hagocytosis, Mucous Flow, and iliary Action

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A.C.

The following presentation is a discussion the physiology of the defense of the respiry tract against inhaled particulate matter, ether living or nonliving. The physics of position in the tract has been described by ners.[3,9]

Nose

Anatomy.—This defense begins in the nose hich acts to prepare the inspired air for ceptance into the lungs. The nose is about 5 cm. long and 5 cm. high. The entrance at the nares which lie practically horizonlly and are very narrow. The exit is at the anae, which are larger than the nares each easuring about 2.5 cm. in height by 1.25 cm. width. The roof is arched; the floor is t. The nose is narrower anteriorly and steriorly and wider in the middle. In cross ction, it is triangular in shape, being wider dow and narrower above. Most of the space filled with the turbinates which, with the ptum, form narrow flues through which the r flows. (Fig. 1*A*). These flues are normally ite narrow and cause the air to flow in flat eets in such manner that no portion of the stream is very far from the moist mucous anket lining the air spaces. The width of e air spaces is adjustable by virtue of swell ies in the septum and turbinates. Preably the size of the air-flow is adjusted to eet varying atmospheric conditions.

Physiology.—Inspired air flows in a jet-e stream through the nostrils, upward and ack, passing above the level of the middle turbinates, then arching back and down into the nasopharynx and larynx. (Fig. 1*B* and 1*C*).[68] Along the flow way there are a number of eddies and changes of direction where special impact occurs. Among these are the preturbinal areas, the anterior portion of the turbinates, the nasopharynx, the base of the tongue, and the pyriform fossae.

Air-Flow Inspiration.—When gases flow through a tube, at low velocity, they flow in layers, one layer next to the periphery being almost stationary and the most rapid flow being in the center. If the velocity exceeds a certain maximum, turbulence ensues. In the trachea, this maximum is exceeded in ordinary respiration, so the tracheal flow is turbulent.[69] In the nose the flow also seems to be turbulent. This is important from the standpoint of deposition.[70]

Deposition.—If air containing particulate matter is passed through a tube in which there is a constriction, deposition tends to occur just behind the constriction, probably due to inertia rather than to gravity or diffusion. Similar deposition occurs at bends in tubes. The nose is characterized not only by constriction followed by expansion but also by changes of direction, so that impaction and deposition.[68] Areas of deposition occur in the anterior third of the nose, in the pharynx, the pyriform fossae, and in areas around the epiglottis—the areas previously mentioned where there is special impact of air.

Respiratory Epithelium.—The lining respiratory epithelium is a highly versatile structure which accommodates to varying circumstances.[11,12] In general, the respiratory epithelium is a pseudostratified columnar ciliated epithelium. Typically it consists of a basement membrane upon which lie 2, 3, or 4 layers of replacement cells and then the elongated columnar cells which extend to the

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Presented at the Skytop, Pa., Conference on Respiratory Disease in Industry, May 14-16, 1962.

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Work supported by grants from the Louis W. and Maud Hill Family Foundation of St. Paul, the Edward C. Congdon Memorial Trust, Miss Elizabeth Congdon, and The Women's Service Guild of St. Luke's Hospital.

Fig. 1—A, [illegible] nograph showing [illegible] nal breathing [illegible] a living nose. [illegible] gram on the right [illegible]

surface. The columnar cells are surmounted by cilia 5 to 7 mm. in length over which lies a thin layer of mucinous secretion—the mucous blanket. However, this typical form is not found everywhere. In the anterior third of the nose, where the impact of inflowing air is first felt, the epithelium is nonciliated; it is many cells deep and is layered very much like skin. Farther back on the turbinates, septum, and spaces most exposed to air flow, the epithelium becomes columnar and relatively thick. The columnar cells are tall. The cilia are well developed but, where most exposed, are apt to appear moth-eaten. In the more protected areas under the turbinates, [illegible] the columnar cells are tall, the [illegible] more regular and better preserved. In areas less exposed to air, such as the sinuses, the epithelium is usually only 2 layers deep, 1 layer of replacement cells and 1 layer of columnar cells which have become so low that they are described as cuboidal. They are very well ciliated. Respiratory air does [illegible] flow through the sinuses.

Extending into the mastoid cells, the epithelium changes its character and becomes most like the epithelium and endothelium of the lungs distal to the respiratory bronchioles where there are no cilia.

The air flow of expiration follows a somewhat different pattern and, for our purposes, is of less importance.

