Organisation of the immunological system

The immunological system in man is divided into three zones:

1. *the epithelial surface of contact and defense (against the exterior);*
2. *the thymolymphatic defense zones;*
3. *the organismic, pluripotent active mesenchyme (= reticulohistiocytary system).*

The biological and pathological reactions of the interdependently arranged systems are intimately implicated into each other.

The division into the three systems has a fundamental importance beyond the didactic value. The epithelial defense surface is the phylogenetically oldest, the thymo-lymphatic interface the youngest mechanism of defense. The systems differ not only in the morphe of their cells but also in many other respects. The most conclusive confirmation of this division into three parts is the fact that in each system special immunoglobulins are formed. Tab. 9 gives a synoptic survey of the theoretical and clinical significance of this division.

The attention of the immunologists has centered on the reticulo-endothelial system for decades. Thymus and the lymphatic system have been main topics of consideration during the last two decades. The importance of the surfaces of contact, which physiologically carry most of the burden in the fight with the environment, has hardly been discussed from the immunological point of view so far.

The epithelial surface of contact and defense

Every living being is part of its environment and needs absolutely the contact with and the defense against it to maintain its biological existence. Surfaces of contact have the function to take in substances that can be utilized by the organism and to keep away from the interior of the body all substances that have no biological functions or even harm the organism. During the phylogenetic development, these functions were first performed by the cell membrane, which takes up and secretes substances from the environment. In the higher developed organism, the surfaces of contact are formed by epithelial groups of cells; the most important surfaces of contact in man are the spaces of the mouth, pharyngeal cavity and nose as space of intersection for the ingestion of foreign substances from the respiratory air, from the digestive tract and for the fight against microbial noxae. In a wider sense, these surfaces of contact include the lining of the gastro-intestinal tract and of the urinary passages.

The air-passages and upper digestive tract lined with epithelium are connected closely with parts of the lympho-reticular connective tissue chiefly in the area of the Waldeyer's lymphatic glands of the fauces. Whereas the epithelial cells are physiologically suitable for the contact with foreign substances and even tolerate – and partly need as metabolic symbionts – microorganisms on their surfaces, the connective tissue below them reacts with regular defense measures if the areas of contact are exceeded.

The epithelia of the respiratory passages and of the digestive tract with their metabolic function are of great importance for the measures of defense against the environment. Usually, noxae are kept off already at this first barrier; they penetrate only in case of a failure and can thus provoke illnesses. The superficial epithelial cells must decide on the necessity of the intake and output of substances. Vital substrates as water, oxygen, carbohydrates, proteins, fats, vitamins and minerals are released by the epithelial cells to be transported on into the interior of the body. Ballast substances of the food shall be recognized at the limiting surfaces and not be taken in.

Tab. 9: **Organization of the immundefense-system. Survey of the guiding symptoms, the use and failure of the defense zones in the human body.**

Defense zones	Immunological principle	Immuno-globulin	Immunological reaction	Immunological depression
I Epithelial contact and defense surface			**Catarrhal**	
Skin Mucosae of the respiratory passages, of the gastrointestinal and urogenital tracts	The *epithelial* contact and defence surface is represented by the skin and the mucosae of the rhino-pharyngeo-oral cavities,conjunctiva and digestive, respiratory and urogenital tracts. These contact surfaces have an ambivalent function: substances likely to be of use to the body are taken up, substances that have no physiological functions or even may be harmful, must be kept away from the interior of the body, and metabolites of the own metabolism must be secreted through the same contact surfaces.	IgA	Dermatitis Rhinitis Sinusitis Pharyngitis Tracheitis Bronchitis (pneumonia) Enteritis Colitis Pyelitis Cystitis Urethritis	Necrobiosis of the skin Dermatitis bullosa exfoliativa toxica necroticans *(Stevens-Johnson* syndrome *Lyell* syndrome) Mucosae: necrotising inflammation noma
II Lymphoreticular defense area			**Proliferative**	
Thymus Lymphatic system Lymph-nodes Adenoids Tonsils Lymphplaques Bone-marrow Spleen, liver Lymphocytes (so-called T-lymphocytes)	The *lymphoreticular* defence areas constitute a colonisation family deriving from thymus, which, fully developed, comprises: lymph-nodes, tonsils, adenoids, lymphplaques, bone-marrow, fragments of tissue from liver and spleen. The lymphoreticular tissues react with proliferation i. e. multiplication of cells, hyperplasia of the thymus, hyperplasia of the tonsils, adenoid vegetations, swellings of lymph-nodes, hepato- and spleno-megaly are the clinical equivalents for the use of this defence area.	IgM	Thymus hyperplasia Lymphonodulitis Hyperplasia of the tonsils Adenoids Region. ileitis (termin.) Leukocytosis Splenomegaly Hepatomegaly	necrobiotic inflammation Pyemia Leukopenia Agranulocyto-sis
III Mesenchymal defense system of the organism			**Exudative**	
Serous membranes (Lepto-) meninges Pleura, pericardium Peritoneum Omentum Mesenterium Articular teguments Interstitium Loose connective tissue, endothelium Monocytes Histiocytes Cells of the mesothelium (= so-called B-lymphocytes)	The *organismic mesenchymal defense* system comprises the cells dispersed over the whole organism that have preserved the mesodermal pluripotency; the most reactive cellular units are in the fluffy connective tissue of the interstices and in the so-called serous membranes i. e. those mostly flat networks of fluffy connective tissue, which line the body-cavities: meninges, pleura, pericardium, omentum, peritoneum, mesenterium and synovia.	IgG	Meningitis Pleuritis Pericarditis Peritonitis Arthritis Arteriitis Angiitis Inflammation of the connective tissue	Empyema Polyserositis Sepsis

