Chapter 6: Physiology of the nose and paranasal sinuses

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Physiology is the science of the normal function and phenomena of living things and their parts. Whereas most works on the physiology of the nose devote considerable attention to the pathophysiology, this chapter will concentrate on the normal nose and its homeostatic reactions. The development of medical sciences has led to considerable overlap between physiology, biochemistry, microanatomy and immunology, so any work on the physiology of an organ will include some details of other subjects. For example, the humidification of the air is facilitated by the specialized endothelial cells of the nasal capillaries; the ultrastructure of these show that there are pores facing the surface epithelium.

The role of the otolaryngologist is to distinguish patients with a normal nose from those who have a pathological condition. This can be very difficult in some cases where factors in the environment modify the normal responses. The variable blockage of the nasal cycle may be exaggerated by underfloor heating or irritant chemicals in the furniture or flooring, but no pathological process is present. An understanding of the physiology of the normal nasal functions will prevent unnecessary surgery to the septum and turbinates.

Although the nose is a paired structure, divided coronally into two chambers, it acts as a functional unit. The paranasal sinuses are mirror images of each other. The relative importance of the sinuses in the physiology appears to be small. When their function is questioned more deeply, no single use can be found. They seem to be like the appendix, although phylogenetically the latter was useful; they are both notable only when diseased.

The nose contains the organ of smell as well as that of respiration. The nose warms, cleans and humidifies the inspired air, and alters the expired air; it also adds quality to speech production. A brief summary of nasal physiology is given in Table 6.1.

Respiration

Respiration provides oxygen for metabolism and removes carbon dioxide from the body. Most of the transfer occurs in the alveoli of the lungs, and it is the function of the nose to modify air so that it is ideal for this purpose and so that exchange can occur without damaging the alveoli. The nose performs three functions: humidification, heat transfer and filtration. The nose can be bypassed during exercise because there is such a great reserve of function within the respiratory tract (Dretner, 1979). Because of its ability to transfer heat, the nose may be more important in temperature regulation than in respiration.

The humidity and temperature of the ambient air in the home is changed by central heating of various types and by air-conditioning. The inspired gases themselves are non-irritant but contain pollutants, such as oxides of nitrogen and sulphur, which are irritant, and carbon monoxide, which affects the oxygen carrying capacity of haemoglobin. The inspired air contains not only domestic dust particles and pollens but also industrial products, bacteria and viruses. Many people burden their respiratory tract further by smoking tobacco. As an adult will inspire over 10^4 litres of air a day, it is surprising that the nose is not diseased more frequently.
Heat exchange

The temperature of the inspired air can vary from -50°C to 50°C and the nose has become modified to suit the local ambient temperatures. Most of the work on heat exchange has been performed on Europeans in temperate or Mediterranean climates.

Table 6.1. Physiological functions of the nose

Respiration
Heat exchange
- direction of blood flow
- latent heat of evaporation
- thermoregulation
Humidification
- anterior serous glands
- mixed serous and mucous glands
- capillary permeability
- other body fluids, eg, tears
Filtration
- vibrissal
- air flow pattern: laminar/turbulent
Nasal resistance
- anatomical, fixed
- neurovascular, variable
Nasal fluids and ciliary function
- mucus, mucins
- proteins including immunoglobulins
- ciliary structure and function
Nasal neurovascular reflexes
- Parasympathetic
  - acetylcholine
  - vasoactive intestinal polypeptide
- Sympathetic
  - noradrenaline
  - neuropeptide Y
- Sensory
  - axon reflexes
  - substance P
Axon reflexes
Sneezing
Central nasopulmonary reflexes
Nasal cycle
Reflexes initiated in the nose
Reflexes acting on the nose
Other
Conduction, convection and radiation

Heat may be transferred by conduction, convection and radiation. When conduction occurs alone there must be no flow and heat is transferred by increased molecular movement. A temperature gradient in gases will lead to convection currents; this will affect air flow in the nose and cause turbulence. The gases in the nose are in motion, so forced convection will occur. Empirically, a formula to express this can be applied:

\[ F_H = h (T_{\text{wall}} - T_f) \]

where \( F_H \) is the heat flux in J/m per s, \( T_f \) is the bulk temperature and \( h \) is the heat transfer coefficient in J/m per s per °C.

The effectiveness of the system's functioning can be expressed by the heat transfer coefficient (Prandtl number),

\[ \text{Pr} = \frac{C_p \eta}{K_H} \]

where \( C_p \) is the heat capacity of the gas in J/g per °C, \( \eta \) is the viscosity and \( K_H \) is the thermal conductivity in J/m per °C.

The nose may be considered as a heat exchange system where two 'fluids' are in thermal but not direct contact. One of the fluids is the inspired air, the other is the blood supply of the nose. The main blood supply comes from the sphenopalatine artery, the branches of which run forward in the nose, particularly over the turbinates. During inspiration, the blood flow is opposite or countercurrent to air flow, and is thus more efficient in warming the inspired air. The efficiency of the system can be measured by comparing the temperature difference between the two 'fluids' (blood and air) at one end, \( \Delta T_1 \), with that at the other end, \( \Delta T_2 \). A log mean temperature difference is used to express the relationship

\[ \Delta T_{LM} = \frac{\Delta T_1 - \Delta T_2}{\log \Delta T_1 - \log \Delta T_2}. \]

Radiation does not play a significant part in warming the inspired air, but the process is complicated by humidification. The surface membrane of the nose is cooled by vaporization. The energy required to vaporize water is 2.352 x 10⁹ J/kg.

In temperate climates, the temperature in the nasopharynx varies by 2-3°C between inspiration and expiration, and the temperature of the expired air on expiration is the core temperature (Swift, 1982). Because humidification and temperature change in the respired gases are complementary, further changes of temperature will be considered in the next section.
Humidification

Inspiration

Saturation of the inspired air rapidly follows the temperature rise. Energy is required for two functions: raising the temperature of the inspired air and the latent heat of evaporation. These functions require about 2100 kJ every day in the adult, of which only one-fifth is used to raise the temperature (Cole, 1982). The amount of energy is dependent on the ambient temperature and the relative humidity of the inspired air. Because the process is inefficient, over 10% of the body heat loss occurs through the nose. In some animals, particularly dogs, which do not sweat, respiration forms the main source of heat loss. In spite of the variations in temperature of the inspired air, the air in the postnasal space is about 31°C and is 95% saturated.

Expiration

The temperature of the expired air in the nose is slightly below body core temperature and is saturated; it drops during passage along the nose and this allows some water to condense into the mucosa. The temperature in the anterior nose at the end of expiration is 32°C, and approximately 30°C at the end of inspiration. About one-third of the water required to humidify the inspired air is recovered this way. People who breathe in through the nose and out through the mouth will dry the nasal mucosa.

Water production

It is generally assumed that the water from humidification comes directly from the capillaries through the surface epithelium. However, fluorescent studies have shown that, except during acute inflammation, little water comes directly through the surface epithelium (Ingelstedt and Ivskern, 1949), but originates in the serous glands which are extensive throughout the nose. Humidification is reduced by atropine, probably acting on the glands rather than the vasculature. During the nasal cycle, reduction of secretions occurs on the more obstructed side. Additional water comes from the expired air, the nasolacrimal duct and the oral cavity.

