# Immunological constituents

## *Antigens*

The concept «antigen» cannot be interpreted by an absolute definition but is associated with the complementary antibody. A foreign or an endogenic substance with a changed structure becomes an antigen by provoking the formation of antibodies as its structure is heterogeneous to the organism. Antigens have macromolecular structures and are found in the many categories of the biochemical substances of the animal and botanic kingdoms. In contrast to earlier views that only albuminoids had an antigenous effect, it is now taken for granted that polysaccharides, proteins, lipoids and complex compounds of these classes of substances can be antigens. Another point, however, is the macroorganism, which marks these substances as «foreign» and reacts with the formation of antibodies.

The *antigenicity* of a substance depends on its molecular weight. Substances with a molecular weight of less than 500 are usually not antigenic. Haptenes and weak antigens have molecular weights of between 5000 and 30,000, antigenic proteins however between 34,000 and 5,000,000 (KWAPINSKI). Antigenic molecules of 200–700 Å can bear up to 23 antigenic determinants.

Much as the *macromolecular vehicle* influences the antigenicity, it does little to contribute to the structure of the antibodies; the macromolecular association accounts probably for the invulnerability of the foreign substance by the enzymes of the contaminated organism. Decisive for the specificity of the resulting antibody is the smallest reacting superficial unit of the macromolecule, the so-called *«determinant group»*. The antigens occurring in nature are multivalent i.e. have several different determinant groups.

Whereas the antigenicity *(capacity of*

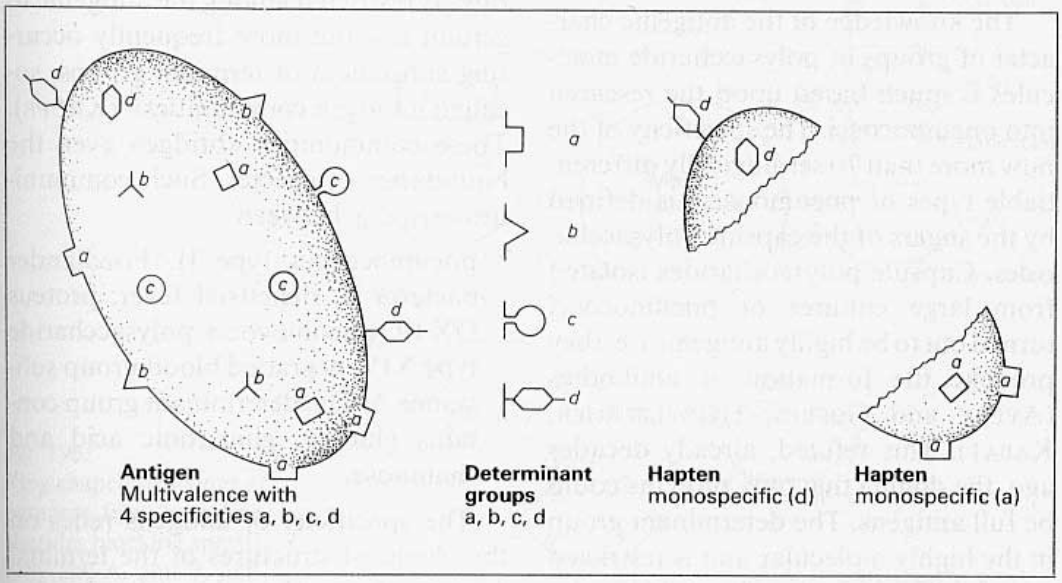



*Fig. 195:*
Antigen – determinants – hapten

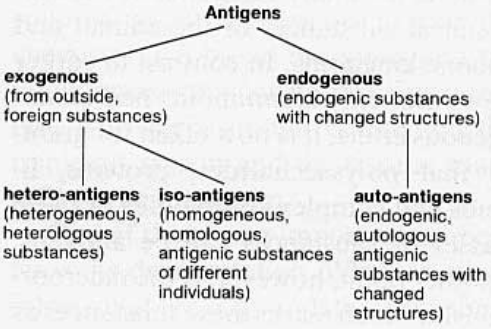
*sensitizing)* requires the macromolecule as a biochemical unit, dissociation products (or natural substances of similar structure) suffice for the reaction with the formed antibodies. These lower molecular, not antigenic but reactive, fragments of antigens (fig. 195) are called *haptenes* (from Gr. haptein = to stitch). In biochemistry, the haptenes have an analogue in the prosthetic groups of the ferments that have no fermentative activity themselves but cause the specificity of the ferment.

If the *depolymerisation* of the antigenic proteins or polysaccharides is continued i. e. if they are broken down into peptides, amino-acids, oligosaccharides or monosaccharides, they can only fill and thus block the «ecological niche» in the antibody. Thus they are capable of inhibiting the reaction between antigen and antibody.

Endogenic cells discern antigens as foreign if the enzymes of a cell have no key to «open» and to disintegrate the foreign substance. The cell as the smallest unit of organization in the higher organisms must detect the «foreign character» . However, it has to be realised that the immunological process involves cells and tissues but takes place in the molecular domain.

