THE COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY TRACT IN RELATION TO CLINICAL PROBLEMS

Lister Oration delivered at the Royal College of Surgeons of England
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by

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THE BESTOWAL OF the Lister Medal and the delivery of this Oration dedicated to the great master fill the recipient with immense pride for the honour, but at the same time with extreme anxiety as to his ability to justify the award.

To me, brought up in the Listerian tradition, it is the culminating point in a career which commenced in the hospital hallowed by the ever-present spirit of this great scientific surgeon.

I started too late to attend King's College Hospital during the time of Lord Lister, but had the privilege of acting as a sidesman at the service in Westminster Abbey on February 16th, 1912, and of paying homage at this moving ceremony.[25 83]

I had, however, the good fortune to act as surgical dresser and house surgeon to Sir Watson Cheyne, who himself was house surgeon and assistant to Lord Lister. Those who worked for Cheyne had the greatest respect and veneration for their chief, and they were imbued with a similar veneration for Lister himself, even though there was not the opportunity of serving under his direction.[12]

The wards and operating theatre of the old King's College Hospital in Portugal Street, so close to this College, carried the all-pervading impress of the master who had there perfected his methods and introduced them to a doubting profession, with final success and with immeasurable benefit to mankind.[52] (Fig. 1.)

One of the most notable examples of the application of research to clinical problems was the work of Lister on infection of wounds.

He commenced by making careful and detailed observations of the circulation in the capillaries of a frog's foot and in the wing of a bat, with many experiments to determine the reaction of the tissues to various irritants.[48 50]

Lister could not at first have been aware of what his research would lead to; it might have been of academic interest but of no clinical significance.

It led, however, to the discovery of the means of alleviating untold misery, with the saving of innumerable lives, with restoration to health and strength.

The application of a knowledge of the processes of inflammation to affections of the respiratory tract is obviously of supreme importance.

Here is a lesson for all who enquire into the reason for unexplained problems ; they should approach the investigation with a mind receptive of the important facts, undaunted by failure and alive to contradictory fallacies.

It takes a long time for new facts to be discovered, and in the mind of the research worker must be the ability to interpret his findings and to apply them to the problem in hand.

How well this is illustrated by the genius of Fleming in realising the importance of an observation that may often have presented itself ; it is the ability to appreciate what he is looking at that determines much

Fig. 1. Albert Ward in the Old King's College Hospital, which was closed in 1913.

of the success of the investigator :[24] "... but chance only favours the mind which is prepared." (Pasteur.)

Research may be barren and months or years of work may fail to provide any information of importance ; and yet the attempt to explain any problem can never fail to make such an investigation interesting.

Another possibility is that research may provide erroneous information and may lead to fallacious conclusions.

In brief, he who conducts research must be prepared to give unlimited time and application. He must be able to interpret his findings and must be resigned for disappointment ; he must not look for some practical benefit, even though useful results in regard to the working of the human body or the alleviation of disease may occasionally appear.

Research does not necessarily imply experiments on animals ; it may involve anatomical and histological studies, the compilation of statistical evidence regarding health or disease, and also the investigation of results of treatment. All these are methods of research and to some of us a combination of all aspects is attractive.

Professor von Eiselsberg of Vienna, who delivered the oration in 1927, spoke as follows :[19] " What made Lister the hero of the scientific world was his systematic and careful investigations on living animals and the exact observations in his clinic, combined with laboratory work in the new science of bacteriology."

Lister adopted all methods and did not hesitate to perform experiments on animals, including a horse and a calf, when he considered it necessary and of possible benefit to the human race ; this determination led to a most unfortunate disagreement with Queen Victoria who, having asked for his views on the subject, ignored them because she found them in opposition to her own opinion.[25 83]

Even when engaged on the preliminary studies of anatomy, physiology and chemistry it was the habit of students of the time, among them Lister, to attend the wards of the hospital.

He was an observer of bird life and, while at school, made dissections of fish and small animals. Sir Rickman Godlee writes in his biography that Hunter was Lister's greatest hero ; in all aspects the latter maintained the great traditions established by the founder of our museum.[25]

I venture to present certain observations derived from a study of the respiratory passages, in all of which the facilities provided by the Royal College of Surgeons, and also the Ferens Institute of the Middlesex Hospital, have played an important part ; furthermore, the influence of such great men as Sir Arthur Keith and Professor Wood Jones has been of inestimable benefit.

Observation of lowly species

It appears of value in interpreting mechanisms of considerable complexity to gain what information is available from lowly species and simple examples.

Consider the *amoeba,* a single celled organism with no directing central nervous system. When the animalcule is in the neighbourhood of intended food such as a diatom, it appears to have some warning of the location of its prey by a sense akin to that of smell, for it protrudes parts of its body as pseudopodia, with some degree of discrimination and engulfs the morsel ; this illustrates not only the means of locating food, but also the mechanism of deglutition in higher species.

It has been suggested that the amoeba's method of progression is by means of combined gelation and solation, which is to say that rearrangement of molecules in one part causes relative solidity of a part of the organism and that into this stiffened area protoplasm flows, with consequent alteration in shape.

If there were not some process similar to this preliminary gelation, movement of protoplasm would not follow any particular direction.

This conception is of basic importance and has been advanced to explain ciliary action, as will be described later.

But further investigations contradict this opinion and ascribe amoeboid movement to alteration of surface tension under the influence of neighbouring particles. It has been observed that electric currents of suitable strength lead to reversible gelation in an amoeba, but with complete cessation of Brownian movement, which is normally present during protrusion of pseudopodia.[6] Flow of endoplasmic granules into the clear ectoplasm, when surface tension at certain points is altered, is thought to explain the process, although certain details are lacking. It does not seem possible to apply this reasoning to ciliary action, which will be considered later.

Olfaction

Since the nose forms the portal of the respiratory tract in most vertebrates and as it was evolved for olfactory purposes it seems appropriate to make some comments on this function.

Fish possess an olfactory recess of various degrees of complexity ; the recess is lined in part by specialised olfactory and secretory epithelium, carried on lamellae of varying number, designed to increase the area. Various mechanisms are present for the circulation of water over the lamellae. Since the organ serves no other function than olfaction, it seems desirable to examine it in some detail.[11 30]

It is known that odorous molecules must go into solution [18 74] and that a sufficient number must impinge on the receptors with sufficient velocity in order to provide olfactory perception ;[21] and furthermore, in Man, the solution must be saline.[46] Since the water vapour in the atmosphere is distilled, there must be some arrangement for giving salinity to the covering of the olfactory mucosa in mammals.