Air flow

The nasal air flow is very different between rest and exercise; most studies have been performed during quiet respiration.

For the purpose of explaining how air flow occurs, the nose may be considered as a tube: most of the work of heat and mass transport has been performed on simple structures with constant cross-sections. Mathematical formulae have been derived to describe behaviour (Swift, 1982).

\[ \text{Air flow: } VA = \text{constant} \]

where \(V\) is the average velocity in m/s and \(A\) is the cross-sectional area in m².
It follows that if the cross-section is decreased then the velocity increases. Gases flow faster through the anterior and posterior nasal apertures. If the shape of the tube changes then the magnitude and direction of velocity also change. This can be seen most clearly when dye is photographed in fluid which has been applied to casts of the nasal passages.

The flow is maximal at the centre of the tube and drops towards the edge. Near the boundaries, flow is further retarded by viscosity of the medium, and at the edge it is zero. Pressure changes which result from viscous changes are irreversible - that energy is used in overcoming viscosity.

If there is a change in velocity then the pressure will also alter. This process is reversible and is described by Bernouilli's equation:

\[ P + \frac{1}{2} \rho V^2 = \text{const} \]

where \( \rho \) is the density.

However, because some viscous forces are always active in the nose, the Bernouilli equation is not strictly applicable. The nose has a variable cross-section and therefore the pressure and velocity will alter continuously. The pressure also varies independently during respiration. The inspiratory phase lasts approximately 2 seconds and reaches a pressure of -10 mmH\(_2\)O, whereas expiration lasts about 3 seconds and reaches a pressure of 8 mmH\(_2\)O. The respiratory rate is between 10-18 cycles a minute in adults at rest.

**Laminar and turbulent air flow**

In circular tubes, the change between laminar and turbulent flow is denoted by changes in the Reynolds number (Re):

\[ \text{Re} = \frac{d v \rho}{\eta} \]

where \( d \) is the diameter in m
\( v \) is the average velocity in m/s
\( \rho \) is the 'fluid' density in g/m\(^3\)
\( \eta \) is the viscosity in g/s per m.

When the Reynolds number varies between 2000 and 4000, the flow changes from laminar to turbulent.

Initial studies by Proetz (1953) were performed on models made from liquid latex, cast at postmortem. Although there is considerable variety of nasal shape, Swift and Proctor (1977) showed that the characteristics of air flow are similar in different noses. These studies used only one side of the nose, but more recently a technique using cast wax has been developed to study the flow in both sides of the nose together (Collins, 1985). Flow studies performed in this way do not take into account the variation in the nasal lumen produced by alterations of the blood flow within the nasal mucosa.
Inspiration

During inspiration, the air flow is directed upwards and backwards from the nasal valve mainly over the anterior part of the inferior turbinate, below and over the middle turbinate and then into the posterior choana. Air reaches the other parts of the nose to a lesser degree. The velocity at the anterior valve is 12-18 m/s during quiet respiration, and it is considered laminar for rhinomanometry, although, in practice, it is turbulent even in quiet respiration, producing eddies in the olfactory region.

Expiration

Expiration lasts longer than inspiration and flow is more turbulent. Extrapulmonary air flow is turbulent because the direction changes, the calibre of the airway varies markedly and the walls of the nasal cavity are not smooth. The surface area is enlarged by both the turbinates and the microanatomy of the epithelium. The Reynolds number is exceeded.

Protection of the lower airway: mechanical and chemical

One of the functions of the nose is to remove particles from the inspired air in order to protect the lower airway. The nose is able to filter out particles as small as 30 µm. This includes most pollen particles, which are among the smallest particles deposited, and it accounts for the fact that the nose is the commonest site of hay fever.

The nose is able to achieve this level of filtration because of its morphology. The inspired air travels through up to 180° and during this time not only the direction but also the velocity changes, dropping markedly just after the nasal valve. Turbulence encountered in the flow will increase the deposition of particles.

Particles in motion will tend to carry on in the same direction: the larger the mass, the greater the tendency. The resistance to change in velocity will be greater in irregular particles because of the larger surface area and the number of facets or surfaces.

The nasal hairs will stop only the largest particles and are therefore relevant only to other organisms, which try to crawl into the nose.

Nasal resistance

The nose accounts for up to half the airway resistance.

The nasal resistance is produced by two resistors in parallel, and each cavity has a variable value produced by the nasal cycle. The resistance is made up of two elements: the bone, cartilage and attached muscles; and the mucosa. The narrowest part of the nose is the nasal valve which, physiologically, is less well defined than the anatomical structures which constitute it. It comprises the lower edge of the upper lateral cartilages, the anterior end of the inferior turbinate and the adjacent nasal septum, together with the surrounding soft tissues. Electromyography shows contraction of the dilator naris alone during inspiration (van Dishoek, 1965). Loss of innervation can result in alar collapse even in quiet respiration. The
anterior valve, being the narrowest part of the nose, is one of the main factors in promoting turbulent air flow as it is the largest resistor in the whole airway (Bridger and Proctor, 1970).

During quiet respiration, the flow is more laminar in quality so that the resistance may be calculated by dividing the pressure by the flow rate. When the flow is turbulent, because the nose is an irregular tube, the resistance is then inversely proportional to the square of the flow rate (Otis, Fenn and Ryhn, 1950).

The nasal resistance is high in infants who, initially, are obligatory nose breathers. Adults breathe preferentially through the nose at rest even though a significant resistance is present and work is required to overcome the resistance. The resistance is important during expiration because the positive pressure is transmitted to the alveolae and keeps them expanded. Removal of this resistance by tracheostomy is a mixed blessing because, although it reduces the dead space, it also allows a degree of alveolar collapse. Furthermore, it may result in reduced alveolar ventilation and a degree of right to left shunting of the pulmonary blood.

**Nasal cycle**

The air flow and nasal resistance are modified by mucosal changes. These changes are produced by vascular activity, in particular by the veins of the pseudoerectile tissue of the nose (capacitance vessels). The changes are cyclical and occur between every 4 and 12 hours; they are constant for each person. The cycle consists of alternate nasal blockage between passages, which passes unnoticed by the majority of people. The cycle has been known by yogis since antiquity, although Kayser (1895) gave it its first physiological description.

The nasal cycle can be demonstrated in over 80% of adults, but it is more difficult to demonstrate in children. It has been shown to be present in early childhood (Van Cauwenberge and Deleye, 1984). The cycle may be demonstrated both by rhinomanometry or, more recently, by thermography (Canter, 1986). The physiological significance has not been established but, in addition to a resistance and flow cycle, nasal secretions are also cyclical, with an increase in secretions from the side with the greatest air flow (Ingelstedt and Ivskern, 1949).

A number of factors may overcome or modify the nasal cycle; these include allergy, infection, exercise, hormones, pregnancy, fear, emotions generally and sexual activity. The nasal cycle is controlled by the autonomic nervous system and vagal overactivity may cause nasal congestion. Drugs which block the action of noradrenaline may cause nasal congestion in the same way as hypotensive agents. The anticholinergic effects of antihistamines can block the parasympathetic activity and produce an increase of sympathetic tone, hence an improved airway. Times of hormonal changes, such as puberty and pregnancy, will affect the nasal mucosa. The hormones act directly on the blood vessels.

