

**Essentials In Immunology**

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**Module No. # 02**

**Lecture No. # 04**

**Cells and Organs of the Immune System – Part 3**

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**SUMMARY OF LECTURE MODULE B2**

Experiment to show the manner of T cell activation. The role of IL-2 & T cell proliferation

Experiment to show the role of macrophages – Susceptibility of soluble antigen to trypsin treatment after various periods of incubation with macrophages

Immunological disorders – immunodeficiencies related to various hematopoietic lineages.

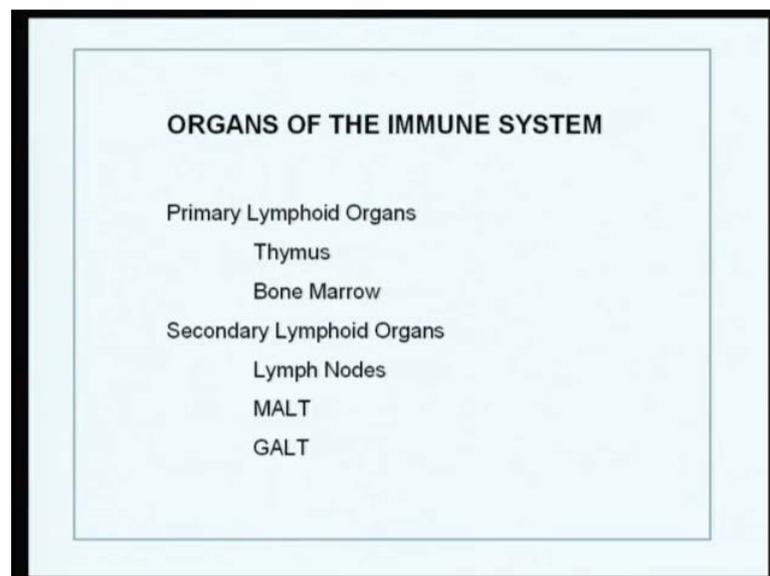
Lymphoid circulation

Hello, welcome. To summarize some of the points from the last lecture, we went through an experiment to show how T cell activation occurs briefly, and how T cells can get activated by the secretion of IL-2, and how to measure the T cell that was activated by virtue of the proliferation that ensures later on by the use of radioactive thymidine that is incorporated into the DNA of the proliferating cells.

We also went through an experiment to show the role of macrophages and how they were taking up to soluble antigen, and by virtue of taking it up into the cell the soluble antigen became resistant to trypsin treatment. And how this antigen was processed within the cell and after various periods of incubation they could stimulate T cell that had been activated to that particular antigen.

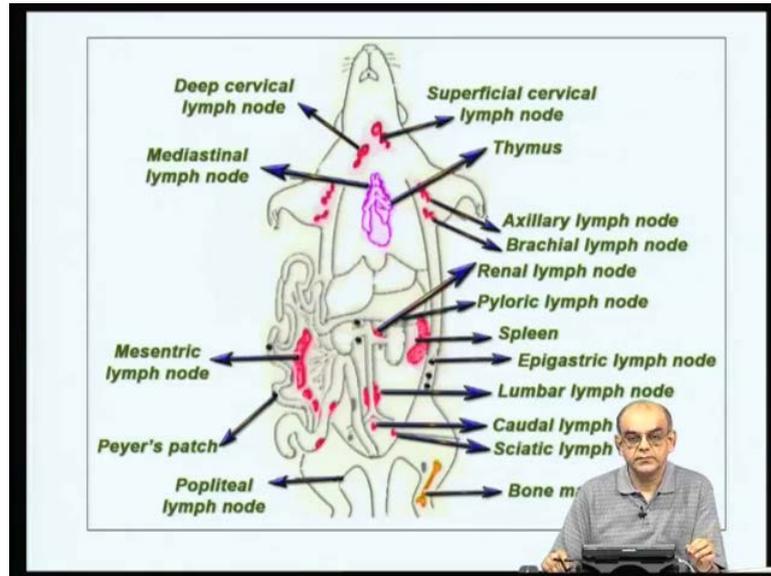
We also went through some of the immunological disorders, specially the immunodeficiencies that were related to the different hematopoietic lineages. We also left the last lecture by looking into some aspects of lymphoid circulation. This lymphoid circulation relates to the different organs of the immune system, and that is what is going to be covered in this lecture.

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So, as we went into this in the last lecture, the organs of the immune system have the thymus and the bone marrow as primary lymphoid organs; and the various lymph nodes and the lymph nodes that was associated with the mucosal surfaces, like the mucosal associated lymphoid tissue and the gut associated lymphoid tissue, that made up to secondary lymphoid organs.

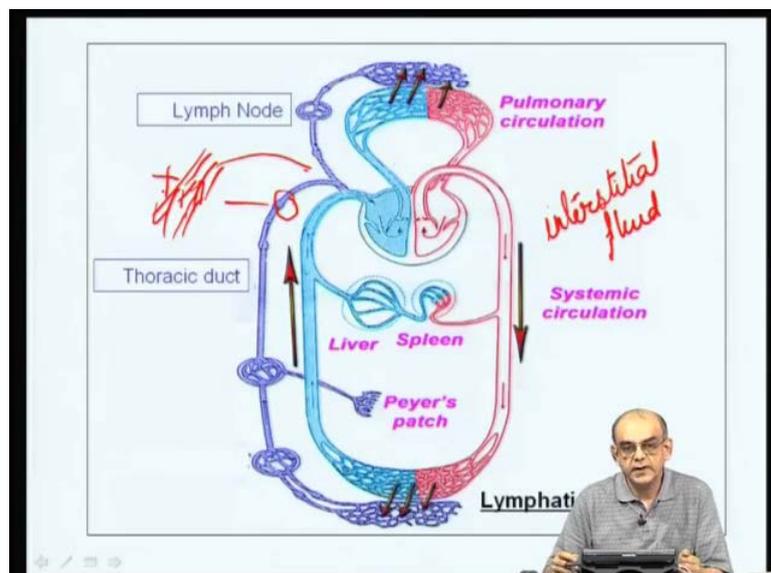
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We also went through some of the aspects of how these different lymph nodes were distributed in various parts of the body, so that the immune reactions that could be started against antigens that enter the body at various locations could be facilitated.

Now, in this lecture, we are going to look at some of the organs of these immune systems, specially the lymphoid organs, namely, the lymph node; with more emphasis to the Peyer's patches that are associated with the mucosal associated lymphoid tissue or malt for short, MALT.

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We look briefly at the organization or the roles of the spleen, then see how all these lymphocytes enter the lymph node and exit the lymph node. And towards this purpose, we had introduced this slide, which looked at the systemic circulation of how the blood is circulated from the heart to various parts of the body. Especially, this is getting smaller and smaller in size at the extremities of the body to small, little capillaries, which is where the exchange of oxygen occurs, to the tissue cells that need that oxygen. And the waste matter and the deoxygenated blood starts to get collected in these capillaries, and then slowly collect and get pumped back into the heart for reoxygenation.

We also mentioned that the various tissue spaces and the tissue cells that were located in various parts of the body have some fluid that drain them, and all this fluid collect together, and this fluid is also referred to as the interstitial fluid. This interstitial fluid is what collects in these tissue spaces, and they all get collected and drained into the thoracic duct. And this fluid that is accumulated is also called as the lymph, and these **are the** fluid or the interstitial fluid that is draining from various parts of the body; various tissue spaces specially where inflammation is occurring and other parts of the skin and so on and so forth contain not only the antigens that infected that site, if it is a virus infection or a bacterial infection of the skin, or be it a virus that effects the heart tissue or other organs.

