General Session

Dr. W. C. Bowie, Chairman

Pulmonary Structure, Function and Defense Mechanism

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Thank you and members of the AABP. It's nice to be able to come to Atlanta and spend some time with you. It is a real honor to come down here. I don't know when I have enjoyed an evening as much as I did last evening. I just hope we can put on as good a show for you in California next year. We would like to try and present here today how maybe structure and some of the defense mechanisms interrelate and may result in production of disease; and then how the bovine lung responds to disease. These may explain possibly why we have such a problem with the resolution of some of the respiratory problems in the bovine lung. I will quickly review some of the anatomy of the lung and see if we can't relate some of it to the disease mechanisms.

We will start down with the lobule. The lobule is the functional unit of the lung itself. What is the lobule? A lobule has a respiratory bronchiole, alveolar ducts, and alveoli which are all supplied by a bronchus that enters usually at the apex. Then along with that are the vascular and the nervous supply to the lobule. Now when you start looking at the different types of morphology of the lung, that of cattle, sheep, and the hog lobules are very well-defined. There is a very extensively interlobular connective tissue present in these three species. Then you go down through these other species, and it becomes less well defined. In the dog you can see it is very poorly defined. In the horse, intermediate between the two. The bovine lobule has a very extensive septum. Again it is a very distinct unit and there is very little or no connection between the adjacent lobules. The sheep, cow and pig are the only species that we deal with that have an anatomy or morphology such as that. Now when you look at the scanning electron micrograph of the bovine lung, looking at the lobule you see how well demarcated the lobule is again. You need an appreciation for the complete septum that is present there.

The one thing in the sheep, cow and the pig that sets them apart is that due to this complete septum there is a lack of colateral ventilation between adjacent lobules. I think this is somewhat important in disease processes as we go along. Looking just briefly at the horse, the septum is not quite complete. Remember that in contrast to the way the bovine appears. In the dog there is no hint of lobular separation as in the bovine and much less in the horse. Now we've kind of established the individual lobule morphology in the lung, let us look at what the terminal airways look like. In the cow, again it goes for the sheep and hog also, the terminal bronchiole is the terminal airway when we get down into the lobule, and the respiratory bronchioles are very poorly developed. What we'll try and hopefully show is the difference between the terminal bronchiole and a respiratory bronchiole. Respiratory bronchioles have alveoli opening off of them. The terminal bronchiole doesn't until right at the end. Then the horse again is somewhat intermediate between the dog and the cow. The dog has respiratory bronchioles developed nicely. In the horse you see no hint of any alveoli opening from the lumen.

Now looking at the pig and the cow, they are very similar. Again we see this same thing, the terminal bronchiole coming down and you see no opening or very little alveolization off of that airway. Now contrast to that of the dog. What that does, when we come down later to clearance mechanisms, and clearance from distal airways, is that it offers a lot more avenues that clearance can take place from. If (like in the cow, the sheep, and the pig) we are limited to just one major opening, clearance problems can be a real problem in the distal airways. But here again, there are many alveoli opening up into the

respiratory bronchioles so there is probably a lot better chance for clearance in that type of an anatomical arrangement.