Fig. 139: Epithelial zone of contact and defence. ▶

1. Physical mechanisms
   film of secretion
   ciliary movement
   roofing-tile formation
   lipoid layer of cytomembranes
2. Biochemical mechanisms
   pH electrolytes
   (Na, K, Mg, Ca, J, Zn, S)
   mucopolysaccharides
   lysozyme
   glucosidases
3. Immune reactions
   IgA
   IgA secretory
   IgM
   IgG
   IgE

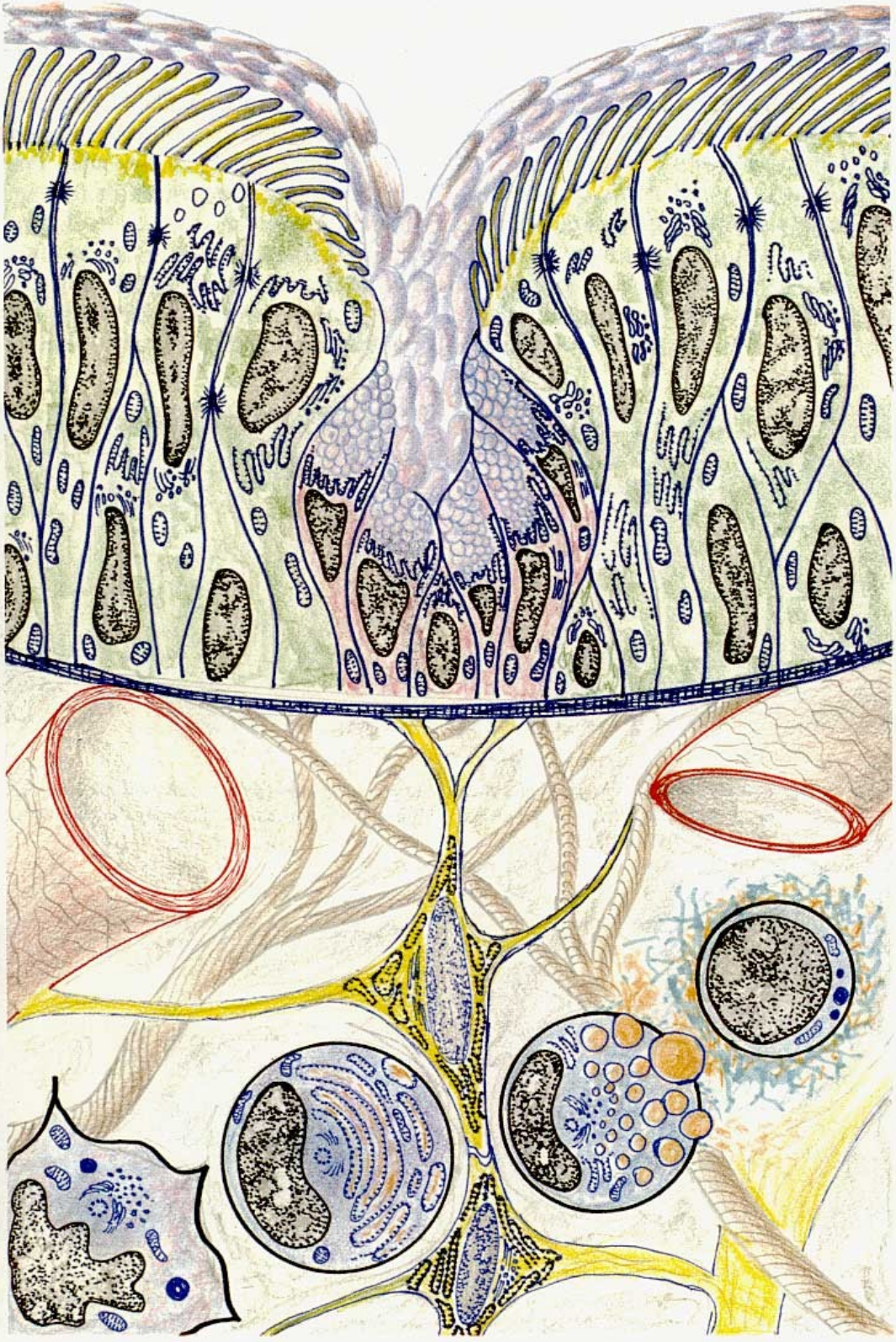

Fig. 139: Epithelial zone of contact and defence.

Metabolic end-products are secreted as e. g. carbon dioxide through the lungs or protein metabolites through the urine.

The upper epithelial cells of the oral and pharyngeal cavities constitute a limiting surface of the organism and are moreover initial links of the metabolic chains. Smears of the pharyngeal or oral mucosa show their various functions when the obtained preparations are subjected to a methodical cytochemical evaluation. Spatula smears of the superficial layer of epithelial cells reveal bizarre, imbricated cells of large volume, with a centrally located nucleus (fig. 140). Even in healthy individuals the surface of the cell membrane shows bacteria, and very frequently each epithelial cell seems to determine both the quantity and the kind of bacteria on the cytomembrane. All variations from individual bacteria to dense lawn of bacteria are found here (fig. 141).