Oestrogens are actively concentrated in nasal tissue, and levels up to a thousand times the serum levels have been demonstrated (Reynolds and Foster, 1940). They also inhibit the function of acetylcholinesterase and so may affect the autonomic sensitivity of the nose as well (Michael, Zumpe and Keverne, 1972).
Rhinometry

The nasal air flow is usually measured as a volume flow in litres/minute and plotted against pressure. Quiet respiration is studied and a sample point of the flow found at 150 pascals pressure is the standard reference (Clement, 1984). Flow is now measured in SI units. The details of rhinomanometry are considered in Volume 4.

Nasal secretions

Nasal secretions are composed of two elements, namely glycoproteins and water with its proteins and ions. Most information on the nature and action of mucus has been obtained from the lower respiratory tract. The glycoproteins are produced by the mucous glands, and the water and ions are produced mainly from the serous glands and indirectly from transduction from the capillary network. The nasal mucus film is divided into two layers: one upper more viscous layer; and a lower more watery layer in which the cilia can move freely, with the tips of the cilia entering the viscous layer to move it. There are also two secretory cell types in the mixed nasal glands, the mucous and serous cells. The glycoproteins found in mucus are produced in two cell types, the goblet cells within the epithelium and the glandular mucous cells.

Glandular mucous and goblet cells contain large secretory granules which can be seen as lucent areas on electron microscopy and which contain the acidic glycoproteins (Lamb and Reid, 1970). Serous cells contain electron dense granules which are discrete; the granules may have material of two densities and the cores of these are of a greater density. The serous cells contain neutral glycoproteins, enzymes such as lysozymes, and lactoferrin, as well as immunoglobulins of the IgA type class. The IgA dimers are conjugated with a secretory piece which is produced in the serous cells. The submucosal glands may be mixed and are arranged around ducts. The anterior part of the nose contains serous glands only in the vestibular region. When stimulated, these glands produce a copious watery secretion. The sinuses have goblet cells and mixed glands although lower in density.

Composition of mucus (Table 6.2)

The water, ions and some enzymes may arise outside the nose, for example, in tears, and the watery layer in mucus merges gradually into the more viscous upper layer. The two layers may be considered a sol layer and a gel layer. The gel layer contains more of the glycoproteins which contribute many of the properties of mucus. The glycoproteins form about 80% of the dry weight of mucus (Masson and Heremans, 1973). They consist of a single sugar side chain and a polypeptide chain which are linked covalently. These units are polymerized by disulphide linkages. Complexes in secretions may weight up to 10^6 daltons. These polymers interact with water and ions to form a gel. Analysis results in dissolution, which alters the mechanical properties.

Hydroxyamino acids form up to 70% of the amino acids and the most common one in nasal mucus is serine (Boat et al, 1974). The glycoproteins are classified as neutral or acidic. The acid is either sialic acid (sialomucins) or a sulphate group (sulphomucins), and the neutral glycoproteins contain fucose (fucomucins). Sialomucins can be subdivided into...
those that are digested by sialidases and those that are not. Cells contain a mixture of different mucins.

The glycoproteins give mucus its two most commonly measured properties, namely viscosity and elasticity. The role of mucus in covering the nasal mucosa, and the action of cilia upon it, are dependent on its elastic properties as the ciliary beat frequency is between 10 and 20 Hz (Widdicombe and Wells, 1982). The viscosity and elasticity may be easier to measure but within the nose, adhesiveness and fluidity may be more important.

The viscosity of mucus is lowered by reducing the ionic content. The temperature of the nasal cavity is fairly constant and therefore does not have much effect on flow characteristics. However, the temperature of the nasal cavity is lower than that of the tracheobronchial tree, although both the constituents and flow have yet to be compared. In conclusion, the rheology of nasal mucus requires further study.

**Table 6.2. Nasal secretions**

<table>
<thead>
<tr>
<th>Water and ions from transudation</th>
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<tbody>
<tr>
<td>Glycoproteins</td>
</tr>
<tr>
<td>sialomucins, fucomucins, sulphomucins</td>
</tr>
<tr>
<td>Enzymes</td>
</tr>
<tr>
<td>lysozymes, lactoferrin</td>
</tr>
<tr>
<td>Circulatory proteins, complement</td>
</tr>
<tr>
<td>alpha2-macroglubulin, C reactive protein</td>
</tr>
<tr>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>IgA, IgE, IgG, IgM, IgD</td>
</tr>
<tr>
<td>Cells</td>
</tr>
<tr>
<td>surface epithelium, basophils, eosinophils, leucocytes.</td>
</tr>
</tbody>
</table>

The other compounds, such as immunoglobulins, albumin etc, do not add much to the flow characteristics. Most of the protein structures help to defend the host from the environment, whereas the water and ions have a role in the respiratory function.

### Proteins in nasal secretion

The proteins in nasal secretion are derived from the circulation or are produced within the mucosa or the surface cells. Comparison of levels within the circulation with levels contained in fluids or nasal secretions will give an indication of local production. Some compounds, such as lactoferrin, are present only in nasal secretions.

Many of the proteins are involved in the immunological responses of the nose and will be considered briefly later.

### Lactoferrin

This is present in nasal secretions and is not present in serum. Its action is to bind iron in a similar way to transferrin, although the latter is not found in secretions in any great quantity. They both bind two divalent metal ions, particularly iron, and have a molecular
weight of 76,000-77,000 daltons. Lactoferrin is produced by the glandular epithelium, mainly by the serous cells. Its action of removing heavy metal ions prevents the growth of certain bacteria, in particular *Staphylococcus* and *Pseudomonas* spp.

**Lysozymes**

These are produced by secretion in the nose from the serous glands, but some originate from tears which gain entry by way of the nasolacrimal duct. They are also produced from leucocytes which are found in nasal secretions and mucosa. The action of lysozymes is non-specific and depends on the absence of bacterial capsules for effect.

**Antiproteases**

A number of different antiproteases have been demonstrated and they increase with infection; however, their role remains open. They include alpha-antitrypsin, alpha$_1$-antichymotrypsin, alpha$_2$-macroglobulin and other antiproteases produced by leucocytes.

**Complement**

Al components have been identified and C3 is produced by the liver and, locally, by macrophages. Its activation is produced by non-specific as well as specific immunological responses through the alternative and classic pathways. It has a variety of functions, acting both on microorganisms including lysis, and neutrophil function including leucotaxis.

A number of other proteins and macromolecules have been identified from plasma, and are probably present as a result of capillary leakage.

**Lipids**

Phospholipids and triglycerides are present; their exact function is unknown.

**Ions and water**

The evaporation of water may account for some of the hyperosmolar Na$^+$ and Cl$^-$ in mucus, but active ion transport also exists (Widdicombe and Welsh, 1980). This occurs within the serous glands which also account for the major proportion of the water in nasal secretions.