Now let's go down deeper into the bovine lung itself, and look down into a bronchus supplying one of the lobules. One thing that I think one might take note of here is that you notice that there are not very many holes between adjacent alveoli. In the younger bovine lung, there just doesn't seem to be as many pores as there are in other species. Looking at this in other types of lungs you would expect us to have pretty much like a shotgun pellet that would hit the thing and there were little holes between all the alveoli. In a little older, more mature bovine lung there are little pores that we are talking about and these communicate with adjacent alveoli. We feel that probably these pores are fairly important in the clearance mechanisms from the lung. Let's say for example, if an alveolus is plugged or has some debris in it, and if there is a connection say from this alveolus to the adjacent one, and considering that it may be open, then air can be forced from the open one up through the other one and hopefully force the debris out of that alveolus. In the young bovine lung you just don't see the connections between adjacent alveoli. So here I think we are starting to mount a little bit of a case against the bovine lung. First off we've got the complete septum and there is no chance for colateral ventilation between septa, then also there is a possibility of connecting airways between adjacent alveoli. Now when you look at the lung itself it is estimated that there are probably about 40 different cell types, and I don't mean to profess by any means that I am familiar with even 25% of them, but the main cells that one does see lower down in the lung are basically just the type 1 cell and it is a sort of a flat cell. Then there is the type 2 cell that is often referred to as the great alveolar cell. The type 2 cells are the ones that seem to proliferate in response to chronic irritation. The bovine lung has a fair number in the alveoli, and in the septum. In chronic insult it is this type cells that seem to proliferate in the bovine lung. This is the real work horse when it comes to the defense mechanism of the lung itself. The alveolar macrophage is a very unique type cell in that it has special metabolic requirements. This cell is very heavily dependent on aerobic glycolysis. Now when you look at this cell in comparison to other macrophages in the body, this cell has 10 times the requirement for an aerobic glycolysis as say does the circulating neutrophil. It is estimated that its requirement for an aerobic glycolysis is probably three times that of the peritoneal macrophages, so remember it is a very unique cell but it has a high dependency on an aerobic situation, so if we get lungs that are full of debris and not that well aerated, then this cell loses a lot of its function. Andre Morrissey at Davis has done some real nice work with the bovine lung and a lot of this stuff is his, but one thing that he has seen in the horse cell (the horse type 2 cell at any rate) is that it has little openings, and it is felt that in the horse this cell probably secretes the surfactant that enables the lung to keep expanding. It seems that in the bovine their type 2 cells don't seem to have these similar openings. Why? This is not really understood. It is not really known for sure that the type 2 cell secretes surfactant, but that is one difference that has been seen so far.

The bovine lung doesn't seem to have as many alveolar macrophages roaming around in the lungs as the horse does. It has been more extensively studied.

Now let's start our journey. We've been down in the alveoli, let's start back up through the airways and talk a little about how the structure differs as you go further up the airways. The major bronchiole comes in and supplies the lobule. The alveolar duct opens up into many alveoli, and the alveolar duct in turn opens up into the respiratory bronchiole. Looking at this situation you can see what a problem may develop in a clearance type situation. We have all this tremendous amount of respiratory tissue but its clearance mechanism is solely dependent on getting the debris from all of that area out from a small airway. So when we talk about treating pneumonias it is well to keep in mind the important part we play in prescribing the different medications that we often do in the form of the antibiotic and other regimes, but I think we also have to respect the host participation in the clearance of a respiratory disease. Again, I think we can put antibiotics into these animals until we are blue in the face, but until that lung can get the debris out of these terminal airways, we really haven't effected much of a resolution. So the other thing I'd like to mention while we are talking in this area here is that it isn't as well ciliated. The cilia are a pretty important part of the defense mechanism. What they do in essence is help by beating in unison, help wash these areas clean. Higher up in the bovine respiratory, or any respiratory system, say in the trachea and the major bronchi, this would almost look like a picture of some grass. There would be continuous cilia throughout the whole field. Down in the area near the terminal bronchiole there are many non-ciliated cells scattered throughout. Well, what this in effect does, it provides a less continuous mechanism than say higher up in the airway. There is also quite a distance between ciliated cells. Now that is in contrast when we get higher up. In a major bronchus, there are very dense ciliated membranes. In this area there is a heavy overlay of a mucous layer, and these cilia beating in unison help move stuff along.

With this brief introduction and, hopefully, we'll refresh our memories about the anatomy, I'd like to go now to the defense mechanisms that operate in the lung using the basic anatomy as a basis for hopefully trying to understand the pulmonary defense mechanisms. Now let us start with the upper airways themselves. The upper airways are extremely important, I think it goes without saying, for air conduction. There is a lot of the defense mechanism that resides in the upper respiratory tract. One thing that