Ciliary Action—Cleansing Mechanism.—The nose prepares the inspired air for the lungs. Much particulate matter is deposited in the nose, especially in the anterior third, whence it is carried down and back into the nasopharynx and eventually into the stomach. The flow takes place through ciliary action. In the anterior third of the nose, where there are no cilia, secretions seem to be removed through traction by the cilia farther back. The flow is relatively slow, 1 to 2 mm. an hour. In the posterior two-thirds of the nose, the rate of flow is 8 to 10 mm. a minute. The direction of flow from the anterior, nonciliated areas is into the meatuses under the turbinates. From the medial walls of the turbinates the flow tends to be down and back and is apt to slide under the margin of the turbinates into the meatuses (Fig. 2). From the septum the flow tends to go back and, on the way, to cross the floor laterally, winding up also under the inferior turbinate. At the posterior ends of the turbinates, the streams flow across the lateral pharyngeal wall, divide around the eustachian tube, and are carried by muscular action down into the esophagus.[12-16]

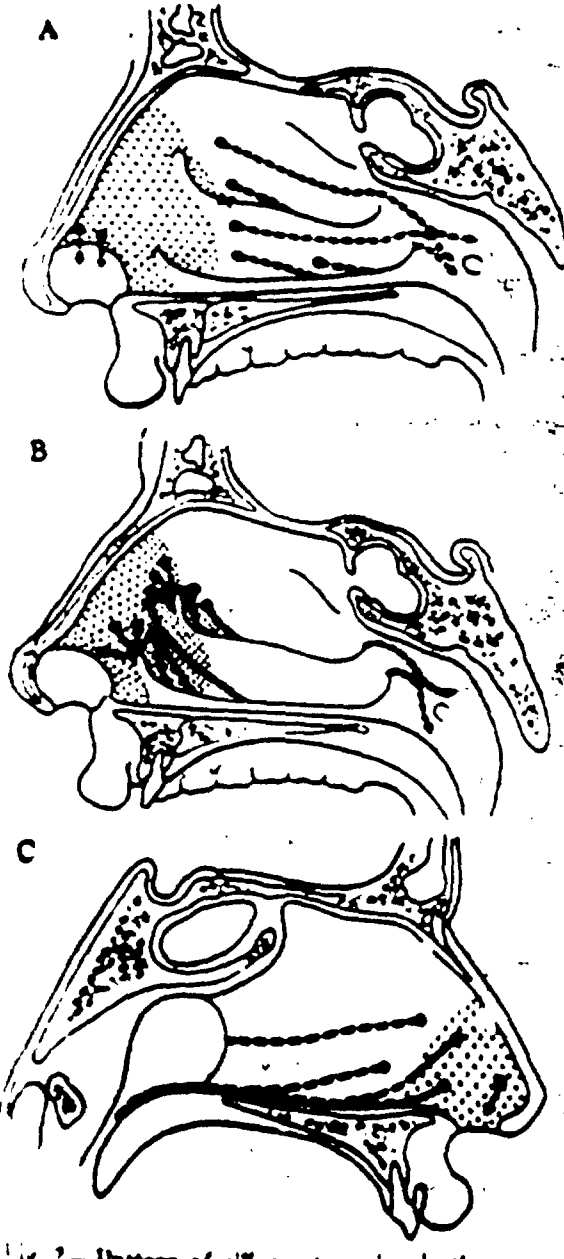

Fig. 2.—Pattern of ciliary streaming in the nose. *A*, the course of flow of mucus on the lateral nasal wall in the active areas; *B*, the course of flow of mucus on the lateral nasal wall in the inactive areas; *C*, the course of flow of mucus on the turbinates. The rate over the inactive area (stippled)

Temperature Adjustment.—The temperature of the air is adjusted, up or down, according to circumstances. By the time the air reaches the pharynx, it is practically at body temperature, even if the reading at the tip of the nose is −20 F.

Humidification.—The moisture content is also adjusted so that by the time the air reaches the pharynx, it is practically saturated. Since we breathe at least 10,000 liters each day, this means that a considerable amount of heat must be radiated from the interior surfaces of the nose and a considerable amount of water evaporated through the mucous blanket. At ordinary room temperatures, and at usual humidity, the air is said to evaporate 1,000 ml. each 24 hours.[42]

Lower Respiratory Tract

Anatomy.—The cross-sectional area of the tracheobronchial tree at different levels is about the same.[17] In other words, the combined cross-sectional area of the 2 main bronchi is about the same as the cross-sectional area of the trachea, and, if one proceeds to subsequent divisions, the same relationships seem to hold true, at least down to bronchi about 1 mm. in diameter. Distal to those, the