**Immunoglobulins**

Immunoglobulins are part of the immune system and all classes have been found in nasal secretions. Because the nose is a mucosal surface, the two immunoglobulins involved with mucosal defence, IgA and IgE, have been found to be present in greater quantities than in serum. IgA accounts for 70% of the total protein content. The immune system will be considered later.
Cilia

Ultrastructure

Cilia are found on the surface of the cells in the respiratory tract, and their function here is to propel mucus backwards in the nose towards the nasopharynx. All cilia have the same ultrastructure although nasal cilia are relatively short, measuring 5 µm, with over 200 per cell. The cilium comprises a surface membrane which encloses an organized ultrastructure of nine paired outer microtubules and a single inner pair of microtubules. The outer paired microtubules are linked together by nexin links and are linked to the inner pair by central spokes. The outer pairs also have inner and outer dynein arms which consist of an ATPase which is lost in Kartagener's syndrome. The microtubules become the basal body, the outer pairs become triplets, and the inner pair disappear. The three outer microtubules are similar to centrioles of mitotic cells and it has been suggested that centrioles migrate to the cell surface to form these structures (Sleigh, 1974).

Ciliary action

The beat frequency is between 10 and 20 Hz at body temperature. The beat consists of a rapid propulsive stroke and a slow recovery phase. During the propulsive phase the cilium is straight and the tip points into the viscous layer of the mucous blanket, whereas in recovery the cilium is bent over into the aqueous layer. Energy is produced by the conversion of ATP to ADP by the ATPase of the dynein arms and the reaction is dependent on Mg²⁺ ions. Motion is initiated by the pair of outer microtubules sliding in relation to each other. ATP is generated by the mitochondria near the cell surface next to the basal bodies of the cilia.

The mucous blanket is propelled backwards by the metachronous movement of the cilia, which means that only those at right angles to the direction of flow are in phase. All those in the direction of flow are slightly out of phase until the cycle is complete. Initiation of ciliary movement is by mechanical action, a reversible domino effect. Mucus flows from the front of the nose posteriorly. Mucus from the sinuses joins that flowing on the lateral wall, with most going through the middle meatus. Most mucus passes around the eustachian orifice and is then swallowed.

The time taken for the cilia to transport mucus may be measured by the progress of saccharin, dye and radiolabelled particles. Saccharin is very inexpensive and is reliable clinically. The time taken is variable and lies between 5 and 20 minutes.

Factors affecting ciliary action

The nose is a remarkably constant environment and changes in it will affect ciliary function. Drying will stop the movement of the cilia but, if this is for only a short period, it is reversible. Temperature will also affect function, with cessation of movement below 10°C and above 45°C. In vitro ciliary beat frequency should be studied on a microscope with a warmed stage. Isotonic saline will preserve activity, but solutions above 5% and below 0.2% will cause paralysis. Similarly, cilia will beat above pH 6.4 and will function in slightly
alkaline fluids of pH 8.5 for long periods. The commonest factor affecting ciliary function in vivo is an upper respiratory tract infection, which may damage the epithelium to such a degree that the surface cells slough away.

**Drugs**

The neurotransmitters will affect ciliary beat frequency. Acetylcholine increases the rate while adrenaline decreases the rate. The effects are reversible and dose dependent for adrenaline below a concentration of 1:1000. Topically active drugs such as ephedrine have not been shown to affect function, but cocaine hydrochloride, in solutions above 10%, causes immediate paralysis. Corticosteroids have been shown to reduce the rate of saccharin clearance following one week's therapy (Holmberg and Pipkorn, 1985).

**Protection of the lower airways: immunological**

The effect of altering the direction and velocity of the inspired air is to deposit particles on the surface epithelium. If the particles are not inert there are other factors which prevent damage to the host. Mucus is a barrier but the respiratory mucosa is not as effective as skin in protecting the internal environment from invasion. Mucus contains a number of different compounds which are able to neutralize antigenically active compounds. It may do this by the innate mechanisms or by the learned or adaptive immunological responses. The two main surface immunoglobulins are IgA and IgE. If the mucosa is breached then the IgM and IgG immunoglobulins are activated. These mechanisms cope with certain bacterial allergens. However, several bacteria and viruses require the activation of the cell-mediated immune response to protect the host.

Lymphocytes are conveniently subdivided into B and T types, and T lymphocytes are further subdivided by surface markers into suppressor, helper and killer cells, respectively. T and some B cells interact with macrophages. Macrophages, in turn, have both specific and non-specific immunological properties.

The lymphatic system can be divided into two types depending on the type of immunoglobulins produced. The first is the unencapsulated type of system, which includes the tonsils, adenoids, Peyer's patches and the aggregations within the respiratory and gastrointestinal tract. The plasma cells produce mainly IgA and IgE and are called either the gut or mucosal associated lymphoid tissue (GALT or MALT). If this system is overcome in the nose then the encapsulated system is activated; this is situated in the lymph nodes and the spleen and it produces IgG and IgM. Certain respiratory diseases can affect a lymphocyte cell type, and the virus causing glandular fever (infectious mononucleosis) replicates in B lymphocytes and may produce tonsillar hypertrophy, lymphadenopathy and splenomegaly (Table 6.3).

**Non-specific immunity**

Lactoferrin, lysozymes, complement, antiproteases and other macromolecules interact with a number of bacteria, particularly those without capsules, to give an innate immunity. The actions of polymorph leucocytes and macrophages result in phagocytosis and destruction
of foreign material. Many organisms and viruses are resistant and specific reactions are therefore required.

Table 6.3. Nasal immune system

<table>
<thead>
<tr>
<th>Surface properties</th>
<th>Innate immunity</th>
<th>Acquired immunity</th>
<th>Distant sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanical</td>
<td>bactericidal activity in mucus</td>
<td>surface IgA, IgM, IgE and IgG</td>
<td>adenoids, lymph nodes and spleen.</td>
</tr>
<tr>
<td>physical characteristics of mucus</td>
<td>proteins</td>
<td>primed macrophages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lactoferrin, lysozymes, alpha2-macroglobulins, C reactive protein, complement system</td>
<td>submucosa macrophages IgM, IgG, T and B lymphocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cellular, polymorphs and macrophages</td>
<td>mucosal associated lymphoid tissue</td>
<td></td>
</tr>
</tbody>
</table>

**Acquired immunity**

Acquired immunity may be produced by the immunoglobulins and interferon. IgG also activates complement which will result in cell lysis and phagocytosis. Viruses and mycobacteria initiate cell-mediated immunity. The nose has two types of acquired cell reaction as a first line defence: the production of IgA which produces insoluble complexes in mucus; and immunologically primed surface active cells which are capable of phagocytosis. IgA is found in considerable quantities in nasal secretions, and for this reason its production will be considered further. IgE produces allergic reactions and, as the nose is the commonest site of allergic reactions, a few comments about it will also be included here.

**IgA**

IgA is divided into two subgroups - IgA1 and IgA2. The former is more frequent in the serum and is a monomer, the latter is more common in nasal secretions and is a dimer. IgA accounts for up to 70% of the total protein in nasal secretions. The monomer has a molecular weight of 160,000 daltons, and two units are joined by a junctional chain (molecular weight 16,000 daltons). These units are produced in the same plasma cell so that antigenically similar IgAs are linked together. The IgA dimer is then transferred passively through the interstitial fluid and is actively taken up by the seromucin glands and the surface epithelium.