probably isn't given its due credit is the function that the upper respiratory system has in warming and humidifying inspired air. The turbinate areas are very vascular, very rich in mucous membranes and they themselves probably play the most important part in humidification. When you see an animal that is open mouth breathing, it is by-passing that mechanism almost entirely. Just to roughly categorize the defenses of the respiratory tract, one first can mention the cough reflex. A lot of times we look at a cough as somewhat deleterious but then when we really consider a cough, it is an important part of the defenses helping rid material that is lower down in the airways. I think, unless we have a non-productive cough that it is really exacerbating the condition, probably we ought not to try to depress the cough reflex. I feel if it is a productive thing we are not creating a lot more irritation with it, and we ought to leave some of those animals coughing. We mentioned the normal movement of the bronchi. Some people would like to lead us to believe that the bronchi maybe contract alternately and maybe help move some of this out. This probably isn't a very important mechanism for clearance. The two that are probably the most important are the mucociliary blanket and the alveolar macrophage *per se*. Now when we stop and consider the lung again, I think it is somewhat unique in the different organ systems of the body, in that it has continuous involuntary exposure to the outside environment. Probably the only other system in the body that has a more intense exposure to the outside environment is the skin, but the skin is inherently better set up to take care of some of the insults that may come upon it. In order to protect the lung from different environmental agents that may get into it, there has to be a very intact and functioning host defense mechanism. You can divide these defense mechanisms into three areas: the circuit fluid, the epithelial components and then some of the immunological reserves. It is important here to stress that all of these three components don't function independently. They function continuously and it is a well-integrated system. When you think about it, it is amazing why we aren't sick more often than we are. There is just no way to say that if I cough in this room that the individual sitting adjacent to me can avoid breathing that in. The thing that takes care of it most often is we do have a functional defense mechanism that very effectively clears some of this material out. As we go on down and start looking at the function of the defense mechanism *per se,* probably the first line of defense is that of the aerodynamic filtration. All this is saying is that there are three factors that help particles settle out when they come into the lung. The first is just inertial impacting. The particle is pounding along so fast that it just impinges on a mucous membrane when it comes in contact. The second factor is that of just sedimentation or gravitational effects. The third is that of a Brownian movement. The particles of large size probably settle out high up in the upper airways. Here again just by the setup of the upper airways, think of the airflow that goes through the turbinate, that is somewhat of a turbulent airflow that is set up in there. By creating that turbulence, it causes a lot of the particles to impact on the mucous membranes. Just consider yourself after spending a day in a dusty corral, how much dust do you find in your upper airways? Dust particles are very large and by breathing in they do settle out here. This is a very important part of the defense mechanism in that humidification plays a very large role. By adding moisture to these particles, they often get bigger, and if they can settle out higher in the upper airways, they are a lot more effectively cleared than they are down lower. Here again there is probably a lot more inertial deposition in these areas mainly just because of changing direction of airflow. They come down through the trachea and hit at the main stem bronchus, where they bifurcate, and there is a direction change there. So these particles are whistling along in one direction, all of a sudden there is a direction change and they again will impact on the airway. If they impact again here, here is a very efficient defense mechanism, that of the mucociliary blanket. It is said that probably 90% of the particles are deposited from this area up. It takes a very small and stable particle (half a micron) to get down into the alveolus. Most viruses are smaller than this, so the individual virus products can penetrate this defense mechanism through the dynamic filtration if they exist again as single particles.

If a particle does settle out, then it is subjected to probably three clearance mechanisms, actually the physical removal of the particle, and then you can categorize it down into four general areas that particles are handled inside after they do settle out. As we've been alluding to, it is very close cooperation between the physical clearance and the inactivation. The mucociliary blanket of the airways is a very important part of the defense mechanism again. It is usually felt that 90% of the material deposited on the mucociliary blanket is probably cleared within an hour. If something impedes or slows down the mucociliary blanket, and we give for example–if a bacterial agent settles out and remains on the mucociliary blanket or in these airways for up to 3-4 hours–probably infection is going to take place. It is very important that this mechanism be kept intact and working. Just because this mechanism slows down, that doesn't mean that the animal is necessarily going to develop a disease, just a cough can effectively bring up a lot of this stuff. The point about these different mechanism relating to each other. If the particle gets below the mucociliary blanket into the distal airways, the alveolar macrophage takes over. It is a fairly efficient mechanism but clearance isn't all that efficient when you relate it to the mucociliary blanket. Again remember how dependent the alveolar macrophage is on aerobic glycolysis. Then the third physical mechanism is that of lymphatic drainage. You can say that briefly the lymphatic drainage is a very inefficient clearance

mechanism in the lower lung. As we've mentioned, all of these three areas, the physical clearance mechanisms, are aided by a cough or colateral ventilation. Again remember that the bovine lung is hampered because it just doesn't have the colateral ventilation that other lungs do.

What are some of the factors that can affect the mucociliary blanket movement? Probably the one most efficient mechanism for impeding mucociliary blanket action is just dehydration. Insult makes the mucous layer more viscid and then it does not move along as well as it should.