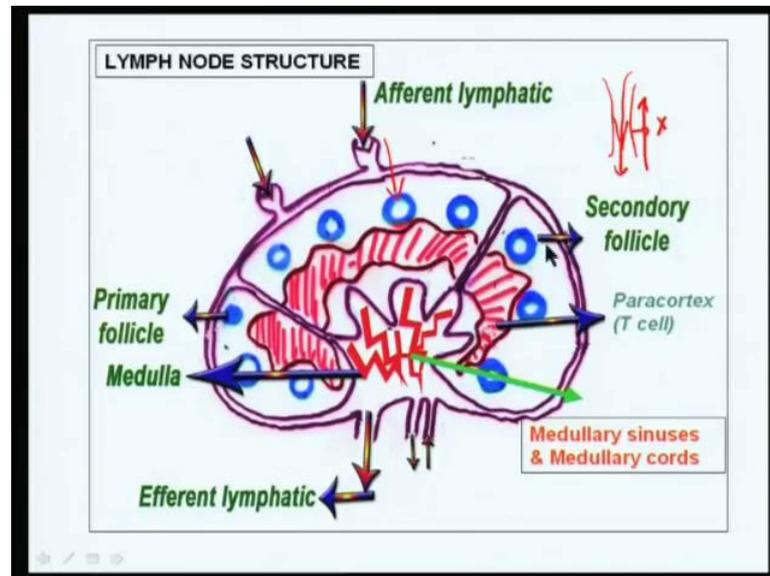
This virus antigen is what is collected in this interstitial fluid that is draining these spaces. Not only that, various cells that are migrating from different parts of the body, specially lymphoid cells, also drain into the thoracic duct.

One of the important parts of this lymphoid or lymph circulation is that all the circulation is not really actively pumped, like what happens with the heart. It is basically the muscles that line these various secondary or participate in the formation of the secondary lymphoid organs, as well as some of the underlying the location where the thoracic duct is located. They are the ones the muscular moments actually help propel the lymphoid or the lymph fluid towards the heart, and this is facilitated by also something called as unidirectional valves. For example, if it is going towards the duct, you have some sort of a valve over here which is probably something like this, and then that goes into the heart.

So, if the thoracic duct is pushed by muscular moments across this valve, this is a one-way valve. So, this sort of flow is prevented.

In fact, this sort of unidirectional flow is also what occurs while the lymph fluid is draining into the lymph nodes, as we look at some of the figures that I have showed you in the last lecture.

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We go into this, where we look at the structure of a lymph node. Now, if you look at this structure, you find that the lymph node is having an outer covering or a capsule. So, this part of it is called as the capsule, which is kind of little more, relatively more tougher than the interior of this lymph node. And beneath the capsule, you find the various cells organized into different modules or different collections of cells.

So what you see here is, beneath the cortex, you have an area where you have a congregation of cells over here, which is located over here where the arrow is, which is called as a primary follicle. This primary follicle contains a collection of cells. Mature B cells which are ready to interact with the own coming antigen, which is actually draining in through the afferent lymphatic's over here through these arrows.

Again, you must realize that this direction of movement of the antigen and the lymph is towards the inside of the lymph node, because you have these valves that are coming in that are positioned over there. And therefore, the muscular movements actually facilitate the movement of the lymph that contains the antigen, as well as cells such as lymphocytes, different kinds of lymphocytes, through this valve, and this movement is prevented by this valve.

So therefore, you find that all the fluid containing the antigen and some cells with it comes into the lymph node, and the first congregation of cells that they interact is with these follicular cells. These primary follicles, as I told you earlier, consist of collection of mature B cells. Not only mature B cells, they also have some antigen presenting cells, follicular dendritic cells, in other words, as well as some helper T cells. So, the antigen that comes in this location is encountered not only by the B cell; they are also encountered by these follicular dendritic cells which take up the antigen, and passes this antigen and present them to T cells, as we saw in the earlier lectures.

Now, this process actually results in the activation of the T cells, which then results in the secretion of lymphokines that help the B cells to proliferate, such as IL-4 and so on. So, this proliferation of B cells actually results in the formation of what is the secondary lymphoid follicle.

Basically, the secondary lymphoid follicle consists of a central core of these germinal cells which, because of their division, they push the dividing cells to the periphery, and therefore, form a kind of a mantle around these terminal center cells which are getting activated.

During all this process that is happening, you find, under this layer or the interior of this layer you have an area called as the paracortex. This red-stripped area is called as the paracortex, or it is also called as the T-dependent area, or the T-cell area because it consists mainly of T helper cells.

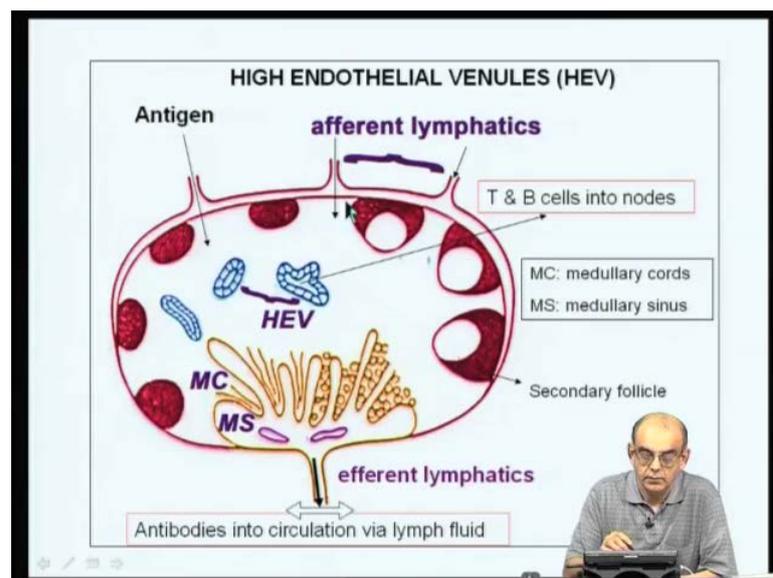
So, all these cells, in one way or another, migrate. Some of them migrate to these follicles, but majority of these T cells are found here; and many of them include cells that are getting activated as these antigens filter through the lymph node from follicular or the outside area into the paracortical area.

From the paracortex, the antigens and **some of this...** of the cells that are activated, especially the B cells which have got activated and differentiated into plasma cells, accumulate in this region. This is a region, which I have marked by these reds, red kind of stripes, which we will look into in the next slide. So, this contains an aggregation, or an association, of plasma cells.

So, what does this medulla contain? It contains a collection of sinuses. Sinuses are basically spaces or medullary... They are also called as medullary chords and medullary sinuses, along which all these plasma cells and T helper cells, which are helping these B cells, migrate and start to accumulate.

In addition to this, of course, you have... At this side of lymph node, you have what is called as an efferent lymphatic, as opposed to the afferent lymphatic where the antigen is draining into the lymph node along with some lymphocytes. On the other hand, the efferent lymphatic is where all these antibodies that are secreted in this region exit the lymph node, along with certain lymph nodes that come into the..., along with certain lymphocytes that enter the lymph node via what are called as post capillary endothelial venules, which you will see in the next slide.

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In addition to this, of course, you have the blood circulation to the lymph node via what is called as an arteriole or a venule. So, looking at the medulla per se, you see that the medulla is organized into medullary chords that you see over here, and you have medullary sinuses. So, these medullary sinuses and medullary chords are lined by these plasma cells or B cells which are secreting the antibody.

So, the antibody that is secreted actually finds its way into this medulla or medullary sinus, after which it finds its way out of the lymph node through the efferent lymphatics.