Origin and affinity to the organism have led to the following subdivision of antigens:

*Tab. 10:* **Division of the antigens according to their origin:**




## *Antigenic determinants*

### *Polysaccharides as antigens*

The knowledge of the antigenic character of groups of polysaccharide molecules is much based upon the research into pneumococci. The specificity of the now more than 70 serologically differentiable types of pneumococci is defined by the sugars of the capsule polysaccharides. Capsule polysaccharides isolated from large cultures of pneumococci turned out to be highly antigenic i. e. they provoke the formation of antibodies (AVERY and GOEBEL, HEIDELBERGER, KABAT). This refuted, already decades ago, the dogma that only proteins could be full antigens. The determinant group in the highly molecular unit is restricted to 1–3 (–6) terminal, «disponible», glucosidically bound sugar molecules.

The abundance of the polysaccharides is restricted among the antigenic to certain few but more frequently occurring substances of terminal groups, so-called «antigen communities» (KRÜPE). These communities «bridge» even the boundaries of species. Such communities exist e. g. between

pneumococcus type II, Friedländer bacteria B, richettsial fever, proteus OX 19, pneumococci polysaccharide type XIV, degraded blood-group substance A. The determinant group contains glucose, glucuronic acid and rhamnose.

The specificity of antigens relies on the chemical structures of the terminal groups so to speak on the molecular profile. It explains also the affinity of such

terminal groups with the human blood-group substances. There is, consequently, even for the polysaccharide antigens a bridge between the capsular substance of bacteria and cellular antigens.

The *ABO and Lewis blood-group* substances of man are *glucopolypeptides*. The specificity-determining polysaccharide has a molecular weight of 300,000–350,000 and consists of the following 4 sugar elements:

L-fucose
N-acetyl-D-glucosamin
D-acetyl-D-galactosamin
D-galactose;

the latter is coupled to non-antigenic polypeptides of 11 amino-acids, which make about 20% of the volume. In the blood-group A the N-acetyl-D-galactosamin, in the group B the D-galactose, in the group 0 the L-fucose are terminal. The Lewis-(a)-substance (MORGAU) is characterized by a determinant group – trisaccharide from N-acetyl-D-glucosamin, D-galactose at the 3rd C-atom in a beta-glucosidic compound, L-fucose at the 4th C-atom in an alpha-glucosidic compound (fig. 196).

The specificity-determining area of antigens is controlled by genes and formed from a mother substance containing all 4 sugars, which is called *«H-substance»* for its heterogeneous origin. This mother substance is found mostly in the blood-group 0.

For specificity, the following items seem to be of importance:

a) the alpha- or beta-glucosidic binding of the terminal sugar-molecule;

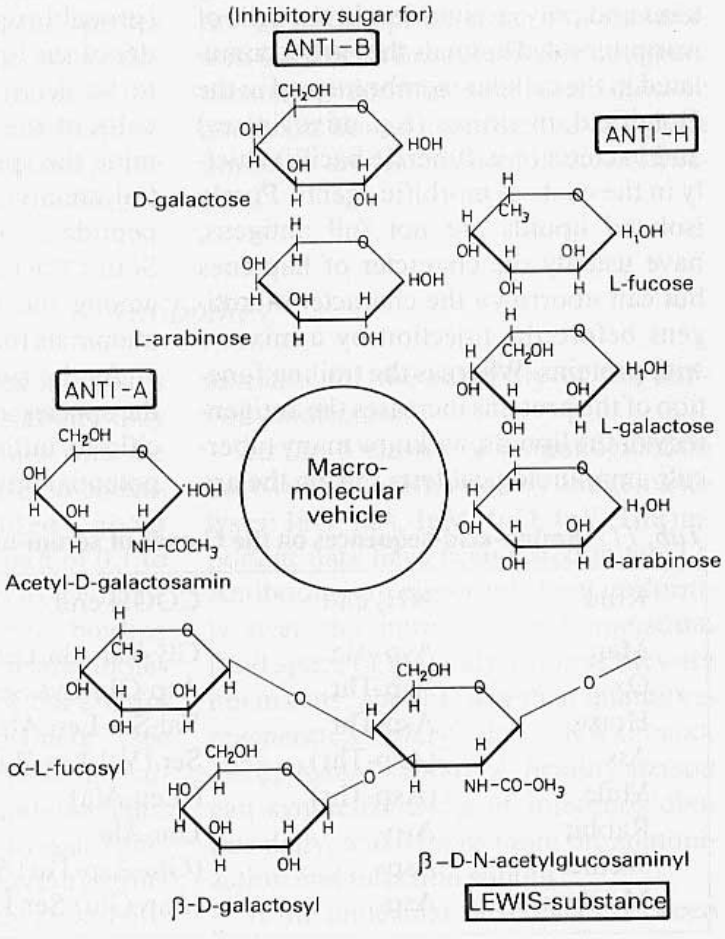



*Fig. 196:*
Ring-shaped structures of pyranose from monosaccharides blocking specifically anti-A, anti-B, anti-H; below: trisaccharide or Lewis-(a)-property.

b) the sugar must be ring-shaped (as pyranose) like in nature;
c) the cis/trans-configuration of the OH groups;
d) the d- or l-stereoisomere structure.