If it dries out further, often the mucous blanket may split so there isn't a continuous layer covering the cilia and there are gaps. Then the cilia become exposed and that is probably when they may become infected. Other things can affect ciliary motion or activity, such as extreme cold. It has to be a very prolonged cold and this will slow down the mucociliary action. Irritant gases such as ammonia and some other gases will slow the mucociliary blanket. Probably the one we are most familiar with is the infectious agent. Research work has demonstrated that infectious agents such as parainfluenza virus may have an effect *in vivo* on some of the defense mechanisms in the upper airways.

Until we can get that type of material cleared out of a lung, I think it is somewhat ineffective to think more antibiotics are going to do it. They are a very important part of therapy but the host has to participate in a resolution of pneumonia. This stuff has to be cleared out of there.

I think it is important just to consider the viruses. Just because a virus gets into the lower airways doesn't necessarily mean it is going to cause disease. First, it is a numbers game and is related to the concentration of virus in the aerosol; then, how persistent and how viable are these viruses. Some viruses are less viable as they come into a more humid medium. Then the thing that isn't stressed that often is how susceptible are cells at different sites in the respiratory system. Different cells in the respiratory system may not have the receptors for that virus and then again how infectious and virulent is the virus itself. Let's just for a minute consider the secretion. It is glibly put that they have a water-proofing effect. We are talking about those secretions that contribute to the mucous part of the mucociliary blanket. I think it is well put as it acts as a physical barrier to inhale the irritant and it is a very important part of the mucous blanket. Substances are contained in the secretions such as secretory antibodies such as IgA. Then in the respiratory system in the secretions this is most often where interferon is found. The importance of the secretions is they seem to increase in response to irritation and infection. That is fine if it doesn't go overboard. With excessive mucus production as sometimes is seen in chronic bronchitis, the cilia are flooded and don't beat as effectively. Again, these secretions may obstruct the airways and render them nonfunctional, again reducing drainage. Then if on the other hand there is insufficient mucus or they dry out, this in turn affects ciliary activity.

What are some of the more important inactivation mechanisms? What we have done (again in review) is talk about the physical clearance mechanisms. Now we'll talk about the inactivation mechanisms that take place if a particle gets down lower into the airways. Here the alveolar macrophage plays a double role. It does act in clearance, and it does act lower on in the inactivation. Cellular immunity is a fairly important part of the inactivation. Humoral immunity, and you can say IgA, seems to be one of the more important ones initially. Then again, we've made mention of the interferon, and we talked about the antioxidant and detoxification. Some of the inhaled gases are detoxified lower in the airways. Going back again to the alveolar macrophage, it has a very high dependence on an aerobic condition. Let's look briefly at some conditions that may affect alveolar macrophage function. These are things that many of you have for years always referred to as stress in recently shipped cattle, or other management effects, but I think now we can start defining what makes up some of these stress mechanisms–in other words, how they really work. Just by starvation you can really slow down the alveolar macrophage. Chilling does it. Alcohol in man is one thing that does it. There is good experimental work that shows the effect of some of the acidodic and ketotic states. Look at how many times we may be involved in those types of situations with recently shipped cattle. Again viral infections are glibly thrown into the pot, but this isn't an all-or-none function with viruses. At different stages of the viral infection, the alveolar macrophage may or may not be impaired, but a lot of viruses do knock out the alveolar macrophage. Then we go down the lines, some of the immunosuppressants, some of the immune disorders, and then just chronic disease can impair the macrophage. There is some interesting work that was done in the lung. Just by doing a simple nephrotomy they could almost bring a complete halt to alveolar macrophage activity. It is a cell that is unique but very susceptible to change in its envrionment.

In pathogenesis there is a balance between the deposition and the clearance of some of the irritant particles. Clearance depends mainly on the mucociliary blanket in the airways. Then the clearance or inactivation lower in the distal airways at the alveolar level depends primarily on the alveolar macrophage. Then the immune and some of the nonimmune systems boost the efficiency of these mechanisms. These systems work one with another in the clearance of infectious particles.

I have briefly reviewed the anatomy and some of the defense mechanisms and hopefully set the stage for some other things to come.

(Editor's Note: This paper was prepared from a tape recording of Dr. Ardans' presentation.)

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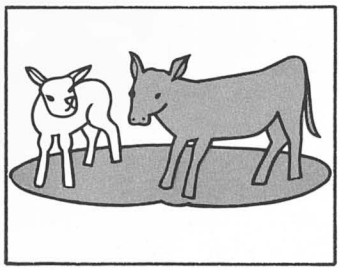

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