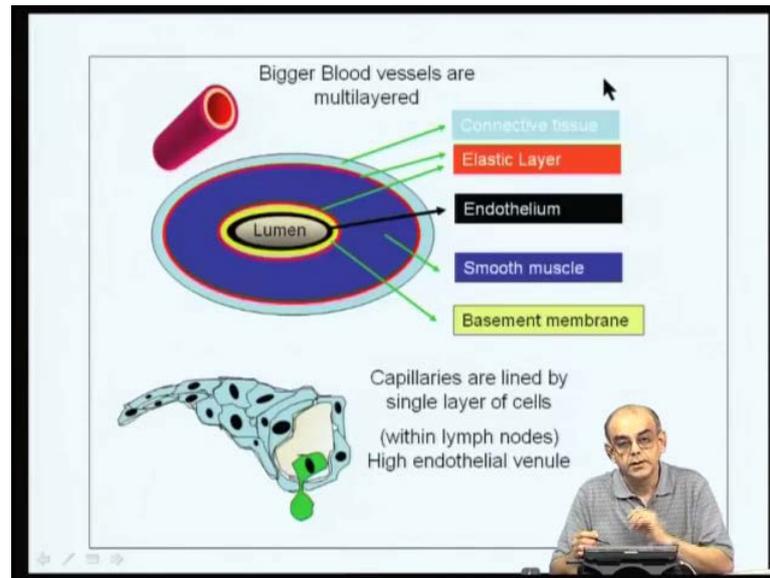
So, **you see that the...** if you look at the overall structure of the lymph node, you see how the antigen is entering the lymph node via the afferent lymphatics, as shown over here by these arrows. As soon as they enter the lymph node, they are met by these—the cells that are making up these follicles. As I shown you here, in the last transparency, these were the primary follicles consisting of an association of mostly mature B cells which are ready to get activated by the antigen. Along with that, of course, there are some antigen presenting cells like follicular dendritic cells as well as some T helper cells.

There are other cells called as the as the interdigitating cells, which actually have long cytoplasmic processes, which bridge the outside where the primary follicles are located, to the paracortex. Therefore, this interdigitating cells help in activating T cells that are located in the paracortex.

So, looking at these, you have these are the secondary lymphoid follicles, and you have other structures called as high endothelial venules, or HEV for short. Now, the high endothelial venules play very important role in what is termed as trafficking of lymphoid cells.

Trafficking means, as the word implies, the movement of cells from one location to another, especially lymphoid cells. So, these lymphoid cells have to move from one location. For example, if they are found in the blood, they have to come out into the lymph node, which is where they have to activate the B cell, and if there are circulating B cell, those B cells also have to come into the lymph node; and the way they come in is via these high endothelial venules, or HEV is for short.

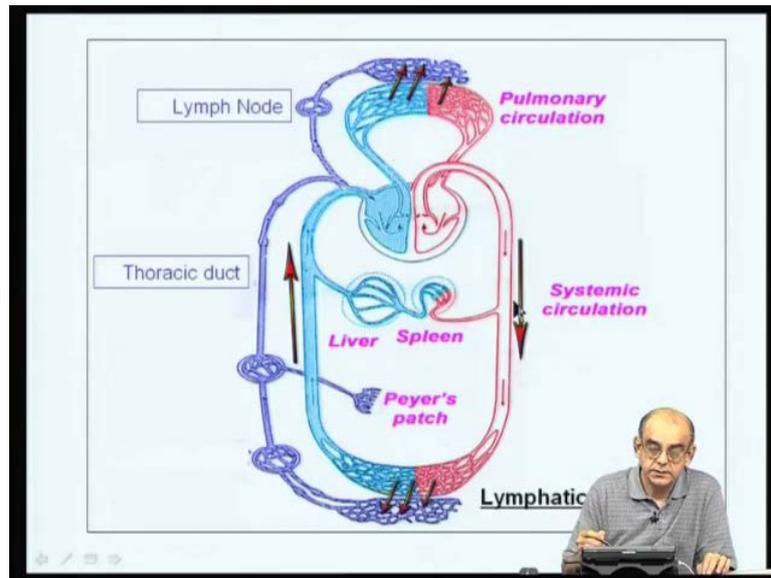
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Now, to understand how these HEV are associated with lymphoid trafficking, let us go to the next slide, where we look at some simple diagrams that make clear what happens to some something like a tissue where you have an artery, and the artery, of course, is made up of different layers; and so you have this lumen, and on the outside you have the connective tissue, and in between you have these various layers, especially the smooth muscle, which is called by different names, and the different layers are called... are named differently in this artery, cross section of the artery, which we need not go into in the slide. Suffice it to say that this endothelial layer is what lines this lumen; and it is this lumen through which the blood is flowing, and the blood contains as all of you know and consists of lymphocytes, whether it is B lymphocytes or T lymphocytes, or for that matter, dendritic cells or antigen presenting cells, in addition to various other kinds hematopoietic cells.

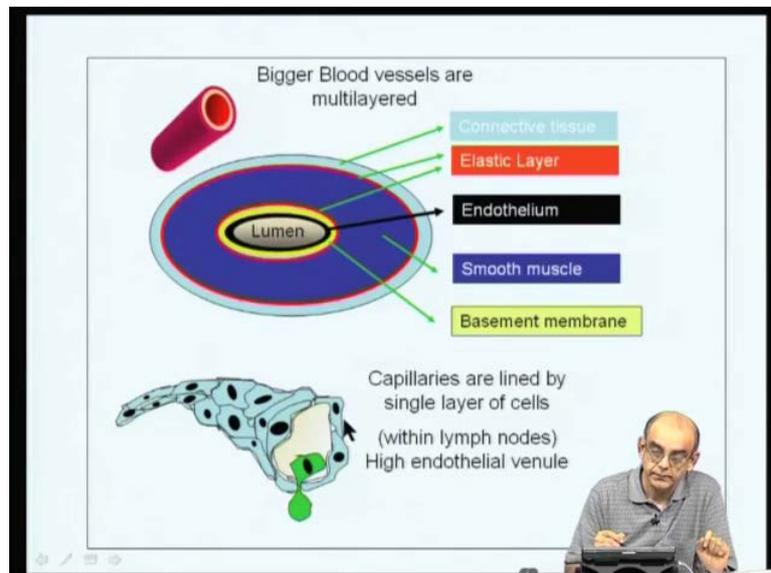
Now, as you can guess by now, that the thickness of this artery makes it very difficult for cells to move out from the lumen into the outside of the artery. But yet, as I told you in the last figure, these cells find their way specifically into the lymph node.

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Now, to imagine that, you need to go back and see that, if you were to look at the lymphoid circulation, it was designated, or you saw these lymph nodes where the thoracic duct as well as these different systemic circulation and the arterioles, they become thinner and thinner in size.

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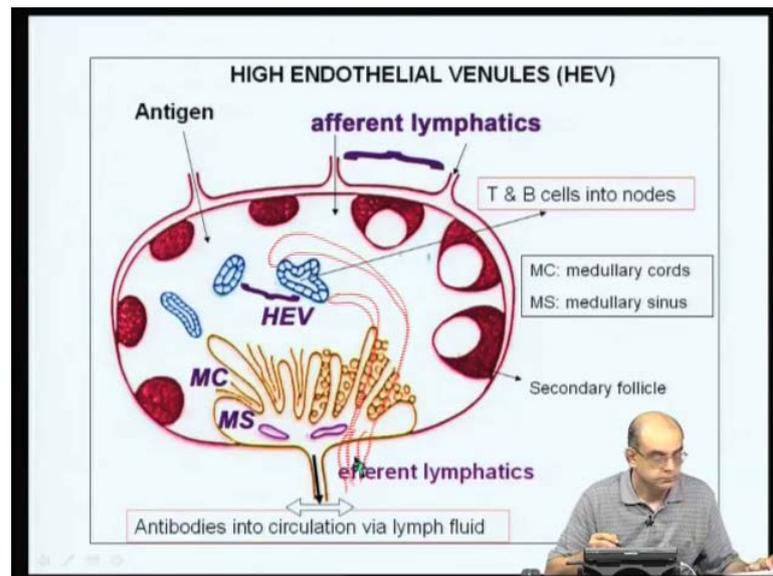


And therefore, the layers of the tissue that make up the arteries or the blood vessels become thinner and thinner, and finally, within the lymph node as these small little

capillaries are going through they actually become only a single or two-cell thick two-cell layers.

Now, these endothelial layers, as you can see, have got certain small pores. So, these are the spaces of the pores through which the lymphocyte actually come out of the blood vessel or the capillary into the lymph node.