For salmonellae and coliform bacteria, a new class of desoxy-sugars, the 3,6-di-desoxy-sugars were found to be specificity-determining (WESTPHAL et al.). The mucous substance from Leuconostoc mesenteroides, the dextran (glucose-polymerisation product), much used in the therapy, has probably an antigenic effect through the glucoside bridges, which do not correspond to the glucogenous structure.

*Lipoids as antigens*

Lipoids occur in the living nature mostly as complex compounds with proteins and polysaccharides. In the cells of warm-blooded animals they are accumulated in the cellular membrane and in the Golgifield, in viruses (e. g. mixoviruses) and bacteria (e. g. tubercle bacilli) chiefly in the coats of morbific agents. Purely isolated lipoids are not full antigens, have usually the character of haptenes but can «borrow» the character of antigens before the injection by a mixture with proteins. Whereas the trailing function of the proteins increases the antigenicity of the lipoids, we know many tuberculo-immunological tests raising the antigenicity of the bacteria or bacterial proteins by mixing with lipoids. Between the two groups of substances, therefore, a completing antigenicity seems to exist.

A known lipoid haptene is the phosphatide acid «cardiolipin» (isolated from ox hearts) used specially in the diagnosis of lues.

*Proteins as antigens*

Thanks to the variabilities in the sequence of their building elements (24 amino-acids) and the binding, pleating and clewing of the polypeptides, proteins are structurally much more variable than polysaccharides or lipoids. However, also in this case, not the macromolecular proteins but the terminal group is the vehicle of the antigenic quality and specificity. These antigenic determinants are oligopeptides from several (probably up to 12) amino-acids. The order of the binding of amino-acids seems to be decisive, and the terminal molecules of the ends of the proteins determine the specificity more than the central amino-acids of the antigenic oligopeptides. As an example, H. E.-SCHULTZE has assembled the conditions among the serum albumins of various mammals (tab. 11).

As the protein structure is bound to the species and controlled by genes specific to individuals, the number of the potential protein antigens is incalculably

*Tab. 11:* **Amino-acid-sequences on the C-ends of serum-albumins**

| Kind | $NH_2$ end | COOH end |
|---|---|---|
| Man | Asp-Ala | Gly-Val-Ala-Leu |
| Ox | Asp-Thr | Asp-Glu-Lys-Ser-Val-Thr-Leu-Ala |
| Horse | Asp-Thr | Val-Ser-Leu-Ala |
| Ass | (Asp-Thr) | Ser-(Val-Lys-)Leu-Ala |
| Mule | (Asp-Thr) | (-Leu-Ala) |
| Rabbit | Asp- | Leu-Ala |
| Wether | Asp- | (Glu-Asp-Thr)-Ser-Val-Lys-Leu-Ala |
| Monkey | Asp- | (Asp-Glu)-Ser-Lys-Val-Leu-Ala |

high. Whether a protein really acts as an antigen depends on the individual readiness of the recipient, on the affinity, the «maturity» and on the biological situation.

*Ferments and hormones* bear their enzymatic potencies in peptide areas, which show the same sequence of amino-acids in the various species of animals. This constant sequence of the amino-acids is a prerequisite for the therapeutic efficiency of ferments and hormones from the animal kingdom in man. The biologically active areas are located in lateral chains of the protein structures specific to each species. Aberrations from the sequence of amino-acids are seen in the best analysed insulin from animals (horned cattle, pig, sheep, horse, whale) only in the 8th, 9th and 10th links of the glycyl chain whereas the terminal groupings are identical for the species mentioned. In long use, the hormones (e.g. ACTH, insulin) may certainly become antigenic, which receives expression in hyperergic symptoms and in the loss of the therapeutic effect (by disintegration or binding).

*Nucleic acids* – macromolecular polymerisation products of the nucleotides – are not complete antigens in spite of their high molecular weight up to 10 million although they bear the marks of species and individuals. The organism of mammals contains the highly molecular DNA (mol. weight 6–10 million) in the chromatin substance of the nuclei, the RNA is located in the nucleolar system and cytoplasm; it occurs soluble (mol. weight 20,000–40,000) and bound to the structure (500,000–2 million). Considering the high constituents of nucleic acid in the microbes (viruses consist of RNA, bacteriophages of DNA, higher microorganisms of both), this statement of lacking antigenicity surprises. The findings of antigenic effects of nuclear material in so-called autoaggression diseases (LE-phenomenon) are no convincing proof either. An explanation is difficult because highly antigenic substances form at once when nucleic acids are bound to proteins, and such bindings are usual in biological structures.