In such simple examples as the King Carp (Cyprinus carpio) or the gold fish (Carassius auratus) there are numerous clear vesicles in the lamellae adjacent to the olfactory mucous membrane, some of which come to the surface and are discharged (Fig. 2). They are obviously not required for moistening, as in mammals, and it appeared that they might have the function of giving salinity to the water in contact with the olfactory hairs ; somewhat similar globules are to be seen in the saccus endolymphaticus.[75]

In certain fish, including carp, clear vesicles, similar to goblet cells, are to be seen on the skin, to provide *mucus* which is normally present on the surface as a protection against fungi, amongst other dangers (Fig. 2). Baldwin describes the rôle of a covering of mucus as a means of preventing flooding by water passing through the semi-permeable skin under the influence of osmotic pressure.[5]

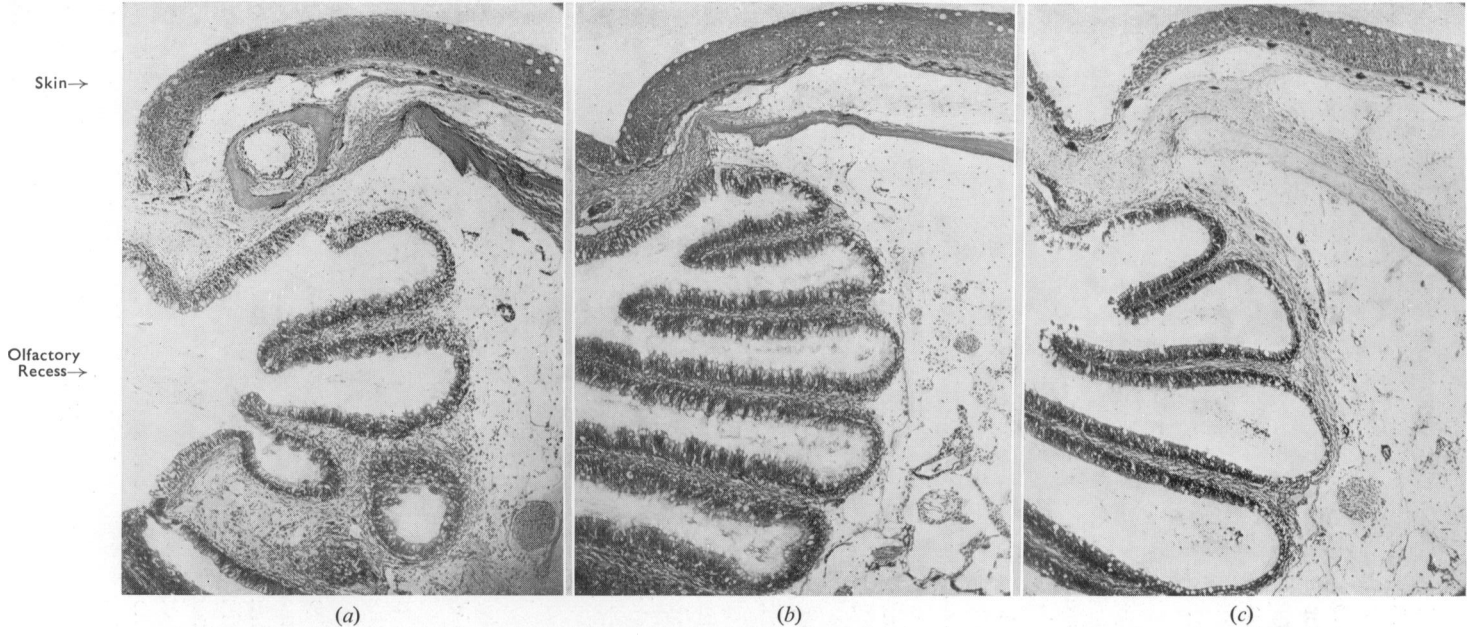

Fig. 2. Olfactory recess of carp, Cyprinus carpio.

(*a*) *Normal.*—Many mucus secreting cells on lamellae, some being cast off. There are similar but less numerous cells in the skin.

(*b*) *Carp kept in distilled water for two hours.*—Increased extrusion of cells with distention by intake of fluid, some distended cells being extruded, giving the lamellae ragged edges. No obvious change in the skin.

(*c*) *Carp kept in 2 per cent. saline solution for three-and-a-half hours.*—The lamellae show few mucus cells of small size. No ragged margins. The cells in the skin have not obviously changed.

Special staining for mucin demonstrates that the cells in the olfactory lamellae of fresh water fish have the function of producing mucus ; they are more numerous in the olfactory recess than on the skin. If fish are kept for some hours in distilled water the clear cells swell up and, if immersed in 2 per cent. Sodium Chloride solution there is a considerable increase in the number of visible cells, with shedding from the surface. This investigation demonstrates that it is probable that the mucus is secreted to serve a protective rôle in the neighbourhood of the delicate olfactory mucosa.

Salmon leaving the sea for rivers often suffer from fungoid infections of the gills, possibly because of reduced production of mucus in fresh water. This suggests that lysozymes are present to resist infection, especially in the delicate olfactory recess.

A further basic necessity for the olfactory sense is the presence of pigment, which may be observed readily in the olfactory lamella of a pike (Esox lucius) and certain other fish, amphibia and reptiles, and less easily in mammals.[4 36 37 38 55 65 66]

It was recorded by Darwin, and has been repeated since, that white pigs in Virginia are undesirable because they eat poisonous herbs which are less nocuous to black animals ; and this is true of some other white species.[16]

It has suggested that the black animals avoid the harmful herbs, unlike white ones, in which the sense of smell is deficient.[55]

Pigment is essential to the functions of the eye, and is also required for the proper functioning of nerve cells.[40 41] Lord Lister's mother, Isabella, was the sixth daughter of Anthony Harris, four of whose brothers were colour blind ; if this defect had been transmitted to Joseph Lister it is possible that he might not have become a surgeon.[15]

Prolonged stimulation of the guinea pig's vestibular nuclei results in a disappearance of pigment, with serious results.

Lord Lister studied the pigment of the skin and included a communication on the subject in his Presidential Address to the British Association in 1896.[49 51] He watched the migration of granules in the web of a frog's foot, and was able to observe the diffusion of black pigment into the hollow offsets of the chromatophorous cells, giving a dark colour to the skin, while on the contrary congregation of granules in the body of the cell uncovered other cells containing yellow pigment and gave to the greater part of the skin a pale colour. It was at first thought that the protrusion of granules was similar in nature to the movements of pseudopodia ; but further observation showed that the processes are hollow and unchanging in shape. By dividing the sciatic nerve he noted the influence of nervous control on the movements ; he was also able to determine the effect of light, either by direct action on the skin or through the medium of the eyes. He found that vision is essential for pigment changes.

It has later been found that in fishes there is a nerve supply to the melanophores, but none in Amphibia ; in them the control of expansion of the pigment cells is through the agency of intermedin, a constituent of the pituitary, the action being counteracted by adrenalin. Humidity, temperature, oxygen supply and illumination are significant factors.[36 66] (Fig. 3).

Some fish, for instance the Trout (Salmo fario), respond much more rapidly in colour changes than Amphibia, because of the direct nervous stimulation.

An important object of cutaneous pigment is protective coloration, to make the animal inconspicuous. The most rapid changes are said to be in Fundulus, a Brazilian fish ; trout change rapidly and so do Chamaeleons, but the common English frog is slow ; Xenopus, a South African toad, shows more rapid alterations of colour.[37 38]

Whether there is a positive function connected with the pigment in the olfactory apparatus is undecided. It is easy to observe the black cells in the submucous layer of such species as a carp (Cyprinus carpio), the sea lamprey (Petromyzon) and a slow worm (Anguis fragilis) ; the distribution in each is around nerve bundles and not in the epithelial layer. (Fig. 4.)

Watching these cells in the living fish has not disclosed any migration of pigment in response to the smell of aniseed nor to stimulation or division of the olfactory tract.