The constituents of these epithelial cells can be prepared by cytochemical

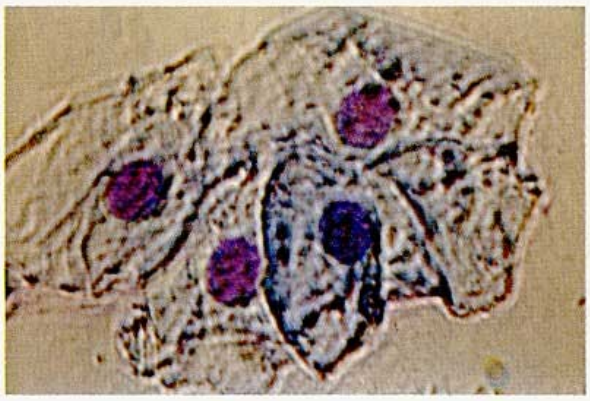

Fig. 140:
Cells of the pharyngeal epithelium arranged like roof-tiles (protective formation). Panchromatic colouration, 1:600, contrast of phases.

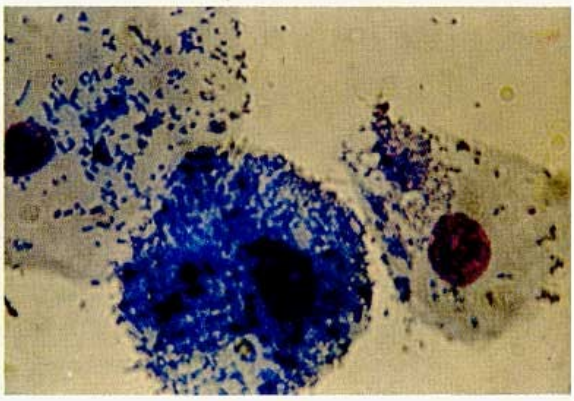

Fig. 141:
Various *settlements of bacteria* on the cells of pharyngeal epithelium; bacteria on the cytomembrane.

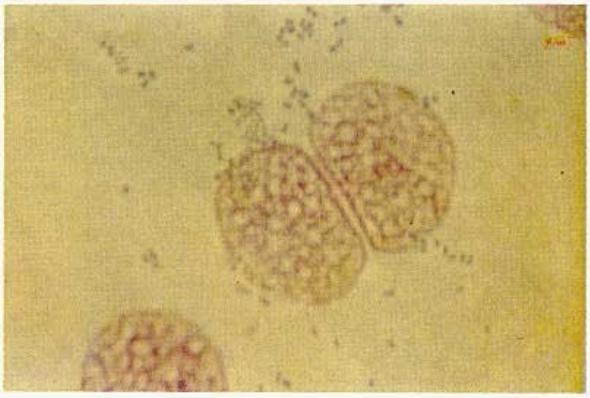

Fig. 142:
Interrelation between the (DNA-)nuclear metabolism and growth of bacteria. Inside the cells, the bacteria multiply with and at the expense of the nuclear substance (DNA); the more bacteria occur in the cell, the greater the chromatin defects in the nuclei. Panchromatic staining.

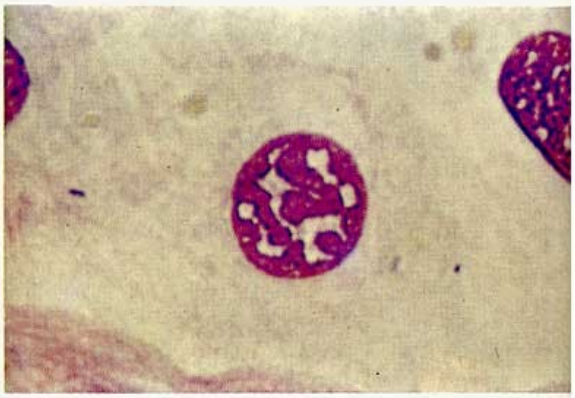

Fig. 143:
In *virus infections*, only indirect conclusions can be drawn on the interrelations between the nucleus and microorganisms. Fine to coarse structural defects of the nucleus may be indications. Panchromatic staining.

methods. Especially in activated epithelial cells (in infections) a dense system of channels can be detected very frequently within the cytoplasm, in which various groups of substances obviously transported there can be noticed. Thus glycogen or ribonucleic acid can be demonstrated whereas the fatty substances are seen chiefly on the nuclear membrane and the membrane of cytoplasm (fig. 146–149).

Lesions of the cytomembrane by physical or chemical noxae (fig. 145, 150) or injuries to the cytoplasm by chemical noxae or infection make the defensive function of the epithelial cells fail and interrupt the initial link of the metabolic chains. Whereas e. g. in normal epithelial cells the system of channels is filled with RNA, the destruction of the tube-system with a coarse precipitation of the RNA particles (fig. 144–147) is seen in inflammation (tonsillitis, phlegmon of the ground of the mouth, pneumonia).

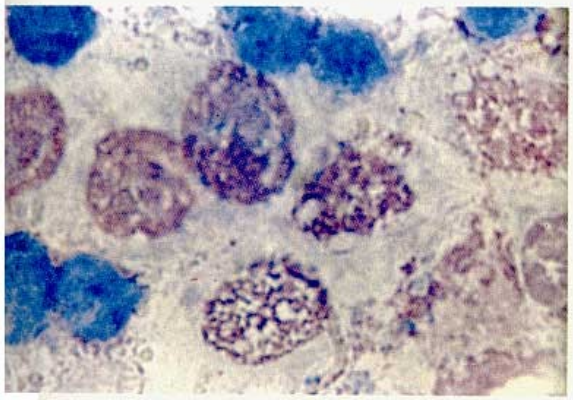

Fig. 144:
Different lesions of epithelial cells in bronchopneumonia. Panchromatic staining.