## *Antibodies*

Antibodies are immunoglobulins formed by antigenic stimulation; they can form complex compounds with the antigenic determinant by stereo-chemical complementarity. Sized about $34 \times 12 \times 7$ Å, only a small part of 0.1 to max. 1% of the surface falls to the niche capable of effecting a specific binding (fig. 201). The specificity of antibodies depends on the sequence of the amino-acids of the variable segment (see fig. 197) of the H-chains whereas the variable segment of the lambda-chains seems to serve rather for formal functions of the secondary and tertiary structures. Free amino-groups are apparently essential for the reactivity of the antibody molecules.

So far, 5 classes of immunoglobulin have been characterized by antigen analyses: IgG, IgA, IgM, IgD, IgE. The important data have been stated in tab. 12. Antibodies are dispersed about uniformly over the intravasal and interstitial fluid space of the body as far as they are not in cells; about 1/4 of their quantity is regenerated every day (KWAPINSKI, 1972; KABAT, 1960). A healthy person can synthetize 2–5 g of immunoglobulins daily, and 7 times more on immunization and infection stimuli.

If the molecular differences between

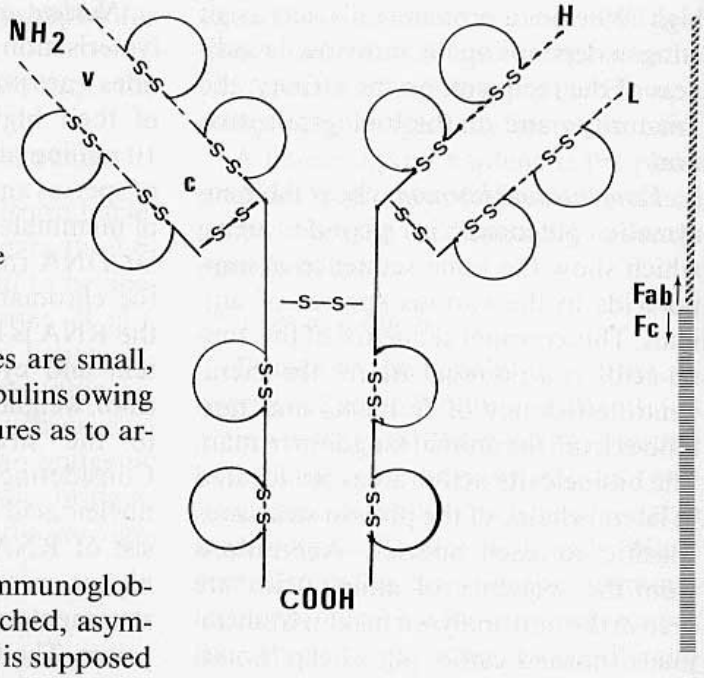



*Fig. 197:*
Diagram of an antibody molecule

various classes of antibodies are small, these are called immunoglobulins owing to their common main features as to architecture and function.

*Form and structure*

In a liquid medium the immunoglobulins have the form of stretched, asymmetric rotation ellipsoids. It is supposed that, unfolded, the IgG molecule takes a Y-shape (fig. 198), the IgM molecule a radial formation (fig. 200). The specifically reacting area makes less than 1% of the total molecular surface and is localized in a pouch-like cavity (niche) formed by the pleats of the peptide chains. The niche relief is complementary to the surface structure of the determinant group on the antigenic molecule (fig. 201–203).

The complementary molecular regions on the antigenic and antibody molecule fit into one another like a key into the lock. They are fixed by hydrogen bridges, coulomb powers and intermolecular-active van-der-Waal attractive powers (KRÜPE). As the groupings of molecules on the antibody can evidently not become the motive of antigens as long as they have not changed, it can be supposed that the antibody includes cavities depending on the structure or relief. This rule, however, has considerable exceptions (ROTHER, 1979).

Two kinds of polypeptide chains form the common ground structure of the antibody molecules. Owing to the different lengths of chains, heavy chains (= eta-chains) with molecular weights of 50,000–70,000 are distinguished from light chains (= lambda-chains) with a molecular weight of about 23,000. Every antibody molecule consists of 2 eta- and 2 lambda-chains (fig. 197) connected by disulfide bridges. The immunochemical differences owing to a different sequence of amino-acids in the eta-chains account for the classification of the 5 main classes. Immunoglobulins M are characterized by mi-chains, IgG by gamma-chains, IgA by alpha-chains, IgD by delta-chains and IgE by epsilon-chains. Of the lighter lambda-chains, 2 types, type kappa (kappa-chains) and type lambda (lambda-chains) are known.

Minor molecular changes induced the subdivision of the main classes; IgG has 4 subclasses namely $IgG_1$, $IgG_2$, $IgG_3$ and $IgG_4$ whereas IgA falls into $IgA_1$ and $IgA_2$. Genetically fixed antigen structures (e. g. Gm-, Am-factors) on the eta-chains, Inv-factors on the lambda-chains provide an additional differentiation of this subdivision (BRANDIS).