Pigment is distributed widely in the body, as for instance in the meninges of fish, with no immediately obvious reason. The black pigment is melanin, formed by the oxidation of tyrosine. An enzyme, tyrosinase, is an essential agent ; it is absent from the skin of albinos. Yellow pigmentation depends on the presence of carotenes, closely related to vitamin A, which is necessary for the formation of the retinal pigment. Both olfactory and auditory pigments in man are yellow, and Professor Ruedi has suggested that in some cases of deafness, the giving of Vitamin A is advantageous ;[70] a similar consideration may apply to some defects of the sense of smell.

It is known that odorous substances strongly absorb infra red radiation, and it has been suggested that the perception of odours depends on the intra molecular vibration of the odorant.[55] The agent of absorption may be the pigment which is always associated with the olfactory apparatus. It has also been suggested that absorption of heat rays may protect the deeper tissues from thermal damage ; so that various possibilities present themselves.

Although Lister was able to demonstrate movement in the pigment cells of a frog, with the object of protective coloration, yet this is no reason for ascribing a purposive function to all such cells ; investigation is required to decide whether pigmentation in the olfactory area is due to inclusion of dermal pigment cells, or whether it is of a separate derivation and with a specialised function ; sections from light and dark Carp

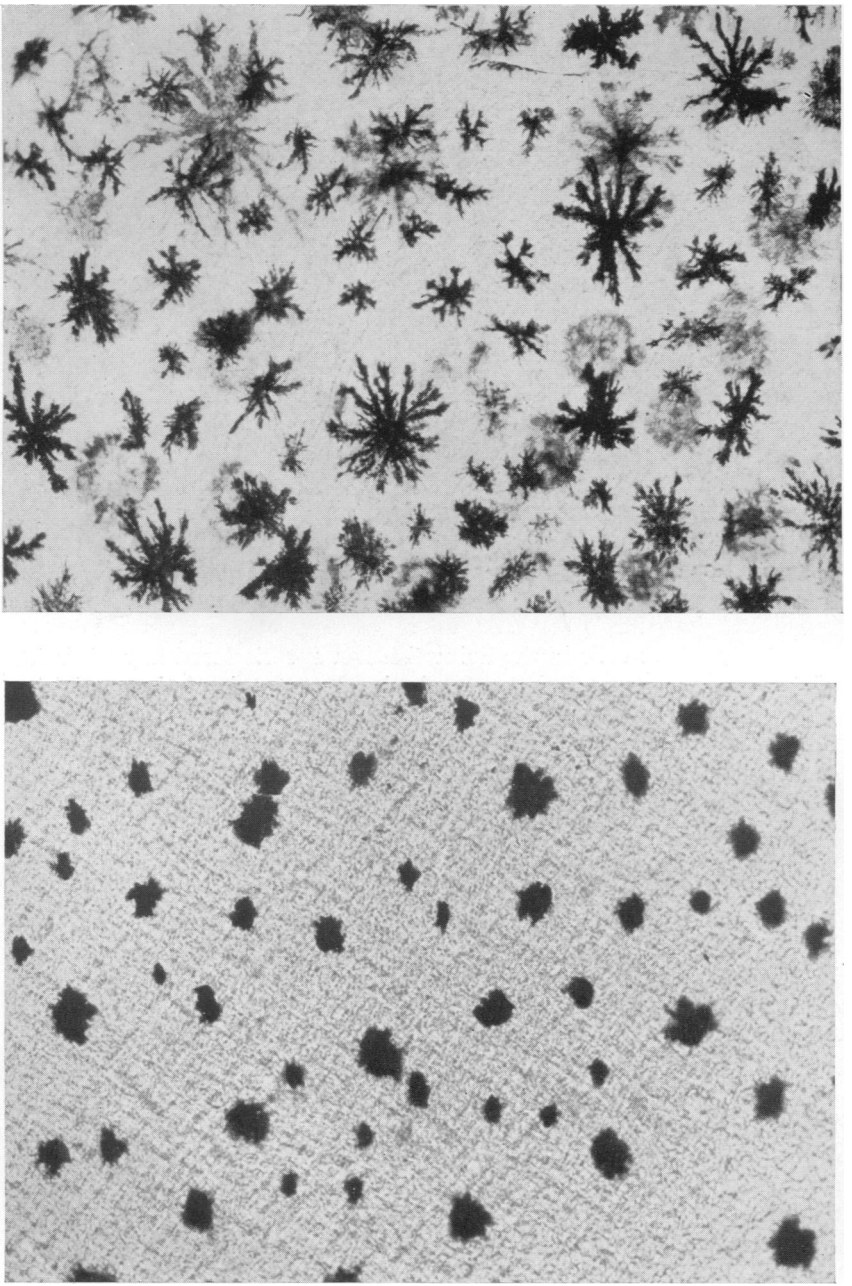

Fig. 3. Skin of a carp to show the pigment cells.

(*a*) With pigment expanded after being in a dark receptacle.
(*b*) With pigment contracted after exposure of the fish to a light background.

and frogs suggests that the pigment cells in the olfactory area do not behave like dermal cells.

Professor Boyd points out that there is apparently unwanted pigment in the human urethra, as well as in numerous other localities.

He observes that pigment cells are akin in derivation to the Schwann cells of nerve sheaths and that they may have a common protective function, but one not necessarily dependent on the pigment granules.[8] Olfactory fatigue is a well recognised phenomenon and it may be that pigment has some protective action in the transmission of nerve impulses.[1]

At this stage three fundamental observations present themselves in an attempt to explain some types of anosmia ; the olfactory area must be

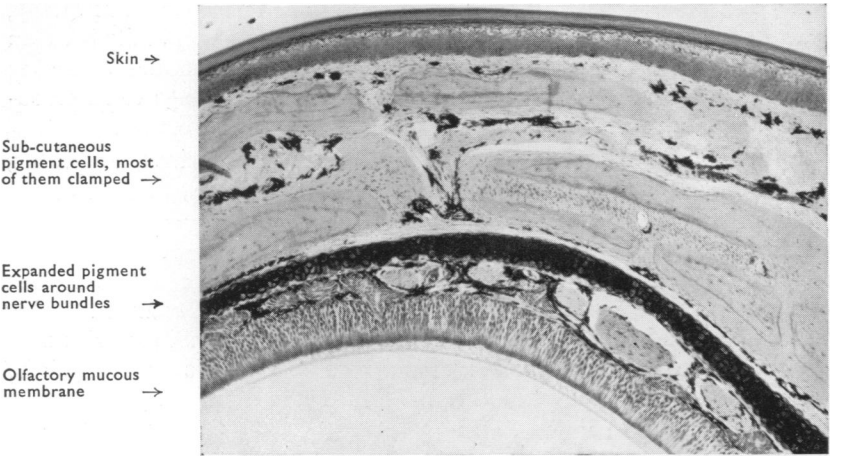

Fig. 4. Coronal section across the nose of a slow worm, Anguis fragilis. To show the pigment in the skin and in the olfactory mucosa ; in the latter situation the pigment cells envelop nerve bundles.

open to the impact of olfactory molecules ; these molecules must go into solution in a saline medium ; and pigment must be present for perception to be possible.