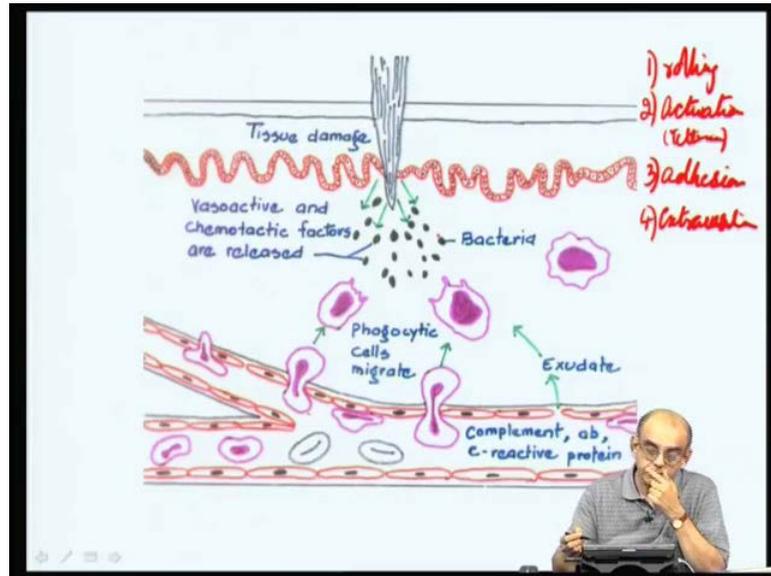
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So, again, when you see here you find that the lumen is inside the HEV; and this HEV is actually the capillary vessel that is coming in from the arteries or the arteriole that you saw in the previous transparency, and the venule that finally go in like that, and this is the venule, and then they come out then exit as a venule.

So, the artery taking in the blood, and then coming out through the venule. So, this is just a cross section of this particular blood vessel. So, the cells are circulating within that arteriole, and then they come within this lumen, and they get out from using those pores that you saw in the endothelial cells.

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Now, to understand this a little further, we have to go back to the slide that I showed you in the first few first class, where I showed you this is the capillary venule that is transporting all the red blood cells and the various kinds of lymphocytes, and I told you that these cells have the ability to sense the antigen or the bacterial infection that is occurring in the tissues, via the various factors that are released from bacteria; for example, the chemotactic factors that are released from bacterial cell walls.

So, these cells that are circulating in the blood capillary have to identify the stimulus, which, by the way, is like going in a dark tunnel, but yet, they recognize the presence of the bacterial infection and they come out through the single layer of high endothelial venule cells or endothelial cell.

This whole process of migration of these cells during the circulation and then out across the endothelial barrier into the site of infection consists of different steps. To imagine this whole process, you have to imagine something of an example that I will try and give you; something similar to the game of cricket where the cricket ball is thrown in the cricket ground. When somebody hits this cricket ball with a bat, the ball can roll on the ground. When it rolls on the ground, if the ground is dry, the cricket ball rolls faster and reaches the boundary.

On the other hand, if there was rain, and there was soggy mud around, the cricket ball finds it harder to reach the boundary, because of the slowing down of the cricket ball;

because it is interacting with the wet mud and the water that is associated with this wet mud.

Now, if you look at these cells, it is something like a ball that is rolling within the fluid that is going in the blood vessel. So, they are actually flowing in this blood, in this blood, and they are rolling. So, if you look at various text books, you will see that **one of them is called...** that these cells are rolling, they are tumbling in this blood; and then, in order to come out from here, there are several steps that occur.

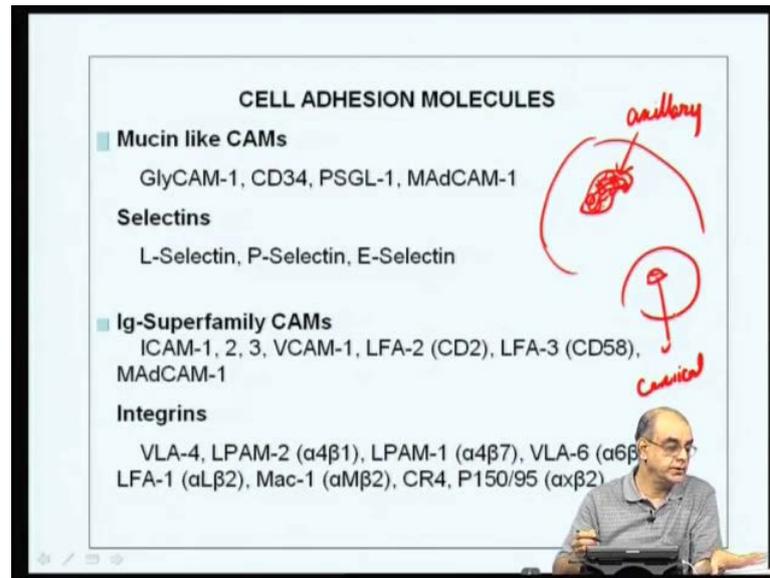
So, after rolling, they undergo what is called as sticking or activation. So, there also this is called as tethering. They are interacting with certain components in the blood vessel wall, and then, of course, you have the adhesion; and then, after adhesion, you have the movement of the cells across this endothelial cell, which is also called as extravasation, or it is also called as trans endothelial migration, after which they migrate towards the bacteria.

So, there are again, there are four steps to this process of cells finding their way from inside the blood vessel towards the site or the locus where there is infection. First, they are rolling in the blood. Something during this rolling, where there is bacterial infection, tells them to start adhering to the cell wall, during which process they are also getting activated.

So, during this activation, actually what happens is— certain molecules that are present on the cell surface of these cells and the molecules that are present on these vascular endothelial cells of the high endothelial venule start to interact with each other. This interaction of these proteins that are present on the cells that are rolling or tethering, with the cells or with the molecules that are expressed on the cell surface of these blood vessel endothelial cells causes an activation of the cells. These cells get activated. When they get activated, certain lymphokines are secreted. They not only are cytokines liberated or secreted, there are also an increase in the surface expression of many other adhesion molecules. These adhesion molecules when expressed on the cell surface causes the stopping or stopping of the cell at that location.

So, they are no longer rolling on the blood vessel wall, but they are now stopping there. At that point, and during this process, a variety of signaling processes are taking place in the cell that is adhering to the endothelial wall.

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Now, as these things are occurring, as these stimulation processes and the and trans membrane signaling processes are activating, this cell that has adhere to the vascular endothelial cell causes the extravasation through the pores that are present between 2 endothelial cells; and therefore, when you look at all these different kinds of lymph nodes, you find that the cells are constantly moving from the heart via the circulation through the lymph nodes, various secondary lymphoid organs, and these lymphocytes actually exit exactly where the lymph nodes are located through the high endothelial cell venules.

So, in order to understand this better, it has been found that many of the cells actually have **specific...** This is essentially protein-protein interaction that is facilitating this process of extravasation into the lymph node, or for that matter, into a site of inflammation.

So, this protein-protein interaction includes ligand-receptor interaction, which actually causes downstream trans-membrane signaling, which then results in various kinds of actions; like for example, the secretion of lymphokines, which then further the whole process.

Now, to understand this better, various experiments were done to show that, in fact, you could have lymphocytes that are actually homing into certain kinds of lympho. I showed

you one slide where there was so many lymph nodes that were distributed in the, in the body of the mouse.

So, what was being done at that time is that, even in these animals, various tumors arise, and these tumors actually belong to various tissue types. If they belong to the blood, they are categorized as leukemia, and there are various kinds of leukemias. So, you can have lymphocytes that have lost their ability to undergo cell cycle regulation, and there could be other kinds of, like for example, B cells that have lost their ability to be regulated. The size cell cycle being regulated there can be T cell that can become cancerous, and there can be other kinds of tumors that are arising.