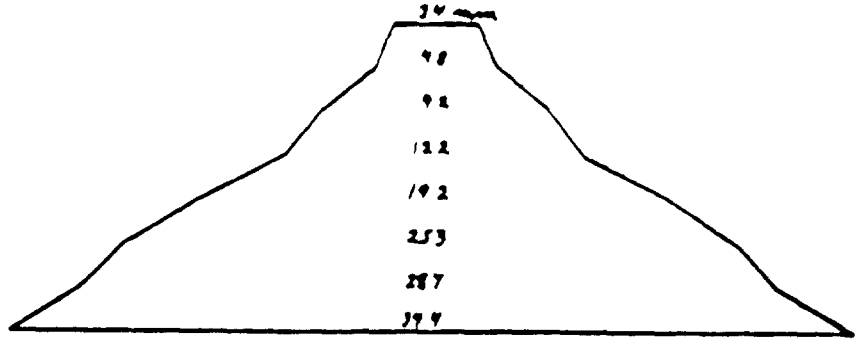

Fig. 3.—Diag... the 10-fold increa... sum of the diam... the bronchi thr... branchings. The... cross sectional ar... mains about the s... all of these levels. ... tesy of Trans. Am... Otolaryng.)

cross-sectional area begins to widen rapidly and eventually becomes very large. The area of the lining mucosa, on the other hand, increases with each subsequent division. The trachea is about 5 cm. in circumference. The 2 main bronchi together are about 7.5 cm. in circumference and, with each subsequent division, the combined circumferences increase, as does the area of the lining mucosa. By the time one reaches the respiratory bronchioles, or terminal bronchioles, where the cilia begin, or end, (depending upon the direction), the total combined circumferences of all the tubes at that level is very great; probably meters in extent (Fig. 3).

Lining Epithelium.—The lower tract, like the upper, is lined by ciliated columnar epithelium, surmounted by a mucous blanket. The cilia beat in coordinated, wave-like movements, about 1,000 times a minute and move the blanket, like an endless escalator, upward toward the larynx and pharynx. Here, the blanket turns downward toward the stomach.

Cilia.—The cilia beat with a purposeful stroke, something like that of a swimmer's arm. From a more or less rigid, straight upright position, the cilia sweep forward through an arc of 30° or 35°, and then bend to make a stroke of recovery. The rhythm is about 1:3, i.e., the effective stroke takes only one-third as long as the recovery stroke.

The cilia are not under nervous control. How they are stimulated to beat and how they are coordinated is unknown. When bits of epithelium are torn loose from their position, and kept moist and warm, the cilia continue to beat. The cells may be separated one from another, but the cilia of a single cell will continue to beat. Even a single cilium will beat if torn away from the cell, pro... it has its rootlet and a bit of cyto... attached. Some believe that ciliary acti... controlled by acetylcholine and cholin... ase [28] others [7] attribute it to serotonin. ... method of stimulation and control ha... been established. In isolated bits of cil... epithelium in vitro the ciliary beat ca... slowed or stopped by cooling. It is pos... actually to freeze respiratory epithe... briefly and have the cilia revive and beat ... thawing. Movement of the mucous blank... very susceptible to drying, i.e., it slows ... excessive dryness, and the cilia eventu... stop beating. An increase in pH to alk... seems to stimulate the rate of ciliary beat ... a decrease to below 6 to decrease the ... However, in vivo it is doubtful that an... these factors alter normal function. Even ... the hottest, driest, or coldest weather, ... unlikely that there is any noticeable effect on ciliary streaming in the tracheobronch... tree, since the air-conditioning function ... the normal nose is so effectual. No ma... what the temperature of inspired air at ... tip of the nose—whether 100 F or −40 F ... by the time the air reaches the pharynx it ... practically at body temperature and satura... with moisture. Great extremes of dryness ... temperature might conceivably have an ... effect in the middle portion of the nose. ... I am unaware of any determinations wh... demonstrate this.

As the mucous blanket flows along ... forms a sort of upside down river. Begin... in the respiratory bronchioles, it moves ... upward and ever into a progressively ... rowing streambed. It begins in a stream ... perhaps meters in extent and, by the ti...

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aches the trachea, the streambed is only
) mm. wide—the circumference of the
achea. During its progress, just as a geo-
graphic river meets obstructions so does this
mucous-flow river. When it encounters the
openings of tributary bronchi, these openings
become obstructions, like islands, and the
ow must pass around them. (Figs. 4, 5A
nd 5B and 6A and 6B). At the upstream
argin of each bronchial opening, there is a

Fig. 4.—Cow trachea split posteriorly and spread open showing the carina and one main bronchus with tributary bronchi entering. Note that the openings constitute obstructions to the ink's flowing upward in the ciliary stream.

4-way split of the mucous blanket.[21] (In studies with radioactive polonium, Casarett[8] found that accumulations occur at bronchiolar branch points when the material has been inhaled.) In the area just upstream from this margin, the cilia change their direction of beat from an axial one to an oblique one so that the blanket is steered around the opening.

In otherwise normal bronchial trees, it is not uncommon to find areas of squamous metaplasia where there are no cilia. Such

Fig. 5A.—Dissection of a human main bronchus showing three large branches entering at almost the same level. These openings served to narrow the stream bed of the ciliary stream at this level.