The *olfactory area* of Man is extremely small and situated in the roof of the nasal fossa, [2 3 9 69] ; it is surprising and unexplained as to how Man's keen discrimination of odours and flavours is determined, but it is at the same time obvious that his olfactory acuity is feeble in comparison with that of macrosmatic animals, with their enormous area of specialised epithelium and their efficient mechanism for saturating inspired air with moisture.[86]

Man's reliance on vision allows for a diminution of the olfactory sense. [13 85]

Not only have animals of keen powers of scent a wide area of olfactory mucosa in the nose, but there is in many an extension of ethmoturbinals, covered with olfactory mucous membrane, into superadded recesses in

the frontal and sphenoid bones; this explains the presence of these cavities in most instances, although not in all. [62 63]

There is another important modification in the formation of a sub-ethmoidal plate, which allows the olfactory mucosa to lie in a recess in which odours may accumulate sufficiently long and in sufficient concentration to be perceived and distinguished; this arrangement is absent in Man.

Olfactory fatigue may be delayed in animals with this accumulator system, as it may be called, where olfactory molecules remain in the vicinity of the sensitive mucosa; in Man the moving currents of air during inspiration and expiration are bound to waft away the odorous particles.

A point of great interest, but one that can be referred to but briefly, is the evolution of the *epiglottis* as a means of ensuring continuity between the nasal and laryngeal passages, thereby preventing mouth breathing even when the mouth is open, with considerable advantage to macrosomatic animals.[56 57]

Man, with his reliance on sight rather than on scent, retains an epiglottis, but it is separated by a wide gap from the palate.

An important observation made by Lister is closely related to the question of the epiglottis. In Man its most important function is support of the ary-epiglottic folds, which protect the laryngeal aperture against entrance of food or water passing down the lateral food channel. These rather thin and delicate folds are maintained in an upstanding position by the pull of the crico-arytenoidei postici muscles; paresis or paralysis of these muscles causes danger of inundation of the air tract.

Flabbiness of the upstanding ary-epiglottic folds leads to stridor in infants and young children through inspiratory sucking in of the boundaries of the laryngeal aperture; the condition has been known as congenital laryngeal stridor, but a more accurate name is laryngo-malacia.[45,84]

Lister made the observation that general anaesthesia sometimes produces a similar condition, on occasion to a dangerous or even fatal degree.[47] He managed to inspect his own larynx by means of mirrors and concluded that the correct treatment of cases of obstruction under anaesthesia was to draw the tongue forcibly forward, thus putting the ary-epiglottic folds on the stretch and thereby preventing their apposition. Having failed to obtain information on the problem he had to make these personal investigations. He wrote that "A work on practical surgery being not a likely quarter for information regarding the physiology of the larynx, it is not remarkable that they should have attracted little attention." It is hoped that the more complete study of the subject has clarified the question.

As well as observations on his own larynx and those of patients, he also investigated the subject in an anaesthetized sheep, but was stopped by an inspector of the slaughter house; in any case a sheep is not comparable to a man in respect of the ary-epiglottic fold (Fig. 5).

A subject for research is the function of the paired *organ of Jacobson,* an organ absent in Man but of obvious importance, although of undiscovered purpose, in many amphibia, reptiles and mammals.

To form a basis for the study of olfaction and respiration I have collected a large number of dissected specimens in the museum of this College and in the Ferens Institute of the Middlesex Hospital, representative of various species of fish, amphibians, reptiles, birds, mammals and Man ; I have also built up a number of transparent, tinted reconstructions from the nose of a variety of animals, in order that the histological details may be studied in addition to the gross anatomy.[63]

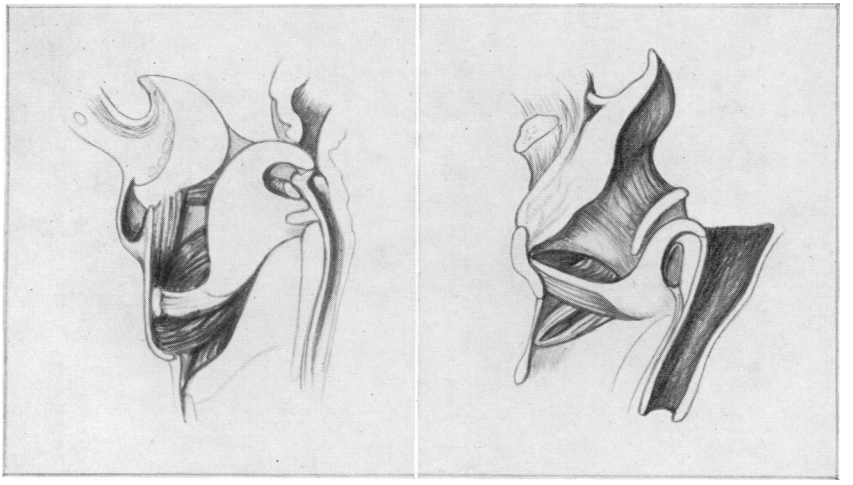

Fig. 5. Dissection of larynx of an ungulate and a man.
(*a*) The arytenoid and the superimposed cartilage of Santorini in the ungulate are so large that little gap remains between them and the epiglottis ; the ary-epiglottic fold is consequently firmly supported.
(*b*) In man a considerable gap intervenes, and although the aryteno-epiglottic fold is stiffened by the cartilage of Wrisberg, yet it is thin and liable to collapse.

Respiration

When certain fish attempted to leave the water in a search for new sources of food there was, in one instance, the climbing Perch (Anabas scandens), the evolution of a diverticulum above the gills, capable of absorbing oxygen if kept moist. The mud hopper (Periopthalmus) is another example of a fish able to stay out of water for considerable periods. Dipnoi, or lung fish, went a stage further by evolving lungs for use when the waters in which they live dry up, or when its oxygen content had fallen to a very low level ; to prevent entrance of food or water a protective valve was required at the mouth of the pulmonary tract in the form of a larynx. It had, in its simplest form, a sphincteric muscle ; later, but of less vital importance, a pair of dilator muscles was added to open the orifice actively, in place of the passive relaxation of the simpler type [57] (Fig. 6).

This simple observation may be used to explain the characteristic changes in the larynx generally known as *Semon's law*, when one or both recurrent laryngeal nerves are paralysed[71]; the sphincteric girdle of muscles, of older origin and of greater primitive importance survive longer than the dilator group. Pressure on, or interference with the recurrent nerve results at first in loss of function of the dilator muscles;