So, during this series of experiments, investigators had isolated **one of the...** One of the ways by which they try to grow these tumors is to isolate these various cells and grow them in the lab in tissue culture, and because these tumors have lost their ability to undergo cell cycle regulation, you can develop methods by which you can isolate these tumor cell. They will keep on constantly dividing the lab, and they will not die, and they will name them by various names like, for example, carcinoma; hepatoma which arises from a from a liver cell; and so on and so forth.

So, these lymphocytes that had become cancerous, and had been isolated, and had been named by various names, these are all called as lymphomas. So, various kinds of lymphomas had been isolated, and one of the experiments that demonstrated that lymphocytes home into specifically into certain kinds of lymph nodes, they did an experiment where they took a cross section of these lymph nodes.

For example, in the mesenteric lymph node or the cervical lymph node, or various other lymph nodes like under the armpit like the axillary lymph node, and peculiar aspect or very interesting thing that they form was that, when they took these cross sections and examine them by histology after layering them with these lymphomas, that they were growing in the lab. They found that those cells actually stick to the high endothelial cell venules in the cross section of the lymph node.

So, in other words, if you were to look at the cross section of the lymph node which you saw in the earlier slide, and you had the high endothelial cell venule having the endothelial cell; so, assuming that the cross section and the layered this cross section on top with these lymphomas that were that they had isolated or cultured over a long period

of time, these lymphomas would stick to the place where these endothelial cells were located.

Now, this is basically because of molecular interaction. The lymphomas had certain, some surface molecules, which interacted with some of the cell surface molecules that were expressed on the endothelial cells in this cross section, and one of the very interesting things that were found is that lymphomas that actually stuck to, for example, in the axillary lymph node HEV or cross section, would not stick to some other lymph node HEV which was arising from the cervical lymph node.

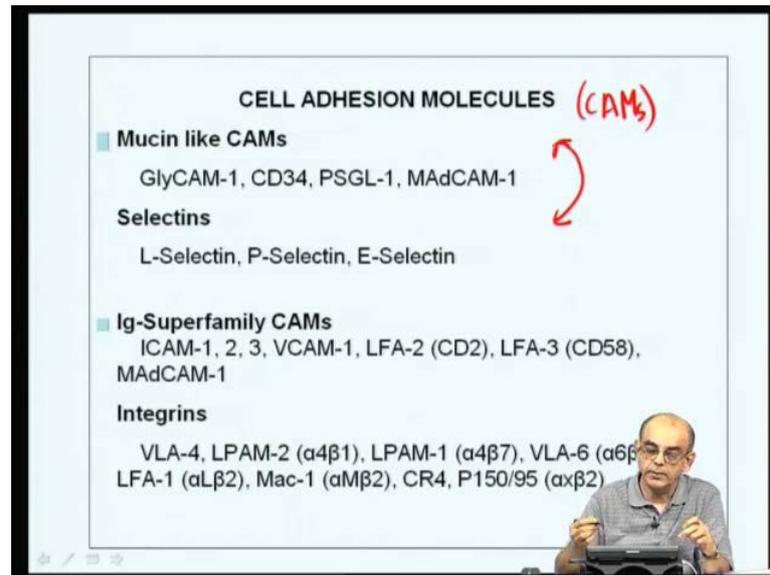
So, in other words, what this experiment demonstrated was that you had certain kinds of cells that would home into. Homing is the word that is used during trafficking because they home into certain lymph node. They would home into axillary lymph node. There were cells that could home into axillary lymph node, but those same cells would not stick to the high endothelial venule cross sections in the cervical lymph node.

So, they had receptors, or molecules that would interact with the high endothelial venule specifically of the axillary lymph node cross sections and not in the cervical lymph node; and yet others, they demonstrated that they had the ability to stick to cross sections or high endothelial venule cross sections in different kinds of lymph node.

So therefore, they found that, in fact, these cells in the blood had actually the ability to look **into a kind of...** You are looking at a certain kind of reaction, or molecular interaction, where these cells are homing into one kind of lymph node and not into other kinds of lymph nodes.

Now, you can imagine the scenario happening in, for example, mucosal associated lymphoid tissue. In the mucosal associated lymphoid tissue, as I mentioned in the previous classes, are lined by immunoglobulin IgA. Therefore, you would like to have B cells that are secreting IgA in those locations and not, for example, those IgA secreting B cells go into some other location where IgA will not play a major role. So, this is a concept of lymphoid or lymphocyte trafficking and lymphocyte homing.

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Now, how does this homing, or lymphocyte or lymphoid trafficking, occur? As I told you earlier, this is happening mainly because of cell interaction via what molecules called as cell adhesion molecules, so CAMs for short. These are also referred to as CAMs— cell adhesion molecules.

So, these cell adhesion molecules play a major role in lymphoid trafficking through the lymph node, out of the lymph node into the heart, as well as in other locations. So, you see, the lymphoid circulation and the systemic circulation play a major role in mobilizing the so-called arm forces that have the B lymphocyte and the T lymphocyte, to a location where it is most needed; to a location where inflammation is occurring; to a location where bacterial infection or virus infection is occurring may be under the skin.

So, what are these cell adhesion molecules? To look at cell adhesion molecules, they have categorized a variety of different families of these cell adhesion molecules. These cell adhesion molecules consist of following families: they are called one of them, one major class is called as the mucin like cell adhesion molecules.

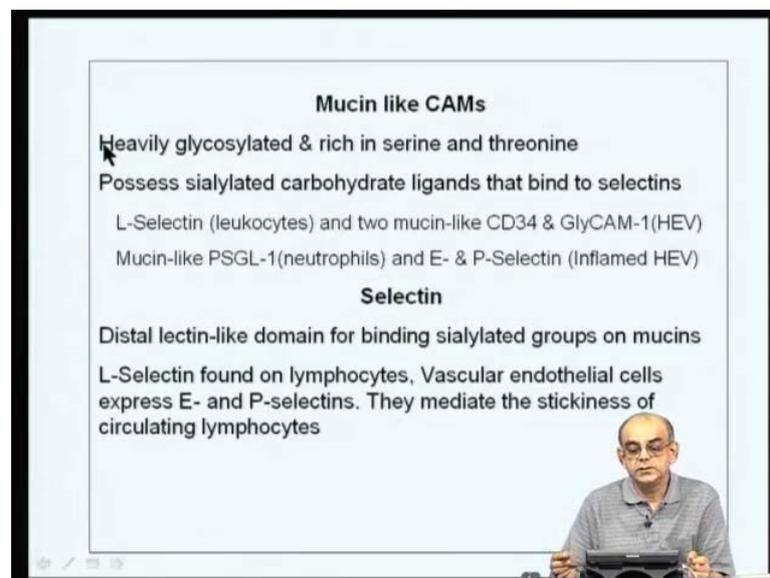
Now, you will come across the word called as addressins, because addressins is a name given for those molecules that are expressed on the internal lumen or the surface of the vascular high endothelial venule cells. Address is something that you use to post a letter, which should reach its location. Similarly, here the lymphocytes that are coming in; they have to find their address and therefore these would termed as addressin molecules.

So, these mucin like cell adhesion molecules are actually playing a role in making those rolling lymphocytes stick at that location.

Now, the members of this CAMs, or mucin like CAMs, also have what are called as GlyCAM-1, CD34— CD standing for cluster of differentiation, and PSGL-1 and MAdCAM-1.

So, when you have other another family called a selectins. Selectins are of three types: L-selectin, P-selectin, and E-selectin. Now, it so happens that these selectins always have an interaction with cell adhesion molecules because of the properties of the selectin themselves.

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So, if you want to look at these properties, let us see what happens in this; and you will see the properties of these mucin like CAMs as well as the cell adhesion molecule. So, these mucin like cell adhesion molecules have the property of being heavily glycosylated, meaning that they have carbohydrate groups and one of these carbohydrates or many of these groups have the property of being adding sialic acid onto these groups, or they are called as sialylated because they have sialic acid on them.