Fig. 5B.—Diagram of the pattern of flow for
(Courtesy of Acta Otolaryng.)

areas might be likened to shallow sand bars under a flowing geographic river. The mucous blanket does not necessarily stop upon them but is dragged across by the cilia surrounding the area. From the standpoint of physics, it would seem that there would have to be slowing at such points. Squamous metaplasia in the trachea does not seem to be as common as in the main bronchi, although it does occur. There are, of course, no branches or tributary bronchi acting as obstructions. The next obstruction encountered by the mucous river is at the transversely placed vocal cords, the margins of which are composed of squamous

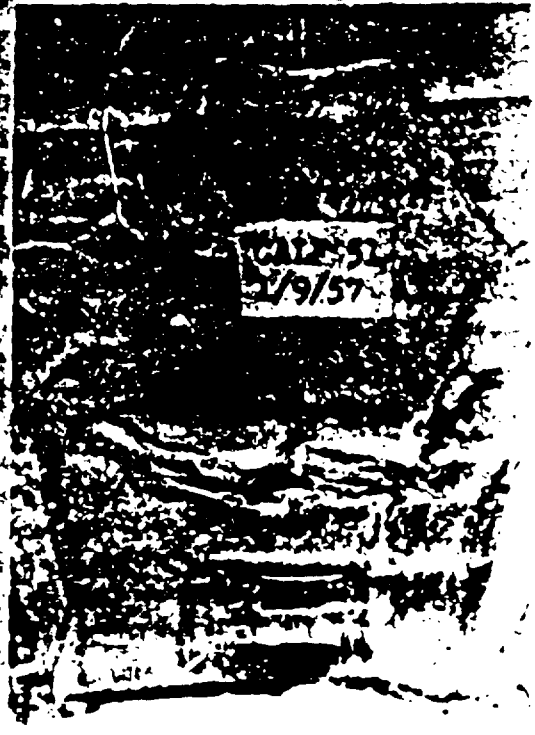
Fig. 6A.—Diagram of pattern of flow found at the upstream margin of a bronchial opening in a cow. (Courtesy of Acta Otolaryng.)

epithelium. The mucus does not flow directly across the cords but ascends the posterior tracheal wall passing between the arytenoids and out into the pharynx. The mucous blanket on the anterior tracheal wall passes straight up to the vocal cords where, at the anterior commissure, it splits into 2 parts, each of which passes posteriorly under the corresponding cord and, thence, past or over the arytenoids and out into the pharynx. The flow on the side walls takes an oblique course when it enters the larynx and passes upward and posteriorly. It is interesting that the ciliary beat in the larynx also seems to change direction inferior to the cords. Instead of being axial and directed upward, the ciliary beat is directed more posteriorly, aiding in moving the blanket in that direction instead

Fig. 6B.—Four-way split at the center primary carina in a cow. (Courtesy of Otolaryng.)

Depth of Blanket.—In such a river mucous flow, progressing into an ever growing streambed, either the depth of mucus must increase or the rate of flow increase. A number of attempts have made by myself and others to measure comparative depths of the mucous blanket different levels and the comparative rat

Fig. 7.—Pattern of ciliary flow through the l of a calf. The ciliary stream flowing up the an wall is dyed with India ink. It flowed a upward, until the cords were reached and the in 2 at the anterior commissure to flow back under the vocal cords. The specimen has been dorsally and spread open.



flow.[22] The data are very unsatisfactory, but, such as they are, they indicate that there is a progressive increase in rate of flow from the small bronchi toward the trachea and that the mucous blanket also increases in depth.

Rate of Flow.—In the trachea it is about 10 mm., possibly as high as 15 mm., per minute, whereas in the smallest tubes measured it is only 1 mm. or less per minute. It seems almost impossible that such a rate of flow as 15 mm. can be attained by 1,000 cycles per minute. Even if the cilia were effective for their full length of 5μ or 6μ, this would account for only 5 or 6 mm. per minute, and the cilia are by no means effective for their full lengths. The effective stroke is probably only 2μ to 3μ in length. The answer seems to lie in the fact that the blanket is moved by the effective stroke only (not the stroke of recovery), which uses only one-fourth of the time of the cycle. Also, during the effective stroke, it is likely that the blanket is in contact only during the peak velocity of the active phase and not so much during the acceleration and deceleration of the cilia. The mucous blanket is tossed from crest to crest of the waves, so to speak, and is in contact with the underlying cilia only at the brief period of peak velocity, when they give the strongest and most rapid "kick." The blanket thus moves continuously and does not stop and start (like a cinema film) with the thrust and recovery of the cilia (Fig. 8.)

Deposition.—Although most inhaled particulate matter is deposited normally in the nose, some of it gets past the nose and into the lower respiratory tract as evidenced by carbon particles in the lungs of all adults.