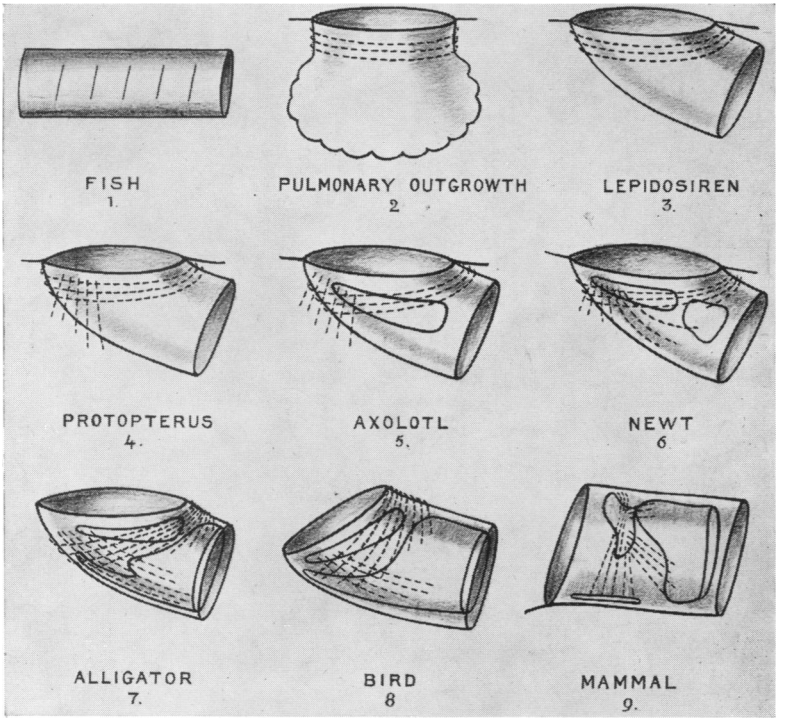

Fig. 6. Evolution of intrinsic laryngeal musculature.
The pulmonary outgrowth is illustrated, surrounded by a simple sphincteric band of muscle (2 and 3), with later addition of dilator fibres (4).
Further modifications are the formation of a lateral cartilage (5) of which part separates (6) and joins with its fellow of the opposite side to form a crico-thyroid ring (7).
The sphincteric band later divides into components (8), of which there are two paired and one single constituents (9); the dilator fibres migrate backwards, with mechanical advantage (9).

the vocal fold is brought near to or into the midline position by the still active sphincteric muscles. If both recurrent nerves are partially paralysed the glottis is a mere chink and dangerous dyspnoea results, usually requiring tracheostomy for its relief.

This observation on the action of the intrinsic laryngeal muscles leads to the question why there are movements of *alternate widening and narrowing of the glottis* during respiration in Man; they are to be seen in

quiet breathing but are more obvious when respiration is laboured.[72] The reason appears to depend on the desirability of co-ordinating air entry into the lungs with blood flow through the pulmonary capillaries.[39]

Although the nose causes some obstruction to passage of air,[81] yet there is still further interference at the glottis, which acts as a choked point on the airway, by reason of its short arytenoid cartilages. Widening of the glottis during inspiration determines the rate of air entry in response to the bellows action of the ribs and diaphragm; reduction of intra-thoracic and intra-pulmonary pressure exerts a pump action and not only draws air into the lungs, but also sucks blood through the great veins into the right side of the heart. The pulmonary capillaries dilate in response to reduced pressure on their walls and blood rushes through, meeting a supply of fresh air which takes up carbon dioxide and gives up oxygen [57] (Fig. 7).

Artificially produced obstruction to inspiration in a cat causes the aortic pressure to rise to a great height.

During expiration the glottis narrows, delaying the escape of air, and raising intra pulmonary pressure; consequently blood flow through the lungs slows up at a time when respiratory exchanges cannot be carried on efficiently (Fig. 7).

In Cetaceans, which submerge for considerable periods, there are big vascular spaces in the liver, for the storage of venous blood at a time when it would be useless for it to flow through the lungs.

When *tracheostomy* is performed in Man this delicate regulating mechanism is lost. I attempted to prove in a Hunterian lecture in 1925, that on experimental evidence this disturbance was of serious importance. The subsequent observation of patients with permanent tracheostomas has demonstrated to me, as to others, that although there may be temporary disturbance, yet eventually there is very good adaptation, so that life can be carried on almost normally. This is an example of the triumph of practical experience over theoretical conjecture.

Tracheostomy does, however, raise other problems.

The operation is usually performed for laryngeal stenosis, sometimes of an alarming degree. In long-standing cases obstruction leads to deficient respiratory exchanges; elimination of CO_2 is reduced and the alveolar percentage may rise from the normal 5·6 per cent. to a figure as high as eight, as shown by an investigation conducted by Dr. R. D. Lawrence and myself. To the non-conditioned subject this would result in an enormous increase in lung ventilation, but if of gradual onset adaptation is effected.[58] The excess acid is fixed by increase in the alkali reserve and at the same time the respiratory centre is adapted to respond to a higher level of CO_2. When full lung ventilation is suddenly restored by tracheostomy the alveolar percentage of CO_2 returns after a few breaths to the normal 5·6 per cent., as may be determined by estimations of alveolar air. With insufficient stimulation, the hypo-sensitive respiratory centre fails to initiate respiratory movements and the patient is in danger

of dying from anoxaemia induced by this condition of acapnoea.[28] Not even the most extreme lack of oxygen will stimulate the respiratory centre and the giving of oxygen is useless. What is required is carbon dioxide, and therefore this agent is kept ready and is administered before respiration ceases, or, if necessary, in conjunction with artificial respiration.

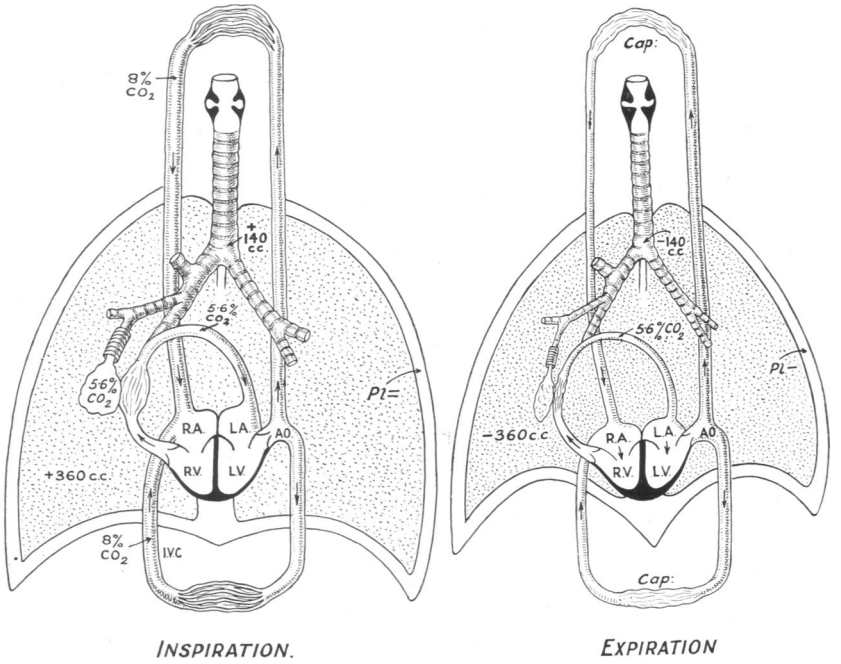

Fig. 7. Regulating effect of glottic movements on respiratory exchanges.
Inspiration.—Glottis open, bronchi expanded and lengthened (+140 c.c. tidal air); bronchiole muscle relaxed; alveoli dilated; pleural pressure much reduced; thoracic capacity increased (+360 c.c. pulmonary tidal air); systemic veins and right auricle distended. Pulmonary capillaries dilated; left auricle filled; increased output from left ventricle.
Expiration.—Glottis partially closed; bronchi contracted and shortened (−140 c.c. tidal air); bronchiole muscle contracted; alveoli partly emptied; pleural pressure slightly reduced; thoracic capacity diminished (−360 c.c. pulmonary tidal air); systemic veins and right auricle poorly filled; pulmonary capillaries collapsed; left auricle receiving less blood; output from left ventricle diminished.