So, these heavily glycosylated moieties— they are rich in serine and threonine because these are the amino acids that help or get glycosylated. So, you find that these are sialylated and these carbohydrates ligands are there, and all these ligands or

carbohydrates that are bound by proteins. These are bound by proteins that are called as lectins. Lectins are molecules that you can isolate, for example, from mung bean or soya bean or peanut agglutinin. These are all molecules, that have proteins that have the ability to bind carbohydrate. So, these are also called as lectins.

So, if you were to look at these different structures that are present, or the family of adhesion molecules, you find that these sialylated carbohydrate ligands are bound by selectins; and why selectins? Because selectins have a distal lectin-like domain, which have the ability to bind sialylated groups on these mucin molecules, and various kinds of selectins are found; and these are, some of them are called as L-selectin, and these are found majorly on lymphocytes.

Vascular endothelial cells, on the other hand, express what are called as E and P type selectins or P-selectins. They are the ones that mediate the stickiness of the circulating lymphocytes. As I told you, these lymphocytes are circulating within the capillary and when they start to stick, these are the selectin molecules that mediate **the interaction with these molecules that are...** or addressins that are expressed on the surface of endothelial cells.

So, some of these, actually these molecules are binding in pairs. We will try and see in the later lectures what are these pairs of molecules that bind to each other. Cell adhesion molecules that bind to each other, for example, a molecule called as a LFA-1 or lymphocyte function associated molecule 1 always binds to what is called as V-CAM 1.

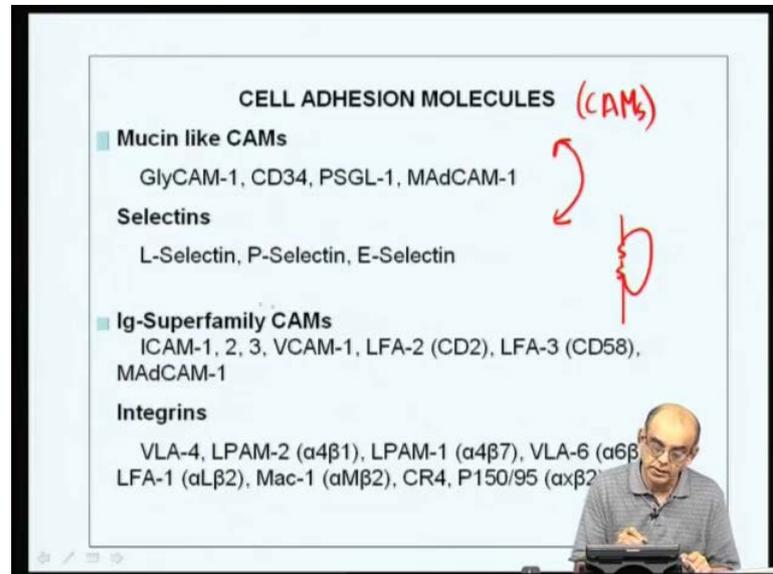
So, here you find that L-selectin which is expressed on leukocytes, as an example, binds to 2 mucin like molecules called a CD-34 and GlyCAM-1, which is expressed on the surface of high endothelial cell venules.

Now, all the expression of all these molecules can be modulated by various kinds of cytokines. In fact, these are the cytokines that are secreted when these cells are activated via these interactions between the cells of its molecules, which leads to G proteins trans-membrane signaling, as I mentioned earlier.

So, you find another example like the mucin like PSGL-1 molecule, which is expressed on the surface of neutrophils, bind to either E type or P type selectin, which is present in

the locations where there is inflamed or inflammation which is occurring, and those HEV's which are located in the inflamed locations.

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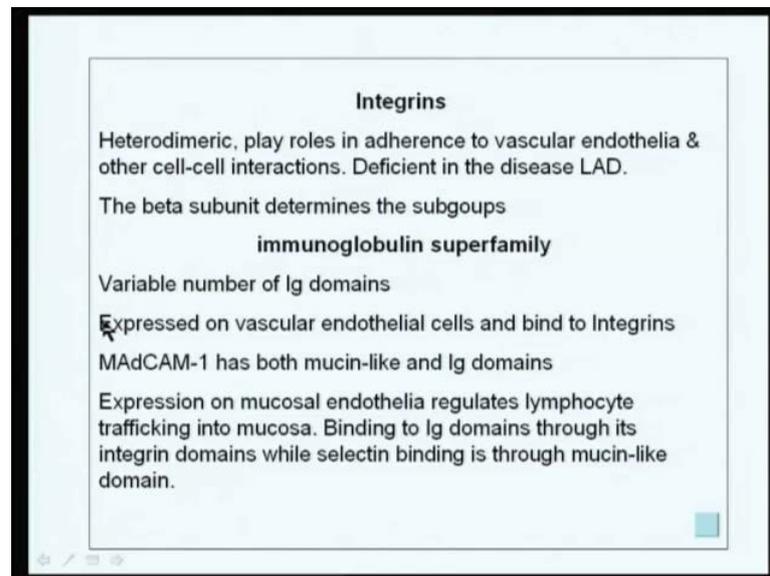
So, now, going back to this family of cell adhesion molecules, so these are the 2 types or 2 families. In addition to these 2 families, you have what is called as the immunoglobulin superfamily of **set** cell adhesion molecules. They are called as immunoglobulin superfamily of cell adhesion molecules because they basically express the immunoglobulin domains which is written, and you will come to learn about this later on when you look at the structure of immunoglobulin molecules.

So, they have this domain which is linked by disulphide bridges. So, this is these the molecules are called as the immunoglobulin domain containing superfamily of molecules.

So, you find that these superfamily contain members like ICAM-1 which is nothing interstitial cell adhesion molecule. So, you have like ICAM-1, ICAM-2, and ICAM-3, different types; and you have what you called as vascular cell adhesion molecule VCAM-1; and as I told you earlier, lymphocyte function associated molecule. This is also called a CD2, and you have what is called as LFA-3, which is now known as CD58. So, in addition to this family, you have what are called as integrin family of cell adhesion molecules.

To learn more **about...** there are different members of this integrin family, and this classification of the integrins into various sub groups actually depends upon the expression of the subunits, which is actually a heterodimer consisting of an alpha subunit or a beta subunit. It is a heteromeric protein. So, they can have different types of alpha subunit or different types of beta subunit; and based upon this constitution, they are organized into different types of integrin molecules. For example, VLA-4, LPAM-1, and LPAM-2, and so on and so forth.

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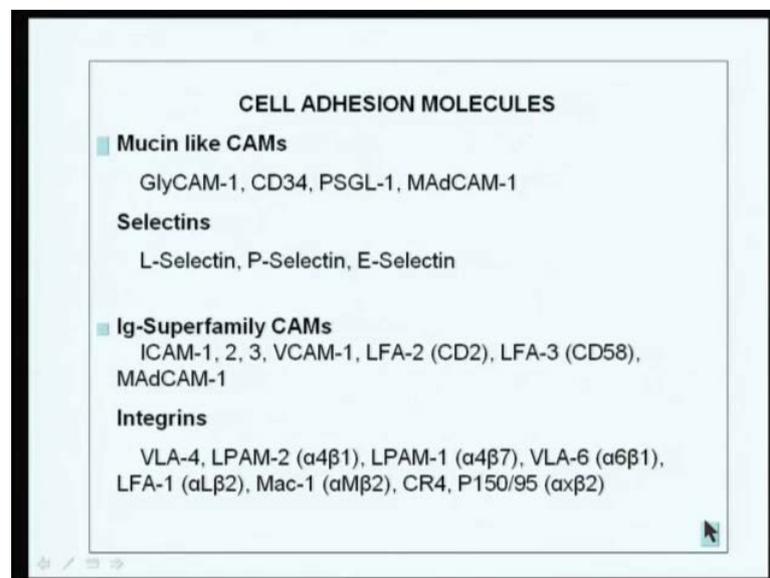
So, if you look at this a little more, so you have integrins which are heterodimeric, and they play roles in adherence to vascular endothelial cells, specially in lymph nodes, and other types of cell-cell interactions which I will describe a little in my next lecture. So, this is a very important type of interaction, even considering from the observation that there is a disease called as leukocyte adhesion deficiency, where you have a deficiency in leukocyte adhesion. So, these molecules the cell-cell interactions are deficient, and the type of beta subunit in this **heteromeric** proteins play a role in the classification to various subgroups.