Fig. 8.—A diagram of my concept of moving cilia and the mucous blanket. The secretion is composed of 2 layers: a deeper, nonviscid layer in which the cilia move and a superficial viscid layer, the mucous blanket. The upper arrow indicates the direction of flow and the lower arrow the direction of the wave progress in the cilia. The mucous blanket is undoubtedly in contact with the cilia during the [illegible] than indicated. (Courtesy Trans.

According to Morrow,[40] the factors controlling deposition of particulates from an air-stream are gravity, inertia, velocity, diffusion, and the viscosity of the medium. The density and the nature of the particles are also involved. A very dense particle is more susceptible to the effects of gravity and inertia. Hatch's work[9] indicates that practically 100% of dust particles, 10μ or larger and 80% of particles at 5μ, are deposited in the upper respiratory tract. (Hatch considers the upper tract to extend down to the respiratory bronchioles, stating, "As a minimum, we may distinguish between 2 significantly different zones of deposition: along the upper respiratory tract, down to and including the terminal bronchioles; and within the pulmonary lobule." The latter is, of course, below the ciliary stream.) Then the retention drops off to reach a minimum of 20% to 30% at 0.25μ to 0.50μ, below which it increases again, returning to 60% or better for submicroscopic (less than 0.10μ) particles. The reason for these changes lies in the fact that gravity acts on the larger particles and diffusion on the smaller particles below 0.2μ. The lowest probability for deposition in the respiratory tract occurs at 0.25μ to 0.50μ, where the combined forces of precipitation, gravity, and diffusion are minimal. Below 1μ to 2μ the effect of gravity decreases, and diffusion has not yet taken over. Diffusion increases as the particle size drops below 0.25μ.

Cigarette Smoke.—Cigarette smoke, probably the greatest pollutant of all, bypasses the nose. It is taken undiluted into the mouth and then fed into the next incoming flow of inspired air through the nose, as it passes through the pharynx. Some smokers inhale smoke in concentrated form without diluting it with the next incoming air. They will take concentrated smoke into the mouth, then, opening the mouth, will gulp a deep breath of air through the mouth, driving the concentrated charge right down into the alveoli. There are many variations in the manner of taking the smoke and in the amount of smoke taken.

In General.—In the lower respiratory [illegible] deposition seems to be a little greater

in the proximal part of the tract, the larynx, and around the carina,[6] but the total amount deposited is probably much greater distally where the surface area is greater. Also, the initial deposit is probably more concentrated in the distal portions than it is in the trachea, because the depth of mucus on which it is deposited is so very much less, i.e., the mucous blanket is so very much thinner. For this reason, as the ciliary stream flows upward, carrying the deposited material with it, the concentration of this material, unless it has been absorbed, may become very much greater in the main bronchi and the trachea than the initial deposit there.

Air Pollutants

In discussing air pollutants, it is essential to consider their solubility, toxicity, and other physiochemical characteristics.

Chemical compounds which are promptly absorbed perhaps may not return to the ciliary stream or may return in reduced amounts. Those which do come back may dissolve slowly or act slowly on the underlying cells. This situation is postulated for carcinogenic compounds. A wide spectrum of known materials have a slowing effect on the ciliary action,[4] so that, in addition to natural obstructions to the mucous flow, the stream itself might be slowed in certain areas or its entire extent by the action of contained chemical compounds. Long ago we demonstrated that blowing a little cigarette smoke over a solution containing ciliated epithelium caused the cilia to cease beating.[10] This observation has been confirmed by other workers who carried the studies even further.[1,8]

Phagocytosis

Phagocytosis has been studied extensively.*

In General.—It is defined as the engulfing of microorganisms, other cells, or other substances by phagocytes. Phagocytes may be fixed endothelial cells or free, wandering cells. The origin of the wandering cells has not been determined to everyone's satisfaction.[2] Some believe they are mesodermal in origin,[2] others that they are ectodermal, and still others that both sources give r... phagocytes.[21,26-28,41] In the lung, for ins... Macklin believes that the so-called pneum... cytes (dust cells, macrophages) origina... epithelium on the walls of the alveoli, w... he describes 3 types of cells. Macklin a... that the pneumonocytes never leave the ... passages and are not to be confused w... phagocytic histiocytes that originate in al... lar septa and may enter lymphatics.

Be that as it may, the process of eng... ment is agreed upon. The surface membr... of a phagocyte is of an undulating nature a... forms indentations, folds, and ruffles.[32] Wh... contact is made with material to be engulf... —dust particles, for instance—an indentati... forms to accommodate the particles, and ... fold develops that covers the indentation a... fuses with the cell membrane on the far si... The indentation pinches off and becomes ... vesicle or vacuole within the cell. The wal... surrounding the vacuoles and vesicles sho... the same structure as the cell walls and ar... composed of 3 layers, 2 denser ones with ... less dense one between.

Phagocytic action may be blocked und... certain circumstances. For instance, tubercl... bacilli are less readily picked up by phagocyte... after other particulate matter has been en... gulfed. Joyner[20] used a number of differe... substances and found trypan blue, cement... silica, coal dust, and India ink effective, i... that order, in blocking the uptake of tuberc... bacilli.