Knowledge of this possibility may be the means of saving the life of a patient on whom the operation appears surgically successful.

The second observation connected with tracheostomy is that the tracheo-bronchial tree, the alveoli and air sacs must be moistened if respiratory exchanges are to be carried on.

The question of humidification will be considered later.

The *Hering Breuer* reflex is deranged by tracheostomy. It depends on filling of the bronchi with air, there being a signal to commence expiration when tidal air has entered in sufficient volume and *vice versa*. Opening

the trachea, with elimination of the delaying action of the glottis, expedites entry and escape of air and consequently accelerates the Hering Breuer reflex. The respiratory rate increases after the operation, but knowledge of the reason prevents alarm.

The nose is the correct channel for respiration by virtue of its air conditioning function. The passage through the nose and nasopharynx to the pharynx and laryngeal aperture in Man is tortuous ; runners stretch out the neck and extend the head in an attempt to straighten the air tract. Fast running animals, on the contrary, have an almost straight air passage.

An interesting observation in regard to breathing through the nose is that there is a *naso-pulmonary reflex* which determines the degree of dilatation of each nasal fossa in relation to ventilation of the homolateral lung ; when lying on the side the ventilation of the lower lung is decreased and the lumen of the nasal passage is reduced or obstructed.[73] There is a further change in the relative freedom of the two fossae known as the nasal cycle, which alternates at one to four hour intervals.[31 80 81 82]

The degree of patency of the nasal passages has been graphically recorded by Slome and Malcolmson and the effect of various influences has been studied.[78]

The final observation about respiratory movements is that connected with the action of muscles surrounding the air passages. The peribronchial and *bronchiolar musculature* appears to execute movements of relaxation during inspiration and contraction during expiration, as may be observed visually through a bronchoscope or felt manually during the extraction of a foreign body.[10 29 44]

Similar movements occur in the trachea. In the horse there is a broad sheet of muscle stretching across the trachea ; its contraction must diminish the capacity of the wind pipe and in conjunction with the bronchial musculature will expel some dead space air, with advantage in respiration.[57]

It is probable that this muscular contraction occurs in a peristaltic manner and it also appears that premature or excessive contraction prevents air from escaping freely from the lungs, thus producing the symptoms of asthma.

Not only the trachea and bronchi, but also the *alae nasi* show active movements of contraction during expiration in order to squeeze out dead space air ; this may be seen readily in a horse on a cold day, and to a less degree, in a breathless man.

The respiratory movements at the glottis form no part of the mechanism ; their partial opening and closure are rapid and precede contraction of the chest muscles, as may be shown graphically by means of a kymograph[57] or a cathode ray oscillograph.[64]

Ciliary Action

The use of permanent protoplasmic protrusions from an epithelial cell is of great interest and of vital importance. A most lucid and comprehensive article was written on the subject in 1834 by Professor William Sharpey, under whom Lister studied at University College.[75] [76]

Lister studied ciliary action in the tongue of a frog, and in scrapings, and observed the effects of the vapours of chloroform, mustard, and ammonia and also the arrest caused by application of heat, acetic or carbolic acid.[49] [50]

In Man the greater part of the nose and paranasal sinuses and the tracheo-bronchial tree are lined by ciliated epithelium.

In Man cilia have the function of scouring rigid or semi-rigid cavities, namely the nose and nasal sinuses, the trachea and the bronchi as far as the atria.

Cilia work in relays, propelling a covering or blanket of mucus along predetermined pathways; in this mucus there are entangled particles of dust and other debris and also bacteria.[68] From the nose the streams pass half way down the nasopharynx where the cilia cease, and from the larynx they escape through the posterior commissure into the hypopharynx, there being no cilia on the vocal folds ; it is easy to understand how sputum laden with tubercle bacilli leads to submucous deposits in the posterior commissure. The mucus with its cargo of organisms and debris is carried away by swallowing movements and is transferred to the stomach, where bacteria are killed by gastric juice.[59]

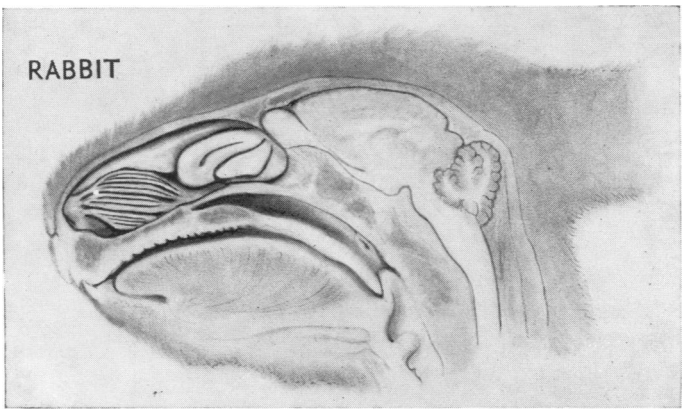

Fig. 8. Sagittal section of nose of a rabbit, Lepus cuniculus.

The branching maxillo-turbinal body is placed in the anterior part of the nose, with the function of warming and moistening inspired air and of retaining heat and moisture from expired air. The posterior half of the nose is occupied by the branching ethmo-turbinal bodies, the greater part of whose surface is covered by olfactory mucosa.

The large olfactory bulb is seen in front of the cerebrum.

To work efficiently there must be a fluid covering of the right degree of viscosity and in the right quantity.

The requisite fluid covering is provided by secretion from goblet cells and racemose glands, diluted by transudate ; if too tenacious the blanket cannot be moved, and if too thin it will not cohere and cannot be dragged by cilia from a distance.[35 68]

Ciliary action is of much greater importance than cough in protecting the air passages. Cough is a pathological process and can do no more than

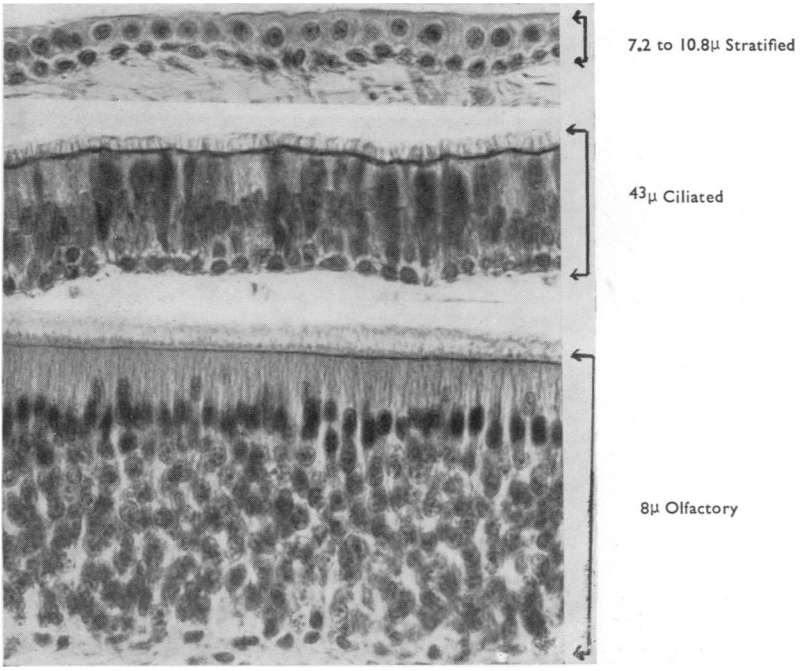

Fig. 9. Epithelia from the nasal mucosa of a rabbit.
Above is the very thin stratified epithelium covering the maxillo-turbinal, allowing passage of warmth and moisture. In some places it is only 5μ in thickness.
In the centre is the ciliated epithelium which covers the nasal septum and lines the sinuses ; it has numerous goblet cells and a well defined basement layer.
Below is the olfactory mucosa, with many layers of nuclei, but no clear basement layer.

eject a large bolus of secretion ; it is of brief duration and disappears in a few seconds after the impact of a foreign body. Ciliary action must be preserved at all costs, by determining the degree of viscosity and the quantity of the mucoid covering ; this can be effected to a certain degree by the use of mildly hygroscopic sprays in the nose, by the use of potassium iodide to increase, or of ephedrine to decrease the quantity.