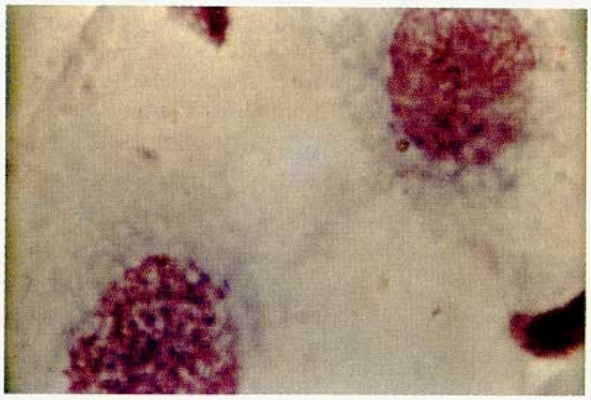

Fig. 145:
Broad-spectrum antibiotics intervene in the cellular metabolism; diffusion of nuclear substance into the perinuclear cytoplasm after treatment with ampicillin-chloramphenicol. Panchromatic staining.

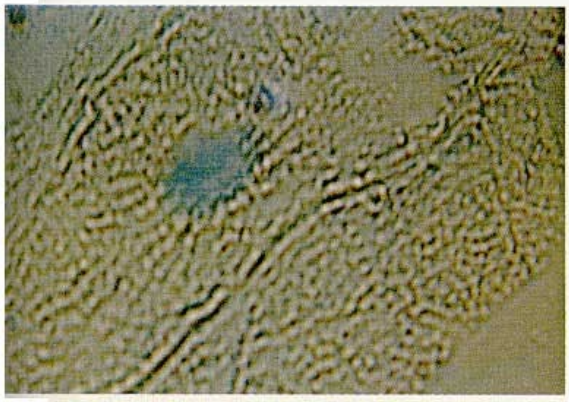

Fig. 146:
Intracytoplasmatic «metabolic channels» in cell of pharyngeal epithelium. Staining: methyl-green-pyronin. DNA = green; RNA = red.

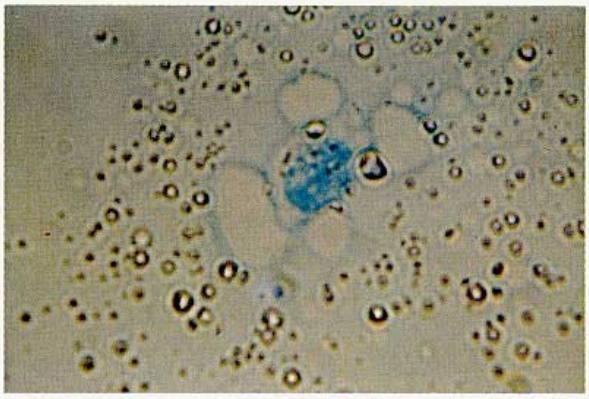

Fig. 147:
Destruction of the intracytoplasmatic metabolic transport-system by infections: phlegmon on the ground of the mouth; coarse particles of RNA. Staining: methyl-green-pyronin; DNA = green, RNA = red.

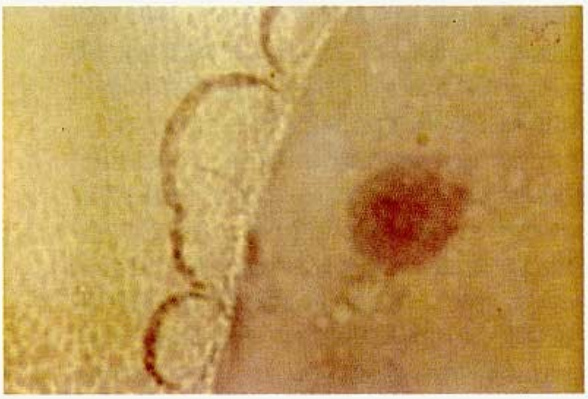

Fig. 148:
Detachment and conglutination of the cellular membrane (oral epithelium) by 44% *alcohol (whisky),* tested in non-alcoholics immediately after drinking whisky. The cellular membrane rich in lipoids is injured. Best-carmine staining.

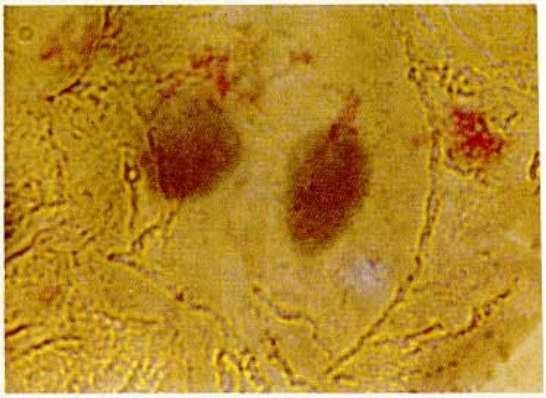

Fig. 149:
Synthesis of the cells of oral epithelium. Intracellular polysaccharide complexes (glycogen) occur already a few minutes after absorption of floracit. Best-carmine staining.

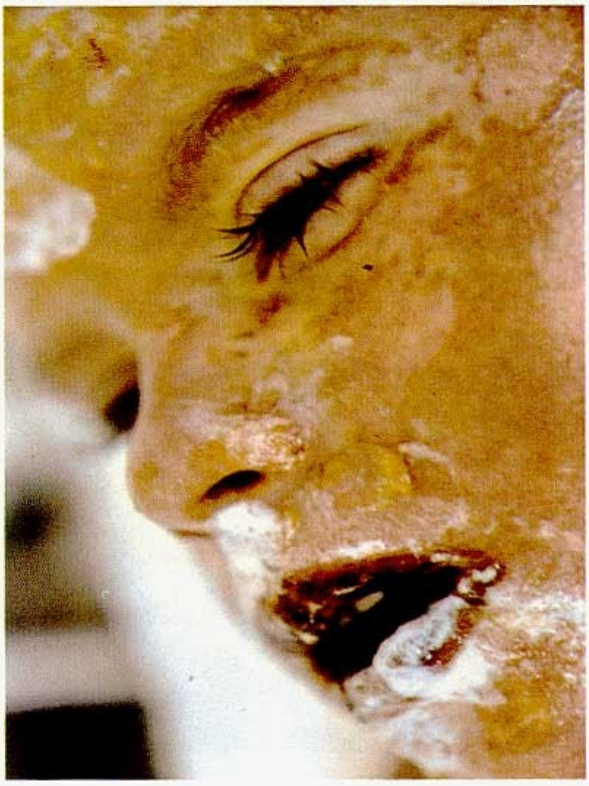

Fig. 150:
Generalised lesion of the epithelial protective surface as part of a *Lyell-syndrome* (by long-term sulphonamide); the layers of the oral mucous epithelium are afflicted more than others.

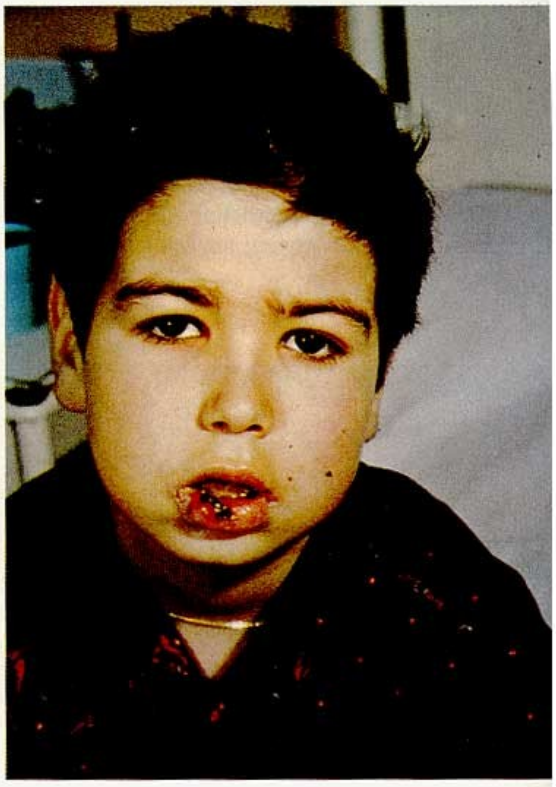

Fig. 151:
Terminal collapse of the epithelial defense surfaces in *leukemia.*

There is apparently a very close biological connection between the bacterial flora of the oral and pharyngeal epithelia and the epithelial cells as such. As long as the microorganisms are on the surface of the cells, they seem to have a symbiont effect and to support the cellular metabolism. If however microorganisms are in the space of cytoplasm, this will usually cause the destruction of the epithelial cells. As for bacteria, the connection can be seen direct whereas in the case of viruses only the defects in the nucleus, which contains DNA, can be detected (fig. 142, 143). In the cytological pictures, an antagonism will arise in that the nucleus gets increasingly low in chromatin whereas the lawn of bacteria becomes denser.

This antagonism between the microorganisms and the cells of the macroorganism reveals the essence of an infectious disease as a concurrent problem. Normally, the epithelial cells utilize the metabolic effects of their superficial bacteria, which they even may use as sources of nucleic acid. If the morbific agents transgress the cytomembrane, the economic relations between the bacteria and the macroorganism are reverted: the microorganisms multiply at the expense of the epithelial cells, especially the nucleic acids, and thus cause the destruction of the cells and injure the surfaces of contact and defense.

The general symptoms of the so-called prodromal stage of infectious diseases are due to these changes of epithelial surfaces of contact. On the other hand, many conditions of lacking immunity are accompanied by a pathological colonization of the epithelial surfaces; just to think of the candidiasis on the mucous membrane in the mouth of dystrophic babies, and of a collapse of the defense against infection in immunity paralysis (terminal stage of leukosis in children, gastrointestinal radiation syndrome, therapy with cystostatics). Also noxae due to medicaments (antibiotics, antiepileptics) can provoke serious aspects in the form of diffuse lesions of the mucosa, or of the skin and mucosa (Stevens-Johnson syndrome, pluriorificial ektodermatosis Glanzmann, Lyell's syndrome; fig. 145, 150, 151).

The thymo-lymphatic defense-zone

If as a result of lesions, injuries or evasion the organism lacks physiological surfaces of contact, foreign substances, chiefly morbific agents, can penetrate into the ducts of blood and lymph. For such cases, the organism is provided with the lymphatic system beneath the epithelial surface of contact. Especially in the pharyngeal cavity, the *Waldeyer's lymphatic glands* constitute a considerable zone of defense, but also the entire gastro-intestinal tract is secured with them (*Payr's lymphoid patches* of the intestine, mesenteric lymph-nodes). Adenoid vegetations, hyperplasia of the tonsils, swellings of cervical and mesenteric lymph-nodes are clinical equivalents of this permanent or relapsing struggle of the lymphatic ring of defence with infectious noxae.

The lymphatic apparatus of defense develops by *colonization from the thymus*. In the absence of the thymus or if it is malformed, this zone of defense will fail or offer insufficient defense. Vehicles of the cellular defense are small lymphocytes (so-called T-cells), which chiefly contain the cellular IgM. As the cytoplasm space of these lymphocytes is comparatively small and does not suffice

to form any substantial quantities of immunoglobulins, immunological use of the lymphatic system causes always a multiplication of lymphatic cells (lymphatic hyperplasia). Unlike the reticulohistiocytary system, which reacts with the secretory processes (exudation), this system responds by proliferation. The differences between these two systems are shown synoptically in tab. 9.

The *lymphatic system* of defense is phylogenetically the youngest. in the course of life it experiences a stage of ripening between birth and an optimum between the 9th and 12th years of life, a stage of maturity and a stage of regression after the 40th year of life. An initial reactive organ after birth is the thymus, which can swell into a large organ owing to the struggles during the first weeks and months of life. Later, the peripheral and inner lymph-nodes take essentially the function of the thymus, which atrophies and beyond puberty loses much of its central function within the lymphatic system.

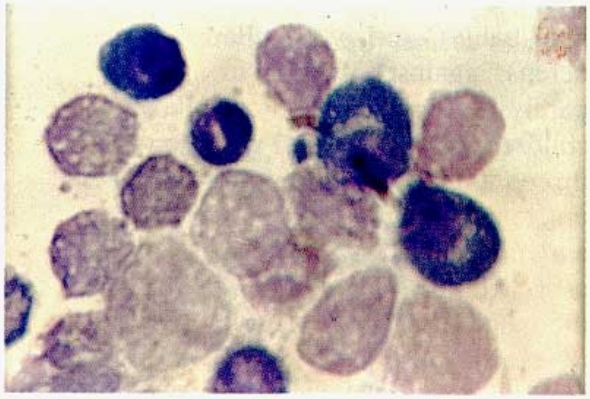

Fig. 152:
Normal *tonsil cytogram* (swab cytogram from middle of tonsils) in 3-year-old child. Abundant intact cell material, lymphocytes, lymphoblasts. Panchromatic staining.

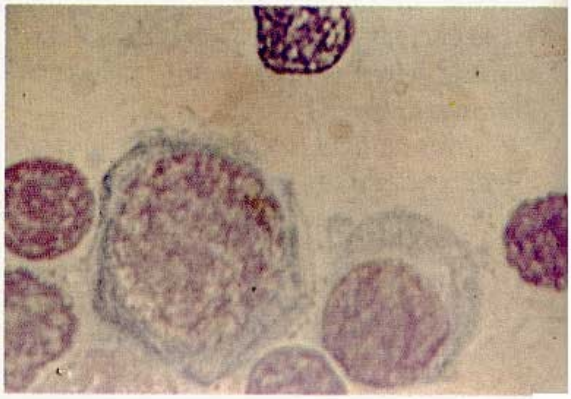

Fig. 153:
Tonsil cytogram in subacute *tonsillitis* of 6-year-old child; rich in cells. Panchromatic staining.

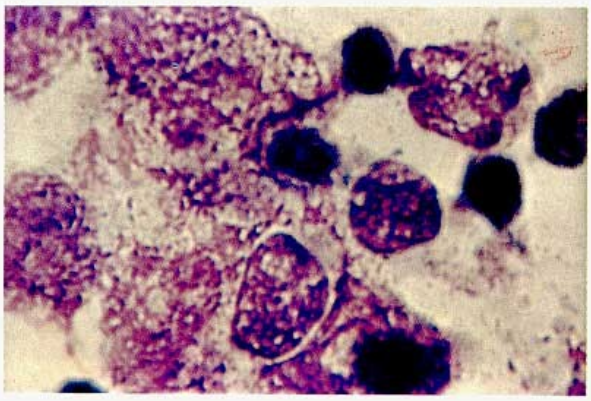

Fig. 154:
Tonsil cytogram of 15-year-old girl; abundance in comparatively small lymphocytes. *Cytolysis.*

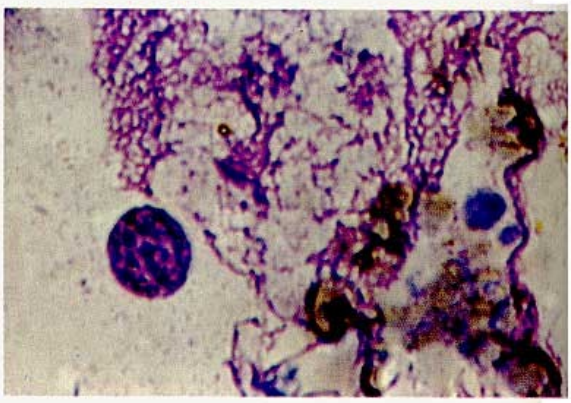

Fig. 155:
Tonsil cytogram of 30-year-old woman. Chronic tonsillitis. Abundance in cytolyses, despiralled chromatin substance.

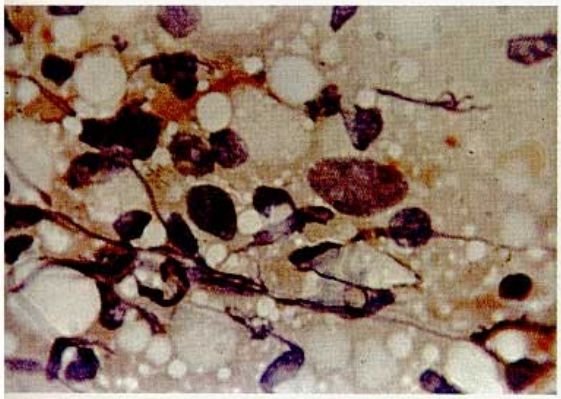

Fig. 156:
Lymph-node smear preparation in proliferative lymph-node *tuberculosis*. Matrix, epitheloid cells, fibres. Panchromatic staining.

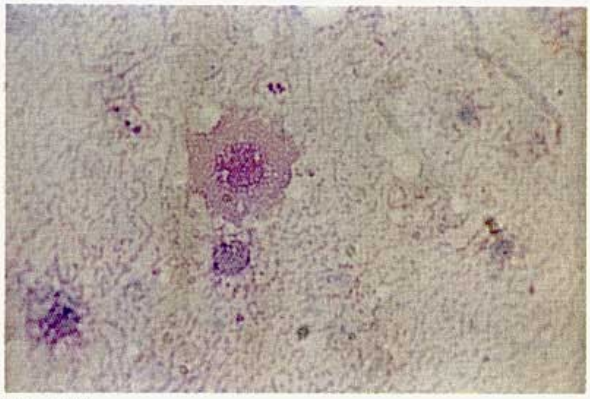

Fig. 157:
Lymph-node tuberculosis, smear from section as in fig. 156. Two minutes after effect of a tuberculin dilution (1:20) all structure elements have dissolved. *Cytolytic effect* between antigen and cellular immunoglobulins M. Panchromatic staining.

The importance of the tonsils in cellular respect is shown by various cytological smears taken at serveral ages of life (fig. 152–155).

As the immunoglobulins remain in the lymphatic cells, a contact of antigens and antibodies in the lymphocytes provokes a cytolysis i. e. disintegration of cells. Cytolysis is a prerequisite for the necrobiotic processes in the lymphatic organs and for the formation of focuses outside the immunological regularities.

Once a focus has formed – e. g. in a tuberculous lymph-node – immunological processes are maintained from there by swept-out antigens whereas the necrobiotic focus cannot be protected by these immunizing processes because he has no intact cells and therefore no aviable immunoglobulins M. These conditions are the basis for the origin of chronic diseases deriving from focuses of necrobiosis (fig. 156, 157).

The reticulo-histiocytary (mesenchymal) defense-system

The 3rd line of defense protecting the organism is a deeply echeloned system that chiefly coats the abdominal cavities and consists of loose connective tissue; it reacts when the 2nd i. e. the thymo-lymphatic line of defense is overcome.

Morphologically, this system includes: serous teguments, leptomeninges, pleura, pericardium, peritoneum, omentum, mesenterium, coats of joints; interstice and the loose connective tissue spread over the entire organism. Cellular representatives of this system are monocytes, histiocytes and mesothelic cells. These cellular derivatives of bone-marrow, loose connective tissue and serous teguments are much identical with the so-called B-cells. The well-known term «B-cells» is ill-suited and cannot express the functional and morphological extent of the system.

Pluripotency is the functional mark of the cellular derivatives of the reticulo-histiocytary system. As part of the immunizing response of an organism, these cells produce immunocytes. In the days

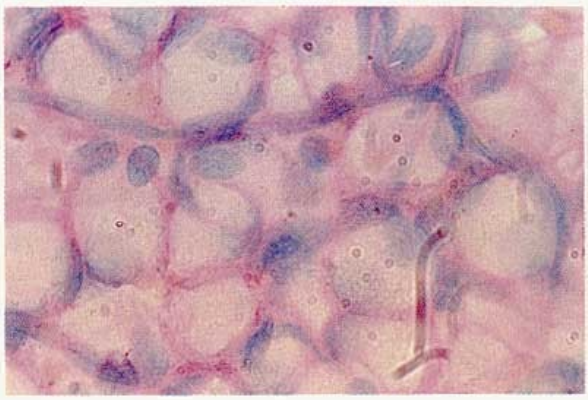

Fig. 158:
Omentum (guinea-pig, fetal) as an example of a *reticulo-histiocytary tissue*.Most of the figures of the immunological section represent derivatives of this tissue.
The methyl-green-pyronin staining provides a good reproduction of the reticular unit. The nuclei rich in DNA (greenish-blue) are located at the intersections of the network rich in RNA (red).

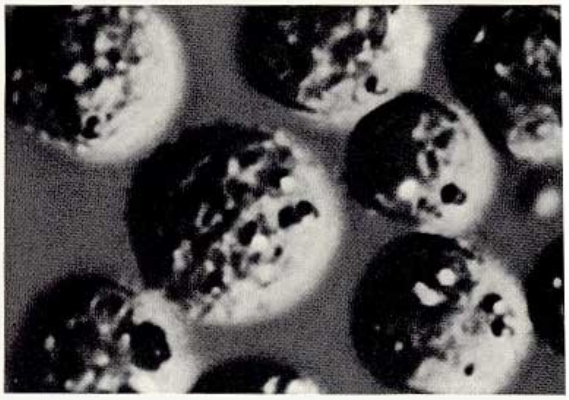

Fig. 159:
«Autonomous cells» of the peritoneal exudate with membrane activity during observation in vivo. The membrane activity expresses the taking (phagocytosis, pinocytosis) and the secretion of material (clasmatosis, secretion).

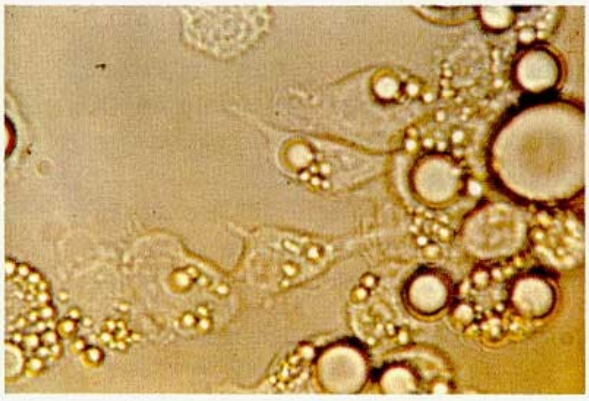

Fig. 160:
Elimination of mononuclear cells from the reticular unit. Observation in living tissue culture. Contrast of phases, 1:600.

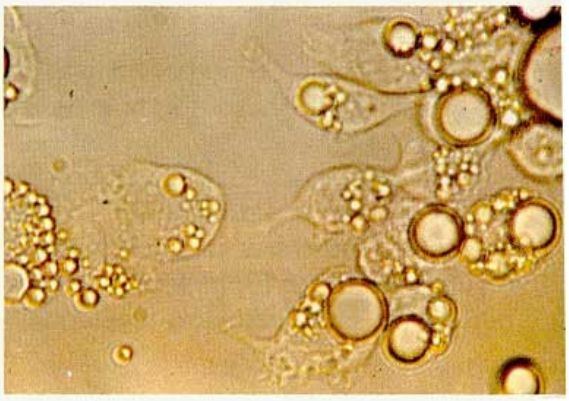

Fig. 161:
After separation of the cytoplasm bridges, the large mononuclear cells grow round in the liquid medium and show symptoms of high metabolic activity on the membrane.

after the supply of antigens, organic acids accumulate in the cytoplasm of the mononuclear cells. The cytoplasm is deeply stained by basic dyestuffs. The development of a dense net of ergastoplasm within the cellular body is an electron-optical equivalent of this process. The immunoglobulins are synthetised on the ribosomes of these tubes of ergastoplasm and then eliminated into the interstices of the ergastoplasm. These widen into cisterns, which get into contact with the surface of the cells and there eliminate the synthetised immunoglobulins into the humoral system. The process of ripening and secreting immunoglobulins takes more than 3–5 weeks, probably according to the kind and quantity of antigens.

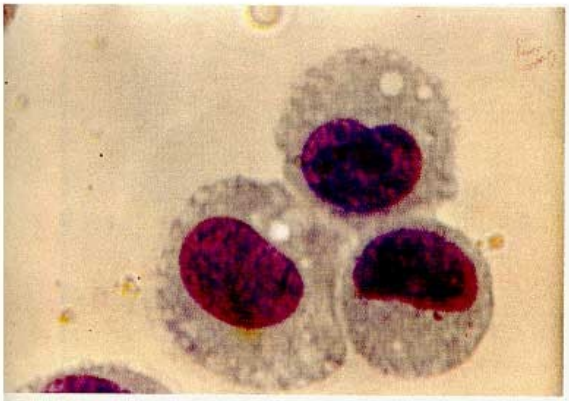

Fig. 162:
Panchromatic staining makes the mononuclear discharged from the reticular unit show the picture of the monocytes: large, loosely structured nucleus, grey-reddish-blue cytoplasm. Peritoneal exudate cells before immunisation, panchromatic colouration.

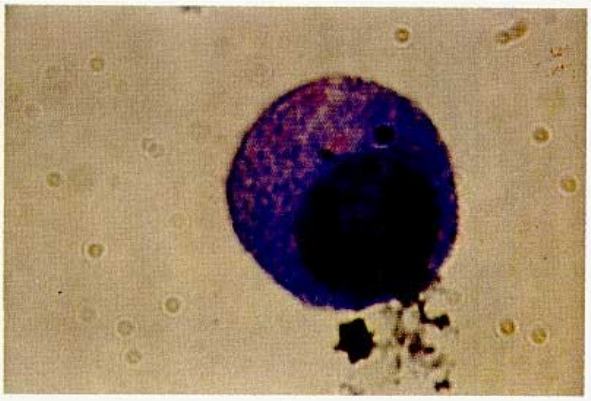

Fig. 163:
After sensitisation (here with BCG) the monocytes transform into immunocytes within 3–7 days. The deep-basophil cytoplasm is evoked by accumulation of organic acids. Panchromatic staining. Stage of the synthesis of the immunocytes.

Phases of this development of the *immunocytes* from large mononuclear cells are shown in the fig. 160–189. From these pictures it appears that a morphological uniform pattern of the immunocytes does not exist but that the shape depends on the momentary functional condition. Exaggerating, one may ask whether plasma-cells (immunocytes) produce immunoglobulins or immunoglobulins plasma-cells. The morphological changes and the various phases of the immunocytes depend on the cytochemical processes during the synthesis and secretion of the immunoglobulins.

The synthesis and secretion of the immunocytes produce above all the immunoglobulin G (IgG). As a secretion is in question, the reaction of the system is exudative i. e. the fluid is augmented. Clinical sequelae therefore are meningitis, pleuritis, pericarditis, peritonitis, arthritis, arteriitis, angiitis and interstitial inflammation. Overstrain provokes suppuration, empyema, polyserositis and sepsis (tab. 9).