*Tab. 12:* **Characteristics of the immunoglobulins and complements factors**

| Protein class | Plasma concentration (mg/100 ml) | Molecular weight | Sedimentation constant | Biological half-life period (days) |
|---|---|---|---|---|
| Immunoglobulin G (IgG) | 800–1600 | 150.000 | 6,5–7,2 | 23 |
| Immunoglobulin A (IgA) | 90–420 | 180.000 (+ polymeres) secretory: 390.000 | 7; 9, 11, 13, 15, 17 11,4 | 6 |
| Immunoglobulin M (IgM) | 60–250 ♂ 70–280 | 950.000 | 18–20 | 5 |
| Immunoglobulin D (IgD) | 0,3–40 | 155.000 | 6,2–6,8 | 3 |
| Immunoglobulin E (IgE) | 0,01–0,14 | 196.000 | 7,9 | ? |
| $C_1$ | 2–3 | | 18 | |
| $C_{1q}$ | | | 11,1 | |
| $C_{1q}$ | | | 7 | |
| $C_{1s}$ | | | 4 | |
| $C_2$ | 1 | | 6 | |
| $C_3$ | 80–140 | | 9,5 | |
| $C_4$ | 20–40 | | 10 | |
| $C_5$ | 3–5 | | 8,7 | |
| $C_6$ | 1 | | 5–6 | |
| $C_7$ | | | 6–7 | |
| $C_8$ | | | 8 | |
| $C_9$ | | | 4 | |

The two main sections of the antibody molecule are referred to as Fab-region and Fc-region, respectively. The molecule can be split at different sites by papain, plasmin and pepsin. Within the Fab-region, the terminal part has a variable structure and is therefore called variable region (v) as distinguished from the constant region (c).

The function of the Fab-regions is to bind the antigenic determinant in the complementary variable niche. As a consequence, an antigen-antibody complex will be formed namely

a precipitation in the fluid medium,
an agglutination in antigens with corpuscular carriers (erythrocytes, viruses, bacteria),
a neutralisation when the antigen is wrapped up (neutralized) by the antibody.

With the antigens bound to the Fab-region, the structure of the Fc-region will change so that the Fc-region becomes effective to cellular (membranous) or humoral systems (complement) (fig. 204).

The chains are divided into several homologizing regions or domains. The site of the antigen binding in the Fab-region consists of 3 segments of each of 5–10 remainders of amino-acids and is very variable as to structure. This site ac-

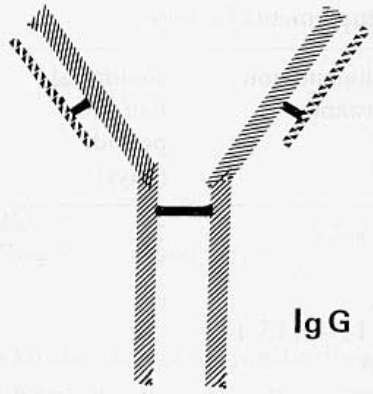



*Fig. 198:*
Diagram showing structures of an IgG molecule

counts for the specificity of the antibody. The complement is bound in the domain $C_{H2}$, the interaction with the Fc-receptor on cellular surfaces depends on $C_{H3}$ (RIESEN and BARANDUN). IgM and IgE contain $C_{H4}$ as a further domain.

*Biology and biochemistry of the antibodies*

Antibodies are palliative structures «wrapping up» foreign substances and estranged endogenic substances so as to render them biologically inert. They appear when appropriate enzymes lack in the body so that the antigenic substance cannot be disintegrated and conveyed into the body's metabolic tracts.

The daily rate of transformation of the gammaglobulins is estimated by KRÜPE at about 35 mg/kg of bodyweight; but this figure is probably a very approximate value. The rate of transformation is certainly lower for the baby and higher for the school-child than this rough estimate applying to the adult.

The expectation of life for the gammaglobulins is expressed by the following half-life periods:

23 days in man,
21 days in cows,
8 days in dogs,
5 days in rabbits,
4.5 days in guinea-pigs;
2 days in mice.

The essential biochemical and physical data have been summarized in tab. 12.

*Immunoglobulin G (IgG)*

With a share of 80% in the total depot of immunoglobulins, IgG is the most important; IgG occurs preferably in body fluids and placenta and is taken up by the new-born via the intestinal mucosa from the colostrum. It can form compounds with complement, bind to macrophages and seems to have special affinities to bacterial toxins.