Nothing must be done to upset the mechanism ; nasal surgery or cauterisation must be restrained ; the removal of adenoids must not entail

scarring of the pharyngeal aponeurosis or muscles; operations on the sinuses should aim at the restoration of normal function without reliance on re-growth of ciliated epithelium; and finally, nasal medication and anaesthesia must be so designed as to preserve ciliary action.

The action of cilia is of particular importance in protection of paranasal sinuses against infection.

As far as can be observed all the sinuses are lined by ciliated epithelium; streams flow always towards the ostium, which is the point from which ingrowth took place during development. If the lining is removed operatively there may be re-growth and in this case the streams will again flow towards the ostium or point of regeneration.

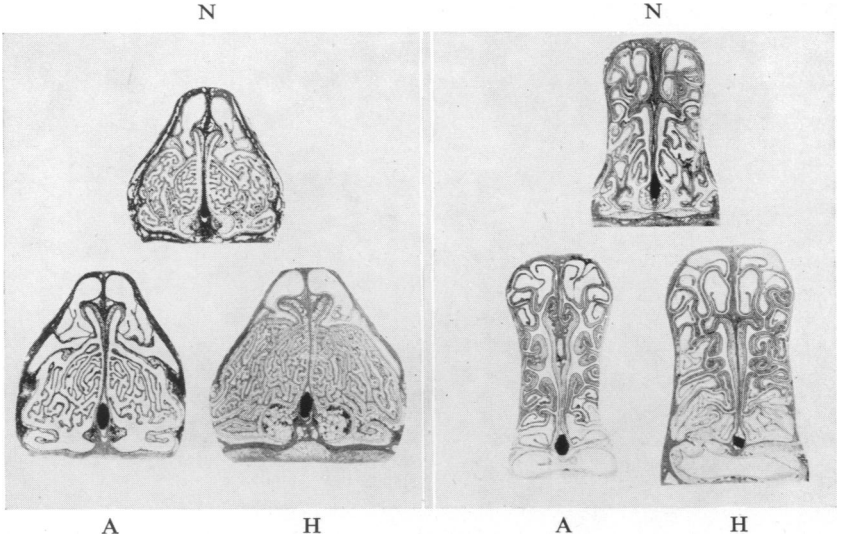

Fig. 10. Coronal sections of the nose of cats.
(i) On the left from the maxillo-turbinal region and (ii) on the right from the ethmoidal area.
In each case a section of a normal nose (N) is shown above and below this one from an animal perfused with adrenalin (A) and histamine (H). The great effect on the vascular mucosa designed for air-conditioning is well shown (i), in contrast to the negligible action on the olfactory membrane (ii).
(*Experiments by J. C. Seymour, Ferens Institute.*)

If the maxillary sinus becomes infected the escaping secretions may coagulate and become so thick as to cause obstruction of the ostium, with continuance of the disease and often with pain; puncture and lavage will unblock the normal outlet of the antrum and allow ciliary action to restart.

A somewhat similar condition may arise in a bronchus when infection leads to swelling and the formation of granulations; the latter are devoid of cilia. Re-establishment of the outlet by bronchoscopic treatment can lead to a cure of what may be called a bronchial abscess.

Hilding has shown that the air passages, commencing as one trachea and two main bronchi, finally divide into as many as 50,000 minute

branches; plugging by thick secretion or by droplets is thereby explained.[17 34 35]

The propulsive power of cilia is considerable and so powerful as to be able to expel air from the frontal sinus, with the production of vacuum headache, to reduce the air pressure in the tympanic cavity with resultant deafness, or to deflate a segment of the lung, as demonstrated by Hilding.[35]

The minute structure of cilia has been elucidated by studies with the electron microscope, carried out by Engstrom in Sweden [7 20] and by Fawcett and Porter in the United States of America,[22] amongst others.

These remarkable researches have shown clearly that each cilium contains longitudinal filaments in a cylindrical column of protoplasm, which in turn is surrounded by a membrane. In cross section there are seen to be nine filaments in a circle and a pair in the centre; the number is constant. The central pair of filaments are arranged side by side; this determines their movement in a pendular movement in a direction at right angles to their axis. All the paired filaments are in the same plane, which causes them all to bend in the same direction and not to strike against one another.[22]

The filaments are thought to be the contractile elements, with active movement both on the forward lashing stroke and also on the less active return stroke, as described by Gray.[26 27]

A process of reversible and partial gelation and solation is said to cause alternate relative stiffness and fluidity; observations on this process have been made above in respect of amoebae.

Each cilium rests on a basal corpuscle, which is anchored by intracellular rootlet fibrils; the basal corpuscle is thought to aid movement of the cilium by alternative waves of polymerization and depolymerization, but this explanation is difficult to understand.

Projecting from the epithelial cell there are a number of filiform processes or microvilli; they are not vibratile but may be connected with metabolism. They have been mistaken for cilia.

Humidification

A supply of moisture is essential for respiratory exchanges and for ciliary action. The nose is able to give up a great deal of moisture and to satisfy both requirements in association with the activity of goblet cells and racemose glands[14 43], together with moisture derived from inspired atmospheric air; it must be realised that the latter vapour consists of distilled water.

But another necessity is the entrapping of olfactory molecules in the front of the nose and their deposition on the specialised olfactory epithelium at the back of the nose.

It is found on examining the nasal fossae of all animals that a very simple and limited air conditioning apparatus appears sufficient for the needs of the lower respiratory tract, as in the Primates and Man. It is

in animals of keen powers of scent, and especially in the carnivores, that a more elaborate structure is provided in the form of a widely branching *maxillo-turbinal* body with an enormous area of mucosa designed to give up heat and moisture.[62 63] (Fig. 8).

In such an animal as the rabbit the mucosa covering the maxillo-turbinal is extremely thin, consisting of two layers of cells and as little as 5μ in thickness; correlation of this elaborate system with the habits of various species similarly provided leads to the conclusion that the extremely efficient air conditioning system is provided for the maintenance of the olfactory sense and not primarily for the protection of the lower air passages.[63] (Fig. 9).

The mucosa of the maxillo-turbinal body is provided with wide vascular spaces, the heat so available being essential for warming incoming air if much moisture is to be carried; cold air cannot take up much water, its absolute humidity being low. There seems no doubt that fluid passes out of the mucosa by transudation, a question sometimes disputed.[42 43]

It is interesting and of importance to enquire how this extremely efficient process of humidification is related to keen powers of olfaction.

Many years ago Zwaardemaker showed that odorous substances tend to condense moisture from the air, and the moisture, condensing in the nasal cavities, helps perception of odours; his conclusions have been recorded by Moncrieff.[55 87 88 89 90 91]

It was found that a spray of water from a fine jet is not electrically charged, but if the water contains an odorant in solution, even in small quantities, then the spray carries a strongly positive charge. The static charge is due primarily to reduction of surface tension by the odorant, but molecular weight and solubility of the odorant also play a part.

Zwaardemaker was able to make a stable fog by atomising 2 per cent. sodium chloride solution; but if an odorous substance was added to the salt solution then the fog was much less stable and soon disappeared. In the former case, when no odorant was used, the positively and negatively charged particles must have been present in equal quantities, since excess of neither remained when the fog was dissipated. In the latter case, when an odorant was present, the vapour imparted a strong positive charge to an insulated metal dish or glass tube inserted into it. It was suggested, therefore, that the fog contained large positively and small negatively charged particles, and that the latter dispersed more easily on account of their small size and higher speed. Whilst all odorous substances exhibit the spray charge phenomenon, not all substances which exhibit the charge are odorous.

It is clear that anything which facilitates condensation of watery vapour containing an odorant in the olfactory regions will promote perception of the odorant. Hence the odorants which generally reduce surface tension promote conditions in the nose under which they will best be perceived.[87]

Adsorption of odorous molecules in the nose may take place through the condensed layer of moisture present on the mucosal surface or by direct attraction of the positively charged particles by an oppositely charged surface.[89 91]

The extraordinary variation in blood content of the warming and moistening apparatus can be demonstrated in the nose of cats perfused with adrenaline or histamine and fixed intravitally, as carried out in the Ferens Institute by J. C. Seymour. (Fig. 10.) Other experiments by Slome and Malcolmson have shown the changes in the nose in response to the action of drugs or after interference with the sympathetic nerve supply.[78]

Expired air is in part utilised to maintain the temperature and moistness of the maxillo-turbinal in a manner similar to that of a protective covering placed over a tracheostoma or a laryngostoma; consequently, the retention of heat and moisture relieves the nose of constantly furnishing a fresh supply for each incoming breath.[14] A copper or gauze mask over the mouth acts in a similar way for those exposed to very cold climates. Although the mouth, pharynx and lower air passages have the faculty of providing a certain amount of warmth and moisture, apart from that derived from the nose, yet they fail if left unprotected.[32 33] After *laryngectomy* a patient in a warm dry room is liable to have stagnation of secretions in the trachea and bronchi, which may become so massive as to cause crusting and dangerous obstruction.

The lesson is that humidification of the room or ward to a relative humidity of at least 50 and possibly as high as 70 per cent., is desirable, until adaptation is attained.

Many investigators have recorded the temperature and humidity of air at different points on the air passages.[14 67] A monograph on this subject was written by Greville Macdonald in 1889.[53]

To study the subject in a slightly different manner and to fill in certain gaps, an air conditioning plant has been constructed in the Ferens Institute, allowing air of any degree of temperature and humidity to be inspired, with recording of the response in the back of the nose or elsewhere by means of a double thermocouple acting as a wet and dry bulb thermometer.[60 61]

It is hoped to measure the electric charges under various degrees of humidity and also to determine the influence of humidification on the olfactory sense by picking up potentials from the olfactory bulb when odorous molecules enter the nose under different atmospheric conditions.

Composition of tissue fluids and exudate

The ionic balance of the fluids within the cells of the nasal mucous membrane is a most important factor in health and in some diseased states.[54 79] Experiments with excised columnar ciliated epithelium allow observations to be made of the effects produced by changes in the electrolyte content and the reaction of the fluid medium.[26 59]

The essential elements of calcium, sodium, potassium, manganese, phosphorus and ammonium must be present in correct proportion ; a rise of sodium leads to increased permeability of cell walls, with swelling and cessation of activity, as may be observed if ciliated cells are kept in normal saline solution ; potassium in excess has a similar effect.

Calcium decreases permeability of cell membranes and is of value if given in cases where the fluid output has increased and where a rise in permeability permits exudate to accumulate in intercellular spaces or to escape in excessive quantity through the epithelium, as occurs in those states of peculiar reaction of the tissues collectively known as *allergy*. The giving of dilute nitrohydrochloric acid helps in this treatment, partly by facilitating the absorption of calcium, but also no doubt by neutralising an abnormal rise in the alkali reserve. The nasal secretion should be neutral or just on the alkaline side for normal functioning ; in allergic states the pH may rise from its normal 7·0 or 7·2 to as high a figure as 8·5.

No doubt a similar process affects the lining of the bronchi ; in both the nasal and bronchial regions of the respiratory tract the result is swelling of the mucosa with obstruction and outpouring of secretions, leading to rhinorrhoea or bronchorrhoea.

The quantity and degree of *viscosity* of mucus has been referred to already as determined by the activity of goblet cells, racemose glands and Bowman's glands in association with transudation ; changes of permeability in the walls of capillaries and epithelial cells can cause considerable disturbance. Consideration must be given to the function of mucus in fish and amphibia in preventing excessive passage of water by osmosis through a semi-permeable membrane as mentioned earlier,[5] with a possible bearing on water logging of the mammalian mucous membrane in what are usually described as allergic conditions. Thyroid deficiency has been considered by Proetz to have an effect in reducing the quantity of secretions, while on the contrary, the taking of potassium iodide increases it.[68]

The bacteriostatic or bactericidal action of mucosal secretions is influenced by changes in the reaction ; a high pH is more favourable to the growth of bacteria than one at or below neutrality.

An important bactericidal constituent of nasal mucus is lysozyme, discovered by Fleming many years ago.[23]

Conclusion

Some of the problems referred to were of interest to Lord Lister ; that they were worthy of note by him is a strong reason for pursuing them now, since many explanations still await discovery.

The interest and fascination to be derived by the enquiring mind from the type of research described in this communication cannot better be summed up than in the words of the great master of surgical science.

At a Graduation Address delivered at Edinburgh in 1876 Lord Lister spoke as follows : " . . . and truly, if we had nothing but pecuniary rewards and worldly honours to look to our profession would not be one to be

desired. But in its practice you will find it to be attended with peculiar privileges, second to none in intense interest and pure pleasures." That those privileges have fallen to my lot makes me very content to have entered the profession of medicine; and the opportunity of paying tribute to this great man fills me with gratitude and pride.

The Sections and Microphotographs are by Mr. D. Bishop, Ferens Institute. Drawings by Mrs. Victor Negus, Mr. S. Steward and Mr. Field Marchant.

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MONTHLY DINNERS

Monthly dinners are held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests : all Diplomates and students of the College and Members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The dinners will be held at 7 p.m. on the following Wednesdays : June 8 and July 13, 1955. There will be no dinners in August or September.

The cost is £1 10s. 0d., which includes cocktails before dinner and wine at the table. Applications for tickets, accompanied by a cheque for the appropriate amount, must be sent to the Deputy Secretary at least a week before the date of the dinner. Cheques should be made payable to " Royal College of Surgeons of England." The dress is Lounge Suit.