On the other hand, Heppleston[19] recently ... reported that single macrophages might con... tain an intimate mixture of coal and hematit... dusts, although these had been inhaled a... different times.

Pulmonary Phagocytosis.—When particu... late matter is deposited in the lungs, some is ... eliminated via the air ways and some via ... interstitial tissue and the lymphatics. Mos... texts on pathology[9] maintain that all elimina... tion is carried out by phagocytes. The gen... erally accepted concept seems to be that the ... phagocytes leave the capillaries or interstitia... tissue to enter the air spaces, where they ... pick up foreign material and reenter the in... terstitial tissue, and proceed through the lym...

* Ref. Nos. 2, 3, 8, 10, 30, 32, 34, 35, 38, 41, 43, 44

...ities to the lymph nodes. Macklin and ...mes take exception to this concept. The ...mer describes small pores or "stomps" ...ough which particulate matter may enter ...ssues. Gross states that the basis for the ...migration-immigration concept is far from ...nvincing. He has demonstrated experi...entally that dust particles may leave the air ...paces and enter the intercellular spaces with...out the agency of phagocytes. Macklin ...aintains that the "pneumonocytes" origi...nate from the epithelium and never leave ...he air spaces and passages. He thinks ...hat particulate matter may be carried into the ...ssues by phagocytes but that these are histio...ytes of mesodermal origin and are not to be ...onfused with pneumonocytes.

There is no doubt that much particulate matter is removed by phagocytes wandering up from the alveoli to the respiratory bronchioles. LaBelle and Brieger[34] developed a method by which the number of free phagocytes in experimental rats could be estimated. They found that the amount of dust eliminated was proportional to the number of phagocytes present. They concluded that transport of particles by phagocytes is the primary mechanism by which inhaled dust particles are eliminated from the lungs.

When the phagocytes reach the headwaters of the ciliary stream, many disintegrate[39] depositing their load to be carried away on the escalator mucous blanket. Many phagocytes do not disintegrate but are carried out intact.

The fate of particulate matter depends upon its nature and the reaction of the engulfing cells. Particulate matter may be broken down and destroyed by intracellular enzymes or, conceivably, be changed to more toxic compounds.[48] If relatively insoluble, particulate matter may be carried unchanged during the cell's life-time. The situation so far as the tissues and inhaled materials are concerned, depends upon the nature of the latter and the reaction of the former.

The concept that insoluble material in the tissues lies enclosed either in lymph nodes or in fibrotic nodules unchanged and static is not necessarily true. According to Hepleston[10] such inert particles continue to move in and out of fibrotic nodules via phagocytes.

Summary

The nose acts as an efficient air-cleaning and air-conditioning mechanism. Much, perhaps most, particulate matter is caught in the nose and escalated back and down on the mucous blanket by ciliary action to the "incinerator" in the stomach. The character of the lining epithelium varies with its exposure to the inflowing air. The mucous blanket is produced by the epithelium and varies in viscosity and probably, general chemical nature according to circumstances. The dense pollutant cigarette smoke, unlike most other pollutants, bypasses the nose entirely.

The physiologic drainage of the bronchial tree is accomplished by the mucous blanket, which, motivated by underlying cilia, constitutes the ciliary stream. From respiratory bronchioles to esophagus, the streambed narrows markedly, and probably the velocity of mucous flow increases as the streambed narrows. The ciliary stream encounters a number of naturally occurring obstructions in the form of squamous islands, bronchial openings, and the vocal cords. Retardation of the ciliary stream may occur at such areas and may be enhanced by cigarette smoke or other air pollutants which slow or temporarily stop ciliary action, facilitating prolonged action of any carcinogen in the ciliary stream at these spots.

Probably most of the particulate matter that gains access to the alveoli and alveolar ducts is removed by phagocytic action and carried out the tracheobronchial tree into the esophagus. Some gains access to the interstitial tissue, lymphatics, and lymph nodes. Whether this is always accomplished by phagocytic action is a moot point.

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DISCUSSION

Dr. P. [illegible] Mellon Institute, 4400 Fifth Ave., Pittsburgh: Pulmonary clearance [illegible] we have a pretty good idea [illegible] the immediate postexposure period [illegible] by Dr. Brieger [illegible] but we may conjecture [illegible] Within [illegible] immediate postexposure period [illegible] pertinent to the size of the burden. [illegible] remains upon [illegible] the form of [illegible] silicotic nodules [illegible] particles disappear from [illegible] virtue of this [illegible]

In the case [illegible] taining imprisoned dust [illegible] months after the imposition of the lung dust burden. It is interesting to note that, according to Nagelschmidt's data no significant dust transport to lymph nodes occurs prior to this 3-month period. We are, therefore, forced to conclude that the silica which is deposited in the lymph nodes after this time is derived mainly from the sequestered dust within silicotic nodules. This is the major component of the delayed phase of alveolar dust clearance.