*Immunoglobulin A (IgA)*

IgA, with a share of 13%, is the second important of the immunoglobulins. It occurs in the serum as a 7S-monomer, but with a polypeptide rich in cystein, the so-called xi-chain, it forms polymers. IgA is synthetized by immunocytes and

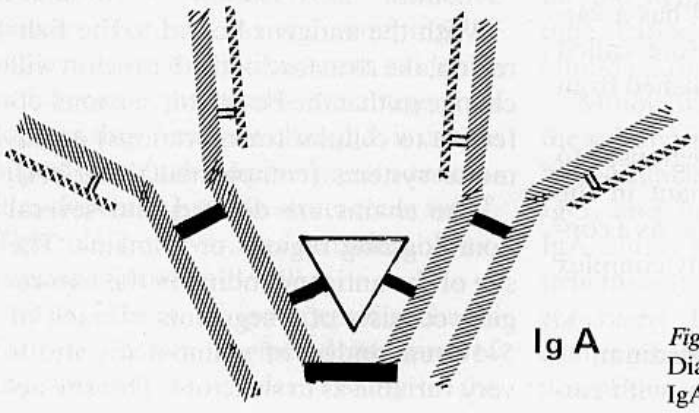



*Fig. 199:*
Diagram showing structures of an IgA molecule

excreted in a dimeric form. It is found concentrated in the secretions of the body's epithelial interfaces, especially in the saliva, lacrimal fluid, nasal secretion and in the mucous layers of the respiratory and gastrointestinal tracts. It is supposed that a synergism exists between IgA, lysocyme and complement for the destruction of colibacilli. Aggregated IgA is capable of binding to polymorphic nuclear leukocytes and, unlike the classical complement-activation (fig. 204), of activating the so-called $C^3$-sideway (ROITT).

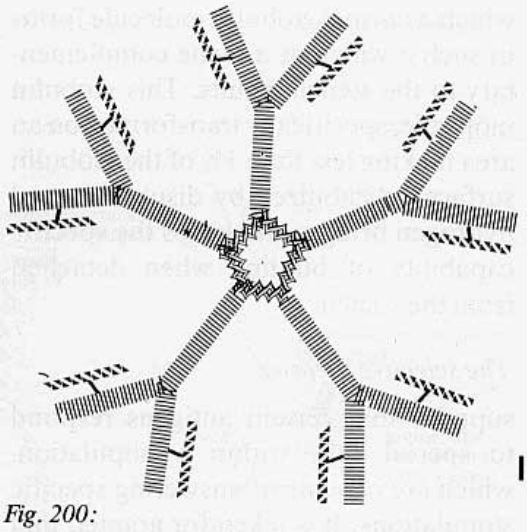



*Fig. 200:*
Diagram structures of an IgM molecule

*Immunoglobulin M (IgM)*

Owing to its high molecular weight of 900,000 and 19 S sedimentation constant, IgM is also called macroglobulin-antibody. The polymerisation of the basic unit depends, also in this case, on the presence of a xi-chain. In small antigens, the binding valence is 10, in larger antigens 5. Thanks to their high binding valence, these antibodies tend very much to agglutination and cytolysis. Topographically, the location in the cells of the lymphatic tissues must be mentioned. The IgM-antibodies include: the isohaemagglutins (anti-A, anti-B), antibodies against the typhoid-0-antigen (endotoxin) and the antibodies in Wassermann's lues reaction.

*Immunoglobulin D (IgD)*

The percentage of IgD is about 1% of the immunoglobulins. The biological function is not yet clear. IgD was found on the surface of lymphocytes in the venous blood of the umbilical cord. It is believed that receptors, which are later conveyed to other immunoglobulins, may be present.

*Immunoglobulin E (IgE)*

IgE, making 0.002% of the globulin reservoir and concentrated 17–450 ng/ml, seems little important as to its quantity but belongs to the most notable immunoglobulins with regard to the clinical effects. IgE makes receptors on the cellular membrane bind to the complement system and thus initiates the output of histamin from basophils and mast-cells (fig. 194, 204). Large quantities are found in parasitosis, especially worm diseases, in allergic rhinitis (pollinosis) and bronchial asthma.

## *Theories of the formation of antibodies*

As the exact course of antibody-synthesis is not known because it takes place beyond optically controllable molecular sizes, much has been theorized about this subject. Beginning from Ehrlich's «side-chain» theory, many versions of instruction-, selection- and seed-leaf theories came and disappeared. The mental substance of those theories will be outlined hereafter.

*The instructive theories*

maintain that the antigen (or its determinant) acts as a stencil, around

which a normal globulin molecule forms in such a way that a niche complementary to the stencil results. This globulin molecule, specifically transformed on an area making less than 1% of the globulin surface, is stabilized by disulphide and hydrogen bridges and keeps the specific capability of binding when detached from the stencil.

*The selective theories*

suppose that certain antigens respond to special cells within a population, which are capable of answering specific stimulations. It is taken for granted that the information for the synthesis of certain antibodies exists already in the genetical material of these reacting cells. The code contained in the gene is said to be just called by the antigen so that the cells are selected by this code to form certain antibodies (Klon's selection theory).

*The germe-layer theory*

presumes that the genomes of the antibody-forming cells have the code for all antibody specificities so that these need just to be called by an antigen stimulation; this theory relies on pluripotent cells.

*The quantum theory*

of the immunogenesis (KWAPINSKI, 1972) regards the immunogenous stimulation as a transmission of an energy quantum from an inductor molecule to a growing globulin molecule, which is more flexible than ripe globulins.

