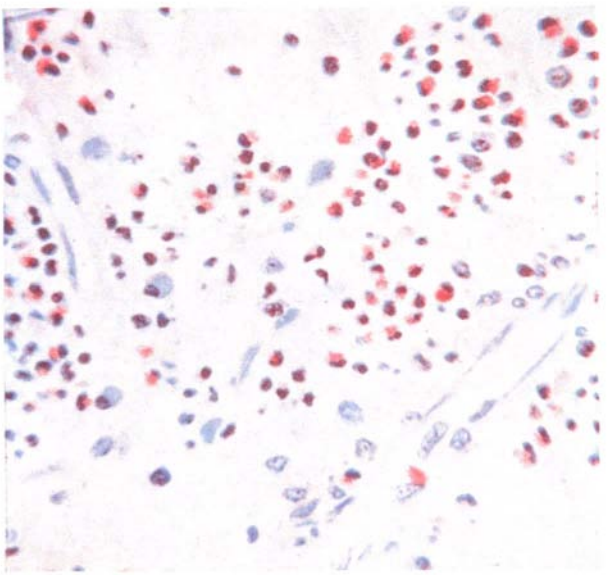


FIG. 9.

Stroma of Allergic Polyp × 375.

Eosinophilic infiltration, œdema and a few plasma cells.

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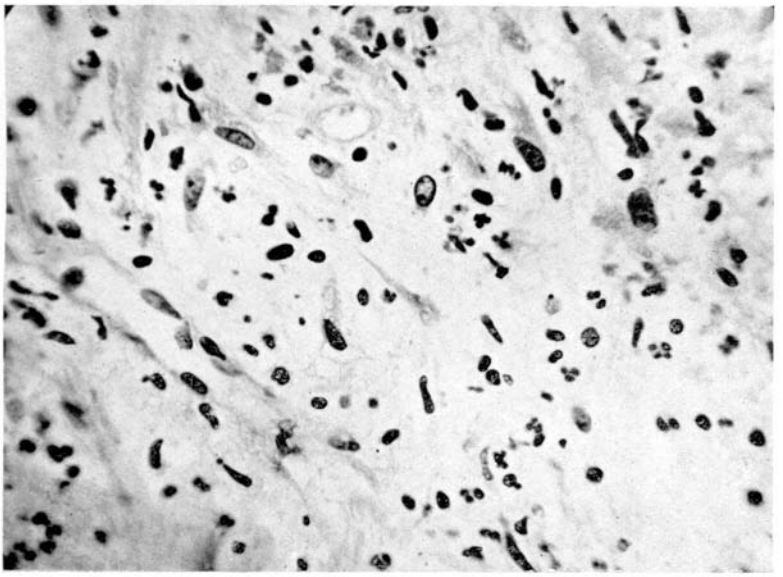


FIG. 10.

Infective Sinusitis × 575.

Polymorphs predominate, histiocytes and early fibrocytes. From a case which had a Caldwell-Luc operation following multiple polypectomies.

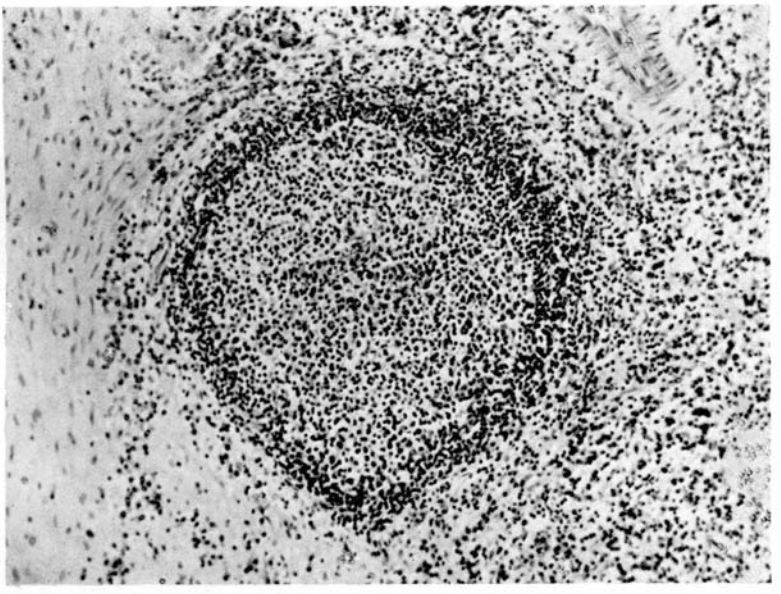


FIG. 11.

Aberrant Lymph Follicle × 140.

The follicle shown is fully developed. These are seen at different stages of development and are found in chronic infective cases and in non-suppurative sinusitis.

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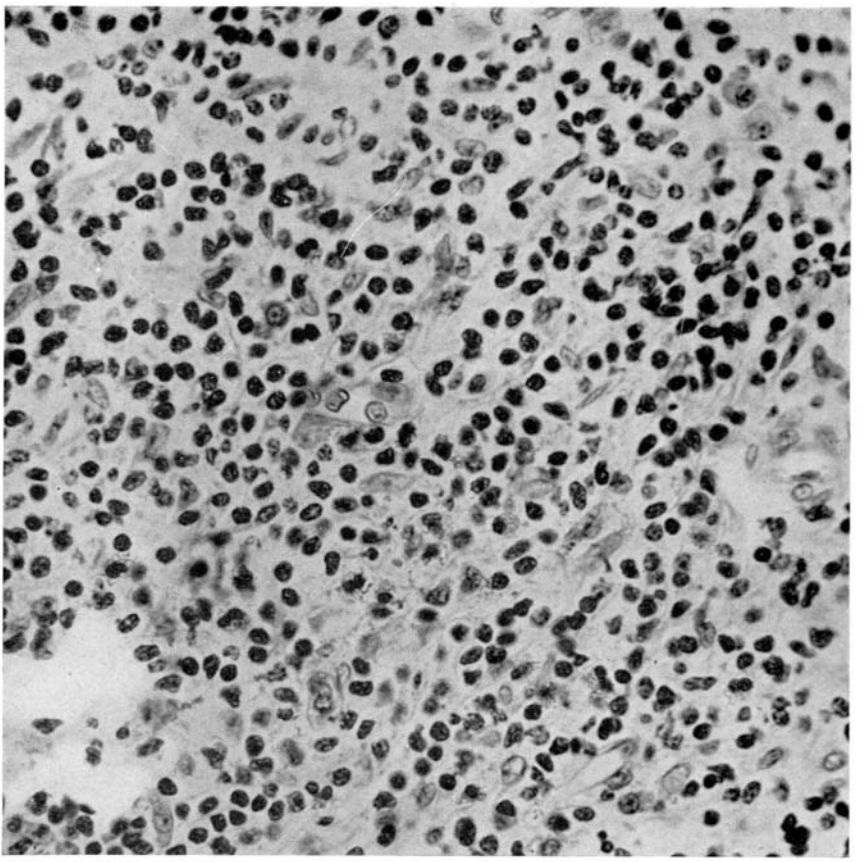


FIG. 12.

Non-Suppurative Sinusitis × 490.

An intense and widespread infiltration of lymphocytes and plasma cells. No polymorphs are present and no eosinophils or other evidence of allergy.

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precedes, and predisposes towards this type of disease in the nose and sinuses.

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