Direct penetration of dust into the lung interstitium plays only a minor role in alveolar clearance. Gloeckner injected colloidal iron intratracheally and was able, with the electron microscope, to demonstrate the rapid penetration of the iron particles into the interstitial space of the alveolar wall between the capillary and the alveolar epithelium. Such penetration by a relatively small portion of a large dust burden probably occurs through alveolar walls

that abut on vessels or bronchi, and it occurs without the aid of phagocytic cells.

Dr. Muno: I would like to ask Dr. Hilding if he can help us out with the situation in the vestibule of the nose which is supposed to be the place of elective localization of Staphylococcus aureus in the carrier. Can you tell us a little bit about the histology of the region and whether or not it is reasonable to suppose that any sort of treatment with antibiotics might have access to the staphylococci which seem to be dug in in the vestibule of the nose?

Dr. A. C. Hilding: I have no special information on this. The vestibule of the nose is lined by skin and staphylococci being on the surface and in the surface cells. I think they would not be reached by antibiotics taken internally.

Dr. Muno: What about immunization? The drainage, I take it, is back away from the vestibule.

Dr. Hilding: No, by the vestibule we mean just this little skin-lined area in front that we blow out to clean. Farther posteriorly, of course, all material goes back. When it has been deposited, unless it is absorbed, it is really still outside the body. It is on its way to the stomach, where it gets into the body only if it is absorbed.

Dr. S. Muno, Chief, Microbiologic Research Program, Veterans Administration Hospital, University and Woodland Avenues, Philadelphia: A serum would have difficulty in gaining access to anything in the vestibule, however.

Dr. Hilding: In the vestibule itself, in this dry, skin-lined area, yes. Farther back, it might, but even there I doubt it.

Dr. R. E. Forster, Professor and Chairman, Department of Physiology, The Graduate School of Medicine, University of Pennsylvania: I would like to ask Dr. Hilding what he thinks is the normal flow of the mucous sheet up the trachea in a normal man.

Dr. Hilding: The volume of mucous flow is also most difficult to measure. The few available data indicate a total volume in a normal bronchial tree in 24 hours of the order of 10 ml. I did some experiments on chickens which consisted essentially in the creation of a barrier to the ciliary stream without interrupting air flow. At the end of the operation, the skin was closed and the bird breathed normally, but all of the mucous flow collected at the barrier. These chickens were operated on in pairs and, at the end of the operation, one was immediately killed. The experiment was terminated at the end of an hour and the collected mucus recovered and weighed. The live birds produced an average of 23 mg. in an hour, a rate of half a gram in 24 hours. For some reason which is not clear, the dead ones averaged exactly twice as much, 46 mg.

Dr. Forster: Have you made any other on fibrosis?

Dr. Hilding: No, I have only had occ... make one single measurement in a human in a nurse who had a laryngectomy some before. One could not know if this is the volume. Over a period, I think, of 12 hou... made collections in Kleenex that had been w... before and immediately put into plastic bag... she produced at the rate of 10 ml. in 24 hours.

Dr. Muno: Although Dr. Brieger four evidence of any selectivity in phagocytosis b... uranium oxide and silica, if you go into the ... case of bacteria, there is tremendous diff... between bacteria which have a film of phagocy... promoting antibodies and those that do no... both polymorphs and macrophages, the ... films tremendously increase phagocytosis.

Dr. H. Barnum, Jefferson Medical Colle... Pennsylvania, Philadelphia: This is a ... more complex problem. I mentioned that th... no evidence that the chemical composition ... investigated materials influences phagocytosis.

Dr. Kass, The Boston City Hospital, 818 Har... Ave., Boston: There is an aspect that has no... ceived as much consideration in the pulmonary ... as it has in other work and that is that it has ... shown repeatedly that the manner in which par... are taken up by the reticuloendothelium is gr... influenced by a variety of materials that may ... the particles.

Dr. Barnum: I agree with you.

Dr. Fairchild: I would like to direct a que... to either Dr. Brieger or Dr. Gross, and per... Dr. Hilding can shed some light on this too. W... is the nature of oil film, that is, inhalation of oil ... particles? We have done a little bit of work ... this, and our pathologist has had much difficult... trying to elucidate the possibility of film layers ... might be made up of this oil. Do either of ... know of a work which would show whether ... actually get a layering effect in the tracheobron... tree as a result of inhaling oils?

Dr. Barnum: I have no personal knowledge ... this.

Dr. Hilding: I did just one experiment with ... on excised epithelium. The oil did not penetrate ... mucous blanket. If it were manipulated in so... way that it were made to penetrate, it gummed ... the cilia badly. That's all the light I can shed ... the question.

Dr. Gross: From clinical experience, it ... that the following are presumably the facts: ... that oil placed in the tracheobronchial ... membrane will gravitate down and flow over ... mucous blanket down to the alveoli; (2) once ... on the alveolar surface it is apt to remain th... and (3) that it is not susceptible to clearance ...

...ulate matter. The reason why oil is resistant to ...cular clearance mechanism is not known.

... Brieger: In some personal experimental ex... I have noted that liquid material in par... form is unable to stimulate phagocytosis, ...t may be phagocytized.

Hilding: All liquids in a particle—in other ... particle-sized liquids, regardless of size?

Brieger: Liquid particles, yes.

... in Meeting: Are they still cleared?

... Brieger: I have no reliable data on clearance, I know that they do not stimulate phagocytosis. ...marks referred to insoluble or only slightly ... solid particles. The fate of soluble particles ...te different. Either they dissolve and enter the ...d stream, or they combine with cell fluid, and ... we have the interesting phenomenon that such ...rial may be identified in the lungs much longer ... solid material.

Dr. Auerbach: I would like to direct the ques... to both Dr. Brieger and Dr. Gross, and perhaps ... Vorwald would also say something. About 30 ...ars ago in South Africa, Great Britain, and United States there were a number of experi...tal studies on the production of silicosis in ...als carried out. In these studies, basically dif...nt animals were exposed to different fibrosis-...ing dusts, and the results were almost uniform ...3 countries. They were attempting to answer ...tions regarding the size of the particles, length ...exposure, and the crystal and chemical character...s of the dust. They came to the conclusion that ... size of the dust was important and that the dust ...ld not penetrate tissue but rather that the tissues ...ulated the dusts. The dust was inhaled, the ...cular phagocytes reacted and, if the dust particles ... small enough, they were absorbed by the ...cular phagocytes after which elimination would ...ur. If the inhalation was equivalent to the elimi...tion, or the elimination kept pace with the inhala..., nothing would happen. However, if the ...lation of particles was great, and the rate of ...mination could not keep up with the rate of in...lation, the excess particles were carried by way ... the lymphatics to the lymph nodes. One impres... I gained from this was that there was an early ...ation of fact, that lymphatic invasion occurred ... early. The difference between a fibrosis-pro...ing dust and an innocuous dust was that the ...-producing dust was capable of preserving ... cell. Therefore, as this dust was deposited along ... of the lymphatics, it would, through chemi... action, produce fibrosis. The impression I gained ... morning is that the action seemed to be prode...mental.

Dr. Vorwald: Of course, the problems that were ...ught up this morning are problems which many ... have been interested in for a long period of time, and many of them are not resolved as yet. Let us consider the amount of dust ultimately retained in the lung and its action on the lung. The amount taken out of the lung by the sputum is of interest. Once it is in the sputum, it is of relatively little interest. Retention of dust is determined by a variety of factors which relate not only to the inhaled concentration of the dust particulate but is tremendously related to the size of the particles. This should be kept in mind when speaking of responses to phagocytosis and particulate material. Another parameter to be considered is the inherent biological toxicity of the particle. If a particle has a low level of biological activity, its ability to clear from the lung is much more rapid, perhaps, than that of the particle which has a high level. There are other variable factors such as length of retention in what I call the strategic segment of the respiratory tract. In some of our recent studies, we have observed rather rapid drainage of radioactive particulates of different rarer elements, some 18 of them, out of the lungs into the tracheobronchial lymph nodes and into other tissues of the body. It would appear that many of these very small inorganic particulate agents penetrate vessels to a surprising degree. So, in silicosis, in so-called benign pneumoconiosis, we find relatively early deposition in the tracheobronchial lymph nodes. It is classic, for example, to observe in human pathology that if an individual is subjected to frequent exposure of small particles which gain access to the pulmonary tissues, the lymph nodes relatively early show damage. In my routine experience and practice, I look at the lymph nodes first, because they are often pretty good indicators of what is happening.

With respect to soluble particles, or to organic material, once it is an aerosol, or in a stream, these fluid particles become more or less solid particles, and they gain access to the pulmonary tissue. For example, as Dr. Brieger mentioned, in dealing with certain organic soluble particles, they may produce an insoluble precipitate in the lung. Therefore, there is not a strict correlation between the degree of solubility of a material and what happens in the lung.

As to Dr. McKusick's presentation of asbestos fibers and carcinoma of the lung, there are many cases of that. A word of caution is indicated with respect to carcinoma of the lung and the presence or absence of inorganic material or organic material. Let us be very cautious before we conclude that the substance found in carcinoma of the lung, a substance which has been inhaled, which is uniformly distributed over the entire lung, that this substance observed in carcinomatous tissue is a factor indeed responsible for the carcinoma or that the absence of a substance means that it has never been there to produce the cancer—just a word of caution.