The selective theories favoured in recent years offend against a fundamental immunological law: antibodies are produced against substances that an organism cannot process metabolically for lack of appropriate enzymes (= genes). EHRLICH's papers already have shown that antibodies are formed against substances (such as dinitrobenzol or sulphanilic acid) that do not occur in the living nature; consequently, a genetic basic information resulting from phylogenesis can hardly exist. The mobilized potential of immunocompetent cells depends on the quantity and kind of antigens rather than on other factors. Needless to say that transformed cells form a functional unit upon an antigenic stimulation. The cellular clonus does not exist primarily, it comes about through the functional community.

The following must be stated:

1. Antibodies are formed by pluripotential cells, which have a special synthetic function.
2. The cell transformation goes through a ripening phase and a longer secretion phase.
3. The production of antibodies is associated with an increase in RNA.
4. The synthesis is induced through m-RNA.
5. The light (lambda-) chains are formed on small ribosomes, travel to large poly-ribosomes where the heavy eta-chains are formed slowly.
6. Antibody synthesis is a cellular «de novo» synthesis.

## *Antigen-antibody relations*

Only fragmentary knowledge exists about the many relations between antigens and antibodies. It is supposed that the higher molecular antibodies (e.g. 7-S-antibody-gammaglobulins) carry at best 2 reactive molecular groups, which can correlate with the antigen determinants. The reactive areas are probably distant, perhaps at the ends of the globulin ellipsoids. Antibodies with one reac-

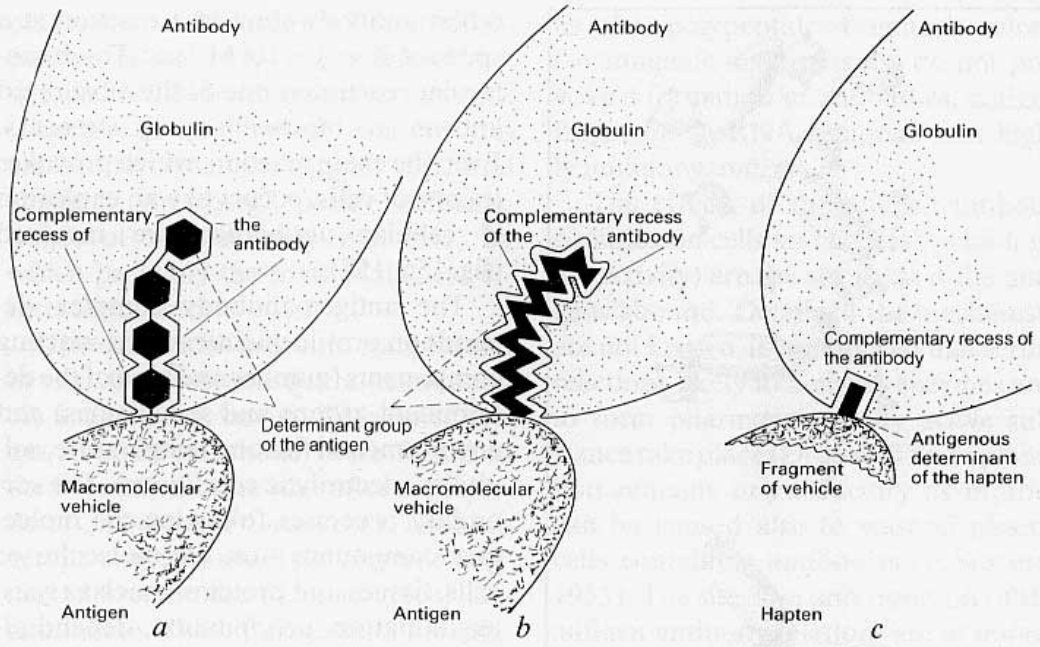



*Fig. 201:*
Spatial relations between antigenous determinants and antibody-globulins; (a) symbolizes an oligosaccharide, (b) a peptide chain, (c) a hapten with determinant.

tive surface are called «monovalent», those with two reactive surfaces «bivalent».

The reactive area is estimated to measure 700–1000 Å, which corresponds to about 1% of the surface of a 7-S-antibody-gammaglobulin. The supposed shape is a pouch-like, peripheral dent in the peptide clusters of the globulin molecules, which is stereochemically complementary to the superficial profile of the determinant group on the antigen molecule. The spacious complementarity is fixed in the antigen-antibody reaction by hydrogen bridges, *coloumb powers* between $NH_2$- and COOH-groups as well as intermolecular *van-der-Waal's electric* powers. The binding condition, however, can be dissolved by many chemical and physical effects.

As long as the antibodies are strictly specific, they probably cover the entire determinant group of the antigen (1–12 molecules), later sometimes only the terminal molecule. This «blurs» the specificity, hyperergy and immunity (so-called cross-immunity) are extended i. e. involve several antigens. In clinical immunopathology, this phenomenon becomes important in the increased sensitisation of the adult allergic patient.