In the epithelium, a secretory piece is attached to the IgA dimer which makes it stable in mucus. When it reacts with an antigen it forms an insoluble complex which is swallowed and destroyed by the stomach acid. IgA does not activate complement.
**IgE**

IgE is the main immunoglobulin to cause allergic reactions and was first identified by Ishizaka and Ishizaka (1967). It is produced mainly in lymphoid aggregates, such as the tonsils and adenoids, and within the submucosa. IgE is firmly attached to mast cells and basophils, and two molecules of allergenic specific IgE have to sit on adjacent receptor sites on mast cells to cause degranulation. IgE has a molecular weight of 190,000 daltons and does not activate complement. It is usually directed against intestinal parasites.

**Surface cells**

In addition to its molecular components, mucus also contains cells. These consist of epithelial cells, leucocytes, basophils, eosinophils, mast cells and macrophages. Leucocytes and macrophages are important for phagocytosis on the surface and may help prevent bacterial or viral invasion. Cytology of the secretion may help in diagnosis. The surface cells migrate through the interstitium from the circulation.

**Nasal vasculature and nerve supply**

**Nasal vasculature**

Comparisons between the nose and the trachea and bronchial tree have limitations. The nose is a rigid box which is devoid of a constricting smooth muscle, thus the changes in its resistance are produced by alterations in the blood flow in resistance vessels and the amount of blood within capacitance vessels. The arrangement of the blood vessels is complex and varies at different sites within the nose. It is best developed where the air flow is maximum, which is over the turbinates and part of the nasal septum, and is less well developed in the sinuses and the floor of the nose. The vascular anatomy was described extensively by Burnham (1935), and the microanatomy has been further studied by Cauna (1970). The blood supply is derived from deep vessels traversing through the bone.

In general, the arteries and arterioles produce the resistance, and the venules and sinusoids the capacitance. Shunting between the arteries and veins deep in the mucosa bypasses the surface vessels and reduces the amount of blood within the system. The anastomotic arteries spiral upwards through the cavernous plexus of veins where most of the shunting occurs. Towards the surface, the arteries ramify and give rise to arterioles which lack an elastic lamina, and end in capillaries which run parallel to and just below the surface epithelium. They also run around the mucous glands. The capillaries are fenestrated with more 'holes' towards the epithelium (Cauna, 1970); this allows transudation to occur, and the parallel course permits maximum heat exchange.

The capillaries drain into a superficial venous system; the smooth muscle is best developed just before the superficial veins drain into the venous sinusoids.

The venous sinusoids are a cavernous plexus of large tortuous anastomotic veins without valves. The sinusoids receive both arterial and venous blood. The drainage of the sinusoids is regulated by cushion or throttle veins which have a circular muscle coat and an incomplete longitudinal crest. They do not close the lumen completely but are able to regulate
the flow into the bone through the deep venous plexus. In cats, about 60% of the blood flow is shunted through arteriovenous anastomosis (Anggard, 1974), and the actual blood flow per cubic millimetre is greater than muscle, brain or liver (Drettner and Aust, 1974).

Although the arterial supply is from a number of different sources, the main supply is from the maxillary artery, and the arterial flow is forward through the nose against the incoming air. The vascular arrangement within the turbinates is often called pseudoerectile because of similarities to the blood supply of the penis.

**Blood flow**

Measurement of the nasal blood flow is difficult because material introduced into the nose will alter the nasal resistance. Blood flow may be inferred by:

1. direct changes in the colour
2. photoelectric plethysmography
3. alteration in the temperature which may be measured by thermocouples.

As the nasal resistance is related to blood flow, rhinometry may be used to assess blood flow indirectly. Capillary leakage may be gauged either by the appearance of labelled albumin in nasal secretion following intravenous injection or by the xenon wash-out method.

A number of combinations of blood flow may exist depending on the balance between arterial flow, arteriovenous shunting and venous pooling: hyperaemia with congestion of the cavernous sinuses, hyperaemia without venous congestion, ischaemia and reduced arterial perfusion with no shunting, giving rise to venous congestion. Control of vascular flow is by both the autonomic nervous system and the local inflammatory reactions, which may sometimes be independent of each other.

*Autonomic nervous system*

The autonomic nervous system controls the vascular reflexes in the nose and the distribution may be seen schematically. The reflexes may be initiated or modified by the sensory input which is by way of the trigeminal nerve. The ethmoid nerves are mainly sensory, whereas the sphenopalatine nerves are mixed.

*Sympathetic nerve supply*

The sympathetic nerve supply is derived from the lateral horn of the grey matter of the spinal cord at the level of the first and second thoracic vertebrae. Preganglionic axons run through the anterior nerve roots, anterior primary rami and white rami, and communicate with the sympathetic chain. They synapse in the superior cervical ganglion. Postganglionic fibres travel along the carotid artery to the deep petrosal and nerves of the pterygoid canal. They continue through the sphenopalatine ganglion and pass into the nerves of the nasal cavity.
Parasympathetic nerve supply

The pons contains the superior salivary nucleus in which preganglionic fibres have their cell bodies. They proceed by way of the intermediate branch of the facial nerve to the geniculate ganglion through which they pass. After continuing along the greater superficial petrosal nerve, and the nerve of the pterygoid canal, they synapse in the sphenopalatine ganglion. Postganglionic fibres then pass to the nasal mucosa.

Sensory nerves

The main sensory nerve supply is mediated by way of the trigeminal nerve. The ophthalmic and maxillary nerves which arise in the trigeminal ganglion supply the nose; sneezing is mediated through the vidian nerve (Malcolmson, 19590. It is uncertain precisely to which modalities the nose may be sensitive, but temperature, pain (or discomfort) and touch or irritation can be appreciated. Thermoreceptors are limited to the nasal vestibule. Proprioception does not appear to be present. It may be impossible to define nasal nerve endings in the same manner as the nerve endings in the skin and the locomotor system. There is some evidence that sensory nerve endings have H1 receptors (Mygind and Lowenstein, 19820. Olfaction will be considered separately.

Neurotransmitters

Both parasympathetic and sympathetic nerve fibres supply the vasculature and glandular epithelium. Postganglionic fibres have been shown to have more than one neurotransmitter, which may account for the discrepancy in behaviour between expected experimental responses and actual reflexes. Classic cholinergic antagonists do not block parasympathetic vasodilation completely (Eccles and Wilson, 1973). (There is a similarity to mast cell reactions where antihistamines do not completely block reactions since there is more than one cellular mediator.)

In addition to acetylcholine and noradrenaline, neuropeptides are present in sympathetic, parasympathetic and sensory nerves (Uddman et al, 1978; Anggard et al, 1979; Lundberg et al, 1982. Detection is by immunofluorescent techniques.

Parasympathetic

The main transmitter in the parasympathetic supply is acetylcholine, but vasoactive intestinal polypeptide (VIP) is present in postganglionic fibres. There are specific receptors for this on the blood vessels but not within the glandular epithelium. The transmitters probably act in combination. The action of acetylcholine is on both the blood vessels and the secretory tissue. Acetylcholine produces widespread vasodilation and increased glandular activity. If the rate of firing is low then acetylcholine probably acts alone on blood vessels. At higher rates, vasoactive intestinal polypeptide causes vasodilation which is atropine resistant, but acetylcholine may cause suppression of vasoactive intestinal polypeptide release by negative feedback (Uddman, Malm and Sundler, 1980). Acetylcholine is secretor motor for glandular tissue alone, but the effects of vasoactive intestinal polypeptide on neighbouring blood vessels may indirectly affect secretion.
**Sympathetic**

The transmitter to postganglionic fibres is acetylcholine, and the main postsynaptic transmitter is noradrenaline. Two neuropeptides may be found, namely neuropeptide Y and pancreatic polypeptide; neuropeptide Y is probably the more effective of the two. In contrast to noradrenaline, which causes both arterial, arteriolar and venous constriction, neuropeptide Y causes only arteriolar constriction (Lundberg and Tatemoto, 1982). Avian pancreatic polypeptide is similar morphologically to substance P and shares its action of vasodilation (Lundberg et al, 1980).

**Sensory**

A number of nasal sensory neurons have been shown to contain the neuropeptide substance P. They are present in the sphenopalatine ganglion, near blood vessels and under the surface epithelium (Anggard et al, 1970). Substance P causes vasodilation and is found in the C fibres.

**Reflexes**

Reflexes may be mediated through the brainstem, but axon reflexes may occur through the sensory nerves alone.

**Axon reflexes**

The neuropeptide substance P has been shown to transmit the reflex, and it may be initiated by mechanical irritation or by way of the mast cells which produce histamine. The reflex is antidromic. In addition to histamine's causing the reflex, substance P is also able to liberate histamine from mast cells. The concept of neurovascular reflexes and mast cell reactions being separate entities may need to be revised.

**Reflexes from nasal stimulae**

Chemical irritation, temperature change and physical stimuli of the nose may all cause widespread cardiovascular and respiratory responses. The degree of the response depends on the intensity of the stimulus, and ranges from sneezing to cardiorespiratory arrest. Sneezing is associated with facial movements, lacrimation, nasal secretions and vascular engorgement. More usually, a change in respiratory rate with closure of the larynx and a variable cardiovascular response occurs.

Animal studies have shown that sensory stimulation of the nose can result in intense vasoconstriction of skin, muscles and visceral arteries, and is accompanied by a lowered cardiac output. This is a modification of the submersion reflex which diverts blood away from the skin to the brain.

**Nasopulmonary reflexes**

Increasing the air flow through one side of the nose is associated with an increased ventilation of the homolateral lung. This follows the nasal cycle. Blowing air through the nose
will cause the bronchial muscle to relax on the same side and increase its respiratory activity (Samzelius-Lejdstron, 1939).

**Reflexes acting on the nose**

The resistance of the nose may vary because of changes in the metabolic requirements of the individual. Exercise, emotion and stress may all cause vasodilation. These changes are mediated by increasing the sympathetic tone and are abolished by stellate ganglion blocks. An increase in arterial CO$_2$ mediated by the chemoreceptors will result in nasal vasoconstriction. Hypoxia has the same effect. Hyperventilation will cause nasal congestion.

**Cutaneous stimulation**

Heating the skin of parts of the body, such as that of the feet, arms or neck, will produce an increase in nasal resistance. Cooling will result in vasoconstriction (Cole, 1954). Adaptation to both will occur and is followed by rebound. Pressure to the axilla on the dependent side will cause ipsilateral nasal blockage (Burrows and Eccles, 1985).

**Central control**

The hypothalamus is associated with cardiorespiratory responses and stimulation causes marked nasal vasoconstriction. Exercise, fight and flight reflexes and reflexes following emotional change are mediated by way of the hypothalamus. The relationship between the rhinencephalon and nasal function needs further evaluation.

**Drugs acting on the vascular tissue of the nose** *(Table 6.4)*

A brief review will be included of the drugs which affect the vasculature of the nasal mucosa. Drugs may be grouped into four sections: sympathomimetics and their antagonists; parasympathomimetics and their antagonists; histamine and antihistamines; and local anaesthetics. The mode of action in humans has not been fully evaluated and some of these drugs, particularly the antihistamines, rely on animal work in cats and dogs for evaluation of their behaviour.

**Table 6.4. Drugs acting on the nasal mucosa**

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics and antagonists</td>
<td>Adrenaline and synthetic analogues</td>
</tr>
<tr>
<td></td>
<td>Antihypertensives particularly beta-blockers</td>
</tr>
<tr>
<td>Parasympathomimetics and antagonists</td>
<td>Atropine, pilocarpine</td>
</tr>
<tr>
<td>Histamine and antihistamines</td>
<td>Antihistamines with this activity</td>
</tr>
<tr>
<td></td>
<td>Mainly H$_1$ blockers</td>
</tr>
<tr>
<td>Local anaesthetics</td>
<td>Sedative and non-sedative</td>
</tr>
<tr>
<td>Hormones</td>
<td>Cocaine, lignocaine</td>
</tr>
<tr>
<td></td>
<td>Sex hormones, thyroxine, corticosteroids.</td>
</tr>
</tbody>
</table>
**Sympathomimetics and their antagonists**

The two naturally occurring sympathomimetics, namely noradrenaline and adrenaline, act on the nose mainly through alpha\(_1\)-receptor sites, although it has been suggested that there may be some alpha\(_2\)-receptors which have a physiological role in the nose. It would appear that, opposed to the action of receptors which vasoconstrict, the agonists such as isoprenaline act on alpha\(_2\)-receptors and cause vasodilation. There are a number of sympathomimetics, related to ephedrine, that are used for vasoconstriction; some, such as neosynephrine hydrochloride, are strong and cause a prolonged vasoconstriction. The main nasal complication is rebound hyperaemia which is associated with rhinorrhoea. Drugs such as cocaine block the uptake of noradrenaline and potentiate their own vasoconstriction. Drugs used in the treatment of hypertension may result in nasal obstruction by blocking sympathetic activity. Reserpine, which is no longer used, was the worst offender. Methyldopa and beta-blockers may all give rise to nasal symptoms.

**Parasympathetics and their antagonists**

Intravenous pilocarpine and carbachol will cause nasal congestion, vasodilation and watery secretions. These actions are blocked by atropine and are a cholinergic effect. As mentioned earlier, atropine-resistant vasodilation does occur and is mediated by vasoactive intestinal polypeptide. Other mediators, such as histamine, are present in normal nasal secretions and may also cause vasodilation.

**Histamine and antihistamines**

The pharmacology of histamine is complex and both H\(_1\) and H\(_2\) receptors have been demonstrated in the nasal mucosa, with H\(_1\) receptors predominating. Histamine acts both on the vasculature, giving vasodilation together with leakage from capillary walls, and on the sensory nerve endings where it is an irritant, resulting in the sensation of irritation and sneezing. Histamine has been shown to be present only in the mast cells and basophils. Histamine, although not as powerful as other inflammatory mediators from mast cells, is present in the greatest quantity. The actions of histamine, therefore, account for only some of the mast cell reactions.

Antihistamines are used widely in medicine and have a number of properties which include blockage of H\(_1\) receptors, anticholinergic activity, local anaesthesia and sedation. Not all actions are present in each compound and the new antihistamines, such as terfenadine and astemizole, have no sedative effect, which makes them safer.

Although antihistamines work clinically, one study would suggest that they do not have any action against histamine in the nose (Bentley and Jackson, 1970), in spite of being shown to block the action of histamine on isolated guinea-pig ileum in other experiments.

**Local anaesthetics**

Local anaesthetics work by the action of an amide group which blocks conduction through the transmembrane channels and affects ion exchange. Two main groups are lignocaine and derivatives, and cocaine. Cocaine is a powerful vasoconstrictor, and it also
potentiates the action of noradrenaline by blocking its recycle through re-uptake into the sympathetic nerve endings. Lignocaine has an effect on the precapillary sphincters which it dilates; thus it has, in fact, a slight vasodilatory activity. If lignocaine is used, it should have a vasoconstrictor added to the solution. All local anaesthetics, if given in high concentrations, have systemic effects on the heart and central nervous system.

**Hormones**

A close link exists between the anterior pituitary and the hypothalamus by way of the hypothalamohypophyseal tract. A complex interrelationship is present between emotional states, the autonomic nervous system and the hormones of the body. In all animals, olfaction is part of sexual behaviour and will be considered in more detail later.

**Sex hormones**

The nasal mucosa is susceptible to sex hormones, particularly oestrogens which it can concentrate. Conditions where oestrogen levels are high are associated with nasal obstruction and with rhinorrhoea. There are changes in nasal function during menstruation, pregnancy, and puberty in both sexes. Higher dose oestrogen contraceptives were associated with rhinitis in some women.

**Thyroxine**

Hyperthyroidism may give rise to rhinitis, although the exact mechanism is unclear, whereas hypothyroidism is associated with nasal obstruction resulting from the deposition of mucopolysaccharides in the extracellular spaces of the submucosa, which is similar to the condition found in the larynx and elsewhere.

**Corticosteroids**

Glucocorticosteroids affect nasal function indirectly and do so mainly during inflammatory reactions which involve mast cells. They affect the mast cell surface membrane and vascular endothelium, making them less permeable.

**Adrenal medulla**

The sympathomimetics have been considered elsewhere, but they produce a direct intense vasoconstriction on the nasal vasculature.

**Emotional states**

Three different responses may be categorized: fight or flight, which cause vasoconstriction; sexual behaviour, which produces a number of different responses; and stress. Vagal overactivity is found in patients with stress. This condition manifests itself in the abdomen by duodenal ulceration, whereas in the nose it results in prolonged congestion and may be the cause of some of the blocked noses encountered in patients in the clinic. Stress may result in migraine which, by way of the hypothalamus, gives rise to nasal symptoms, usually congestion and clear rhinorrhoea.
The nose and the voice

The voice is produced by modifying the vibrating column of air from the larynx. The larynx gives rise to the vowel sounds and the pitch voice and the main frequencies are under 1000 Hz (F₁ 300-400 Hz, F₂ 500-1900 Hz, F₃ 1800-2600 Hz). High frequency sound which produces the consonants is added by the pharynx, tongue, lips and teeth. The nose adds quality by allowing some air to escape through it. The sound resonates within the nose and mouth; if too little air escapes from the nose then rhinolalia clausa occurs, if too much then rhinolalia aperta ensues. The nose is most effective when resonating at the laryngeal F₁ frequencies. It is doubtful whether the sinuses have any effect on modifying the voice, although they may help with auditory feedback. Transmission of sound through the facial skeleton helps monitor voice quality.

Olfaction

Olfaction initiates and modifies behaviour in many creatures. Humans minimize its importance, however, by concentrating on the audiovisual aspects of behaviour; and yet much money is spent annually on products which modify body odour and are supposed to make the wearer less offensive and more attractive to the opposite sex.

Odours are a complex mixture of different compounds, each one at a low concentration; however, studies in olfaction concentrate on single compounds or mixtures with two or three chemicals. Olfactory compounds have to come into contact with the nasal mucosa and, in order to produce a smell, need both a high water and lipid solubility. Man discriminates a large number of different smells, and the olfactory mucosa and pathway are rapidly fatigued, although they recover quickly.

Sniffing

The maximum exposure of the olfactory area to the smell is produced by sniffing which causes a turbulent air flow. Animal studies suggest that by increasing the velocity of air flow, the olfactory stimulus is increased (Ottoson, 1956).

Olfactory area

The olfactory area varies according to species, with dogs and rabbits having larger areas than human beings. The human being has 200-400 mm² with a density of about $5 \times 10^4$ cells/mm². The receptor cells carry modified cilia which increase the surface area and project like normal cilia into the mucus.

Stimulus

Odours are absorbed into the water of the mucus, and the lipid reacts with the lipid bilayer of the receptor cells at specific sites, which causes K⁺ and Cl⁻ to flow out and thus to depolarize the cells (Takagi et al, 1968). After a latent period of up to 400 ms, a slow compound action potential may be recorded from the olfactory mucosa (Ottoson, 19560, and this is called the electro-olfactogram. The speed of the rising phase varies with the intensity
of the stimulus. The recovery phase or falling phase is an exponential decay with time constant of 0.9-1.45 ms.

**Threshold**

The olfactory response shows variation in both threshold and adaptation. The threshold concentration can vary by $10^{10}$ depending on the chemical nature of the stimulus. The threshold of perception is lower than identification: that is, a smell is sensed before it is recognized. Threshold values vary widely between studies and they reflect the nature of smell and the different methods of detection. Smell does not have an absolute threshold, but the threshold depends on the level of inhibitory activity which is generated by the higher centres. Some animals, particularly dogs, have a much lower threshold for detection.

**Adaptation**

The olfactory response shows marked adaptation: the threshold increases with exposure and recovery of the electro-olfactogram is rapid when the stimulus is withdrawn.

$$R = a + Be^c$$

where $R$ is the perceived intensity, $a$ is the asymptote, $b$ is a constant and $c$ is the rate of decline which is a function of time ($t$). Adaptation is both a peripheral and a central phenomenon. Cross-adaptation is present between odours at high concentrations, whereas cross-facilitation occurs near threshold values.

**Other factors affecting threshold**

Changes in the nasal mucus and its pH will alter olfactory perception. Threshold increases with age and is both decreased and altered by hormones, particularly the sex hormones. In man, some genetic variation occurs which is similar to colour blindness: there is a familial lack of perception of certain odours which is more common in males.

**Discrimination**

Man appears to be better at detecting the pleasantness of an odour than at recognizing it. The pleasantness is largely determined by cultural factors and is therefore learned. If two odours are mixed, the resulting intensity is always less than the sum of the two individually perceived intensities and is dominated by the stronger component.

**Pathways**

There is no interaction between the individual receptor cells, and receptor cells are connected to the olfactory bulb by non-myelinated nerve fibres. These fibres end on olfactory glomeruli: about 25,000 fibres end on each glomerulus, which then act as an integrator. The conduction time between the receptor cells and the glomerulus is 50 ms for, even though the fibres are slow, they are short. The glomerulus fires with an all or none response into the mitral or tufted cells whose axons transport the signal through the lateral olfactory tract. Inhibition comes from feedback from the high cortical centres.
**Higher centres**

The anterior olfactory nucleus sends impulses to the opposite bulb and to the ipsilateral forebrain through the anterior commissure. The primary olfactory cortex lies rostral to the telencephalon and includes the olfactory tubercle, the prepyriform and preamygdaloid areas. There are projections into the thalamus where they are integrated with taste fibres, and there are also projections to the hypothalamus. Communication between the receptor cell and the brainstem occurs with only two synapses.

**Perceived intensity**

The perception of smell is a complex activity involving both the pathways and the higher centres which have learned to recognize the smell. It is possible to determine a mathematical relationship between the perceived intensity of the stimulus \( R \) and the stimulus concentration \( S \): 

\[
R = CS^n
\]

where \( C \) is a constant and the value of \( n \) is below one. As \( n \) is below one, the system attenuates particularly at high concentrations.

**Trigeminal input**

Most smell is independent of the trigeminal nerve, but at high concentrations irritation occurs which is a factor in detecting the intensity of certain compounds, such as butyl acetate, and may account for 30% of the odour intensity (Cain, 1974). Patients who are anosmic can distinguish only sweet, sour, salt and bitter and whether a compound is irritant. The irritant effect cannot be bypassed in normal people and does contribute to the nature of smell. It is important when testing olfaction to use compounds which are not irritant.

**Classification of odours**

There is no satisfactory classification of odours but Amoore (1969) has suggested that there are up to 30 primary odours for humans, basing his theory on the stereochemistry of compounds and the variations of anosmia to substances which are present in man. The human being has difficulty in detecting and recognizing variation in intensity of more than 17 odours. Furthermore, because the human being does not rely on conscious detection of odour, only its quality, training is necessary for scientific experiments and for occupations which require a 'good nose'. An obvious discriminatory mechanism has not been found in the nose at either the receptor site or in the olfactory bulb. Some cells in the olfactory bulb increase their discharge rate and some decrease their rate of discharge on stimulation.

**Theories of smell**

It is a general rule in medicine and science that if there is no single theory of function then no one really knows or has proven the mechanism involved. There are a number of hypotheses which have been advanced to explain the nature of smell.
Molecular structure

Moncrieff (1967) has suggested that molecular structure is important; however, not stereospecific olfactory receptors have been demonstrated.

Electrochemical reactions

Some cells contain carotenoids similar to those in the eye and these could be responsible for the occurrence of reactions similar to the photochemical reactions in the eye (Briggs and Duncan, 1962).

Stereospatial patterns

Certain receptors could have a stereospatial, lock and key form, and receptor cells fire when the surface membrane is altered (Mozell, 1970).

Molecular properties

A modification of the previous theory would hold that basic molecular properties account for receptor specificity and include molecular volume at boiling point, proton affinity and donation, and local polarization within the molecule (Laffort, Patte and Etcmeto, 1974). Theoretical thresholds correlate with experimental values.

Olfactory mucosa morphology

The pattern of the stimulus within the mucosal configuration of the receptor cells detects the nature of the smell. This theory of discrimination is based partly on specific receptor sites and partly on their position within the olfactory mucosa (Holley and Doving, 1977).

Olfaction may well be an analogue system. A number of different patterns from a few receptor sties would give rise to a large number of different smells.

Olfaction and behaviour

Olfaction is important in regulating behaviour in all animals, including man and insects. The degree of development depends on the species. Smell is used in four main areas of behaviour: the detection and consumption of food, recognition, territorial markings, and sexual behaviour. In humans, eating and sexual behaviour are highlighted.

Eating

Olfaction is related to two aspects of eating, namely the recognition of food types and the initiation of digestion. The initiation of digestion is mediated by way of the lateral and ventromedial hypothalamus, and it causes salivation and increases the output of gastric acid and enzymes.
Sexual behaviour

Pheromones were first described in relation to insects. The term was used to describe the chemical which were produced by glands and were responsible for sexual attraction. They have since been encountered widely in all animals. Three types of pheromone have been described, which are releaser pheromones, primer pheromones and imprinting pheromones. Releaser pheromones produce an immediate and reversible response and act through the nervous systems, whereas primer pheromones require prolonged stimulation and act on the anterior pituitary where they cause hormones to be released. Imprinting pheromones, which are chemicals encountered during development, modify behaviour and may subsequently initiate a response.

The degree of involvement in human behaviour is uncertain but the influence of smell is probably underestimated as most activity occurs at the subconscious level.

The paranasal sinuses

The physiological role of the paranasal sinuses is uncertain. They are a continuation of the respiratory cavity and are covered by a respiratory mucosa. They share certain features with the nose but the responses are much less marked on account of the relatively poorly developed vasculature and nerve supply. In man, the sinuses’ main interest is in disease, and this subject is outside the scope of this chapter.

The development of the paranasal sinuses takes up to 25 years: the ethmoids and maxillary sinuses are present rudimentarily at birth, while the frontal sinuses develop after the age of 6 years but may be completely absent; the sphenoid sinus differs considerably in the degree of development. It holds true that whatever physiological role the sinuses play, it is not essential and of only minor importance.

Mucosa

The mucosa runs in continuity from the nose and is respiratory in type; however, there are differences between the nose and the sinuses. In the sinus mucosa, goblet cells and cilia are less numerous in general but more frequent near the ostia; the blood supply is less well developed with no cavernous plexuses. The poorer blood supply results in a pale, semitranslucent mucosa. As the nerve supply is less well developed, the sinus mucosa is able to give only a basic vasomotor response and increase mucus production on parasympathetic stimulation.

Drainage

Mucociliary clearance in the maxillary sinus is spiral, and towards the natural ostium, and may be seen by means of dyes and carbon particles (Toremalm, Mercke and Reimor, 1975). Drainage of the frontal and sphenoidal sinuses is downwards and is aided by gravity; the blood supply is better developed in the frontal sinuses and the ostium is relatively large in the sphenoid sinus. The secretions join the nasal mucus in the middle meatus and may contribute to the total amount and effectiveness of the nasal mucus.
**Oxygen tension**

The \( PO_2 \) is lower in the maxillary sinuses than in the nose and it is lower still in the frontal sinuses. If the ostium becomes blocked, the oxygen tension drops further. Ciliary motion remains normal if the blood supply is adequate. If the blood supply is impaired then ciliary activity is reduced and stasis of secretions results.

**Ostium size**

Blockage of the natural sinus ostium results in a reduction of ventilation and stasis of secretions. If the ostium size is below 2.5 mm, it predisposes to the development of disease (Aust, Drettner and Hemmingsson, 1976).

**Pressure changes**

The pressure in the maxillary sinus varies with respiration but lags behind by 0.2 s. There is little fluctuation when the nose is patent, and the variation of pressure during quiet respiration is \( \pm 4 \) mmH\(_2\)O which reaches 17-20 mmH\(_2\)O on exercise. If the nose is blocked then the pressure fluctuations are much more marked.

Barotrauma is five times less common than in the ear and is most frequently seen in the maxillary sinuses, particularly in divers.

**Physiological functions of the sinuses**

The possible functions of the sinuses are as follows:

- air conditioning
- pressure damping
- reduction of skull weight
- heat insulation
- flotation of skull in water
- increasing the olfactory area
- mechanical rigidity
- vocal resonance and diminution of auditory feedback.

On the other hand, the sinuses may have no function at all.

**Comments**

The volume of the largest sinus is under 50 mL and, therefore, the sinuses contribute little to air conditioning. Similarly, a damper has to have a large volume to be effective. The reduction of skull weight is small compared to the overall weight. Most of the cranial activity is away from the sinuses so they play little part in insulating the brain. Man has long ceased to be an amphibian.

It is probable that apart from mucus production and some strengthening of the facial bones, the paranasal sinuses have little or no physiological function.