Now, you have the immunoglobulin superfamily, as I told you in the last slide. These have variable number of immunoglobulin domains, and these are expressed on vascular endothelial cells and they bind to integrins. Therefore, integrins have the ability to bind these immunoglobulin domains. So, these are kind of a pair. They, they interact with

each other; and there are important molecules such as MAdCAM-1, which is a member of the immunoglobulin superfamily as well as the mucin superfamily because they express both type of domains

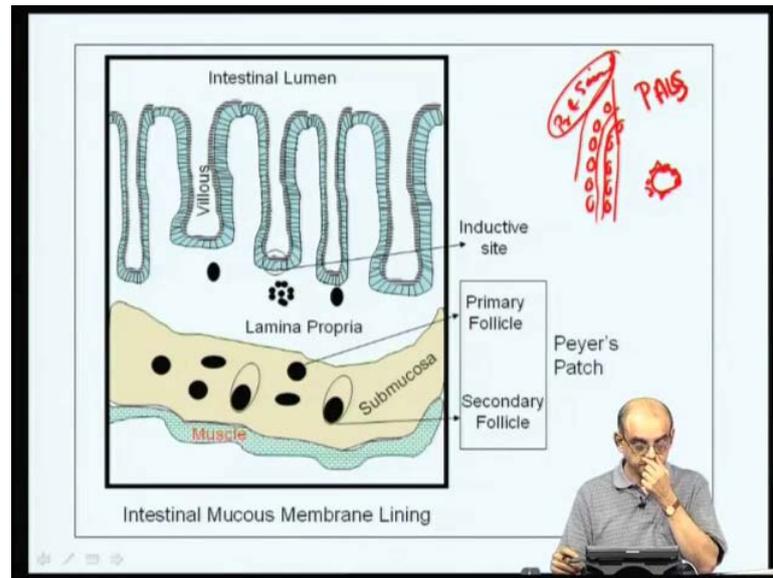
So, the expression on the mucosal endothelia regulates lymphocyte trafficking into mucosa, into the mucosal lining, or into the lumen of various kinds of lymph nodes; and the binding to immunoglobulin domains through the integrin domains actually characterize one type of interaction, while the selectin binding through the mucin like domain characterize another type of interaction that occurs with this particular molecule, which has both mucin like as well as the immunoglobulin domain.

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So, therefore, going back to the cell adhesion molecules, to summarize, there are four different families of these cell adhesion molecules which I have just now described; and these are the molecules that take part in pairwise interaction with counter parts that are expressed on the vascular endothelial cells, as well as the lymphocytes that need to traffic particularly or specifically into specific lymph nodes.

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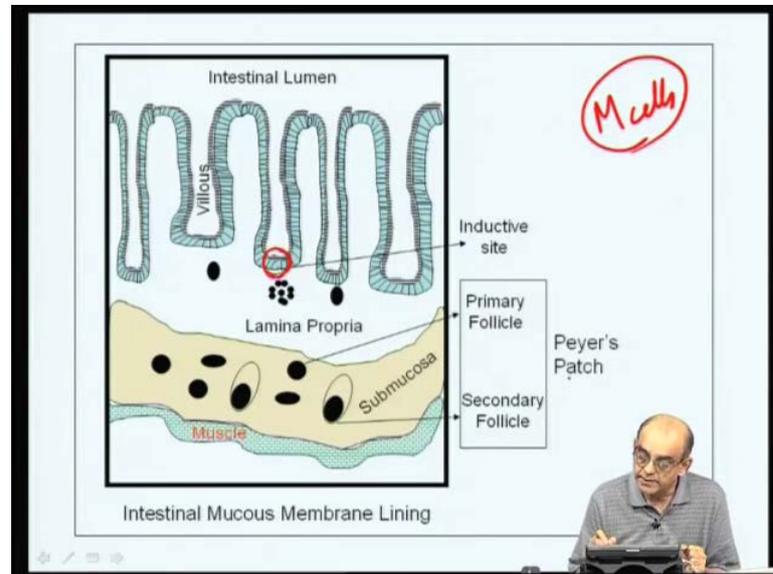
So, going on further, we have covered now the structure and the roles of secondary lymphoid organs like the various types of lymph node. Now, you also have secondary lymphoid organs such as the spleen. Now, the spleen is a more organized and differentiated kind of a lymph node, but most of the functions are the same. The spleen also takes place a major role in RBC destruction. Therefore, if you look at the section of the lymph node, you see that there is a red cell area or a red cell pulp and a white cell pulp.

Now, the red cell pulp is beneath the capsule, which consists of a lot of RBCs which are coming into the spleen for destruction; and beneath that, you have the white pulp which is **basically...** The difference between the lymph node and the spleen is that you have a variety of structures called as periarteriolar lymphoid sheaths, which is nothing but, you have blood vessels that are going into the spleen, and these blood vessels are lined on the side by the B cells as well as P cells majorly. But, you have other types of cells. So, if you were to look at a cross section of this arteriole, you find all these cells aggregating just outside of that lumen of the arteriole. This is called as periarteriolar lymphoid sheath because these B cells are aggregating or surrounding this arteriole.

This is basically, again, to meet the antigen that might be coming out of the cells, and beyond this periarteriolar sheath you have the organization of the various primary and

secondary lymphoid follicles, in order to further the activation of the B cells and the secretion of the B cells.

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Now, going on to other kinds of lymph node, for example, I told you one of the major lymph node, lymphoid structures that are associated with the secondary lymphoid organs, is the malt or the mucosal associated lymphoid tissue. Mucosal associated lymphoid tissue is very different from the organization of an ideal lymph node; for this is the organization that I show you of the lymph node, of the of the Peyer's patch, for example, which I said was found within the intestine. As you all know, the intestine or the digestive system or the elementary canal is exposed to a variety of pathogens and bacteria that we take in while we ingest our food.

Now, the malt associated or the mucosal associated lymphoid tissue is very much different in its organization, and I show you here. This is the intestinal mucosal membrane lining, so these are the villi. So, you have the villi in the intestine for increasing the absorptive surface of nutrients, which is very much familiar to everybody. So, these villi are lined by the cilia that are there to help in the movement, or way, of various nutrient or granular particles associated with the ingested food.

Now, you find that along these kind of mucosal lining, you have the cells that are associated with malt which are basically called as M cells. These are specialized kind of cells, which are basically found in the lumen of these villi, which I have showed over

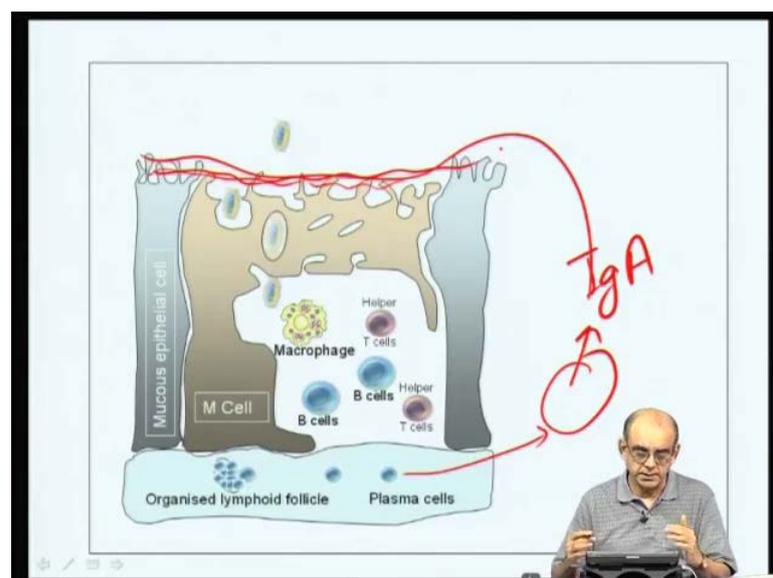
here, which I will show you in more detail in the next slide. Basically, these are the places where antigen, or for that matter, bacterial or viral antigens, come in contact with the immune system represented by the Peyer's patches or a secondary lymph node.

Now, what happens here? These are the lymph node under which you have a loosely organized association or conglomeration of these lymphocytes consisting of B cells. So, essentially, this is a follicle. So, you have a kind of a loose minimal center of these B cells consisting of antigen presenting cells and some T cells; just under this what is called as an inductive site which contains these M cells.

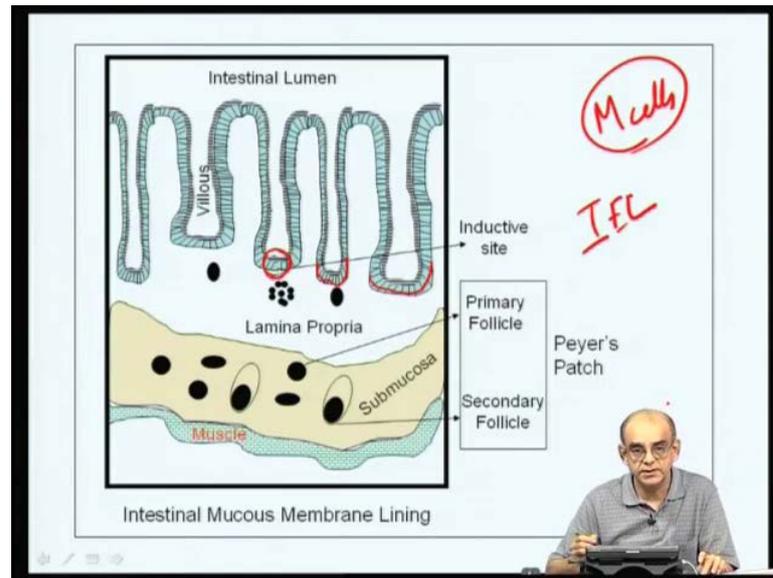
Now, the M cells, as I told you, are specialized cells which take in the antigen in a specialized way, and into these; and then get them or expose them to these lymphoid or loosely organized lymphoid conglomerations, or associations which are found in the lamina propria just underneath these mucosal membrane lining.

Beneath the lamina propria, you have a much more organized structure of lymph node containing the primary follicle and the secondary follicle, which actually make up the organization of the Peyer's patch which is found in this layer, which is called as the submucosa; under which there is, of course, muscle that lines your intestine.

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So, in order to see the nature of the M cells, we will go into the next slide, which is basically showing you the structure of an M cell. Now, what you are seeing here is this particular area, which is consisting of the other villi cells, and an M cell associated along with these various kinds of mucosal villi cells.

Now, if you at this M cell, you find that these M cell structure, in contrast to containing various all these villi structures that contain all the cilia, they are made up mostly of vesicular structures. So, these are the vesicles into which the antigen is taken up. Once it is taken up, this antigen is internalized into vesicular structures. So, basically, a process of a similar to endocytosis; and once it is taken up, this particular antigen that is taken up into these vesicles is actually released into a pocket that is existent within the M cell. So, you have this M cell; between the M cell and the neighboring mucosal epithelial cell you have a kind of a structure or a space which is a pocket.

Now, it is very interesting that this **pocket...** So, you see you have something like a cell which is actually kind of a bigger godown which is consisting of smaller little cells, which has an association. A sprinkling of macrophages, which is needed to break this antigen and present this antigen, and then you have the helper T cells, and then you have, of course, the B cells. Therefore, you have these three major players, which are now responding to the antigen that is taken up by this M cell from the lumen of the intestine.

So, this M cell plays a major role in buffering some of the harmful effects of this antigen on the lymphoid cells, which are the B cells and the T cells. So, there is some sort of a treatment within the M cell, which then comes out into this pocket. And in this pocket, these various kinds of lymphoid cells meet the antigen, and the antigen presentation takes place by uptake into this macrophage, and then the antigen is presented.

Now, as I told you in the previous transparency, beneath this particular inductive site you have a conglomeration of different kind, like the B-lymphocytes. So, if you were to look at that organized lymphoid follicle over here, these B cells are actually coming over here and then getting activated. They activate more T cells in this area. More macrophages are found over here, like the follicular dendritic cells. These then activate the B cells to become plasma cells, and one of the major functions of this plasma cell, specially in this location, is to secrete IgA molecules. So, these are the secretory IgA molecules which actually lie in the mucosal lining of the intestine.

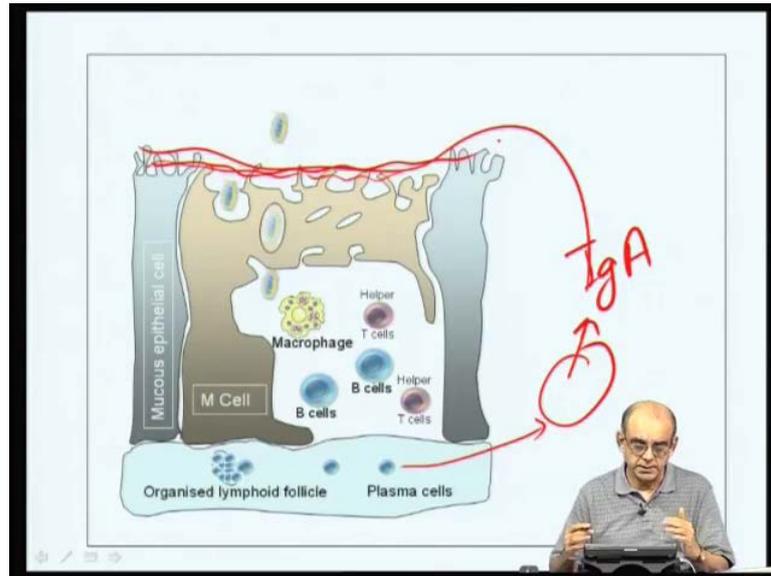
So, these, this IgA that is secreted by these plasma cells actually get come out, and then get stuck to lining of the intestine, and act as a barrier for the incoming pathogens.

So, in this class, now to summarize, we have gone through the structure of the secondary lymphoid tissue, such as the lymph node and the malt or the mucosal associated lymphoid tissue, which is..., which has a different type of organization, in that it contains the M cell. And then, of course, you have other kinds of lymphoid tissue, like lymphoid tissue that is operational, or associated with the skin like the cutaneous associated lymphoid tissue which has got keratinocytes and, of course, other kinds of lymphocytes called as the... something similar to what are called as the intraepithelial lymphocytes.

Now, the IEL is actually a very important type of cell, which I forgot to mention earlier. These IELs are lymphocytes that are actually going between these various kinds of cells.

Now, the IELs are very important because they have a different type of reaction. They have what are called as different like gamma delta T cells, which recognize a class of antigens very different from the major type of T cell, which has got the alpha beta T cell receptor. We will come to that more when we cover the T cell receptor, and see how these different kinds of T cells react with different kinds of antigens.

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So, just like the IELs or the intraepithelial lymphocyte, you have similar such lymphocytes under the skin. And basically, antigen presentation occurs under the skin via the follicular or the dendritic cells, and then the same sort of response is completed.

So, I will complete this lecture by summarizing again that we looked at the various kinds of lymph node, and we looked at various kinds of molecules that take part in homing of these lymphocytes to various kinds of lymph nodes. Therefore, the participation of the cell adhesion molecules, and the homing via the addressin molecules, and how these molecules actually take part in cell-cell interaction when T cells are interacting with each other. And how T cells, during the activation of T cells, the same sort of cell adhesion molecules take part, and how these take part we will come to in a later class, where we look at T cell receptor and how the T cell receptor is activated.