Gammaglobulins carry one (monovalent) to two (bivalent) reactive areas. It has not yet been proved whether the higher molecular $beta_2$- globulins carry more reactive areas and more specificities, but their multiplication in chronic diseases accompanied by polyvalent hyperergia suggests so.

*Antigen-antibody complexes*

When antigens and antibodies meet in a solution with equal or similar complementary reactive areas, a specific complex will arise. This antigen-antibody complex is the basis of the definitions and of the customary serological and immunological methods. The antigen-antibody compound takes place at an incredible speed. Tests by SINGER using a simple haptene and a purified

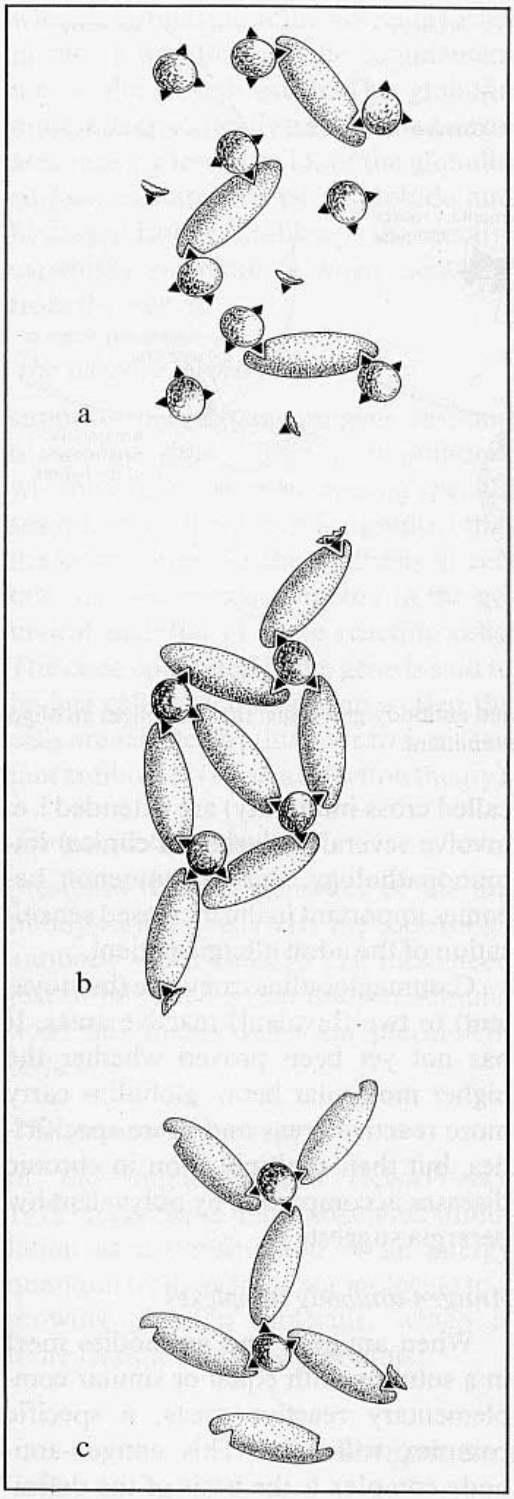



*Fig. 202:*
Quantitative proportions of antigen/antibody.
a: Surplus of antigens.
b: Ideal, well poised proportion.
c: Surplus of antibodies.

rabbit antibody showed a reaction at a speed of $K = 1 \times 10^8\ M^{-1}$ sec. This bimolecular reaction is one of the most rapid known in biochemistry (CAMPBELL). Even the chain reaction, which provokes lesions of cells, occurs like an explosion if cellular antibodies are involved (fig. 156, 157).

The antigen-antibody complex depends on profile qualities of the reacting components (number and kind of the determinant groups and specificities) and environmental factors (temperature, solubility, electrolytic conditions). The secondary processes following the molecular compounds – on the molecules or cells, tissues and proteins – such as lysis, agglutination, precipitation, depend also on environmental conditions. Of decisive importance, however, is the quantitative proportion between antigen and antibodies (reacting components) from which the following possibilities result (CAMPBELL, SINGER, CUSHING and CAMPBELL):

1. Antigen is abundant, not all antigen-reactive areas are bound. The situation is similar for haptene or abundance of antigen-haptene (fig. 202a).
2. The quantities of antigen and antibodies are equivalent and form a saturated complex (fig. 202b).
3. The antibodies are abundant; all antigens and haptenes are bound, excessive antibodies still free (fig. 202c).

In precipitational reactions of dissolved antigens and antibodies in vitro, these quantitative reactivities appear in 3 zones (CAMPBELL). The antibodies have 2 reactive areas so that usually 1 antibody molecule binds 2 antigen molecules. This proportion $Ag_2$ : Ak is a biologically inactive complex. Also in molecular groups, the number of the antibody molecules is smaller than the antigenic molecules ($Ag_x > AK_y$). The com-

plex is dissociable at pH 3.5. Even a proportion of $Ag_3 : AK_2$ is biologically active and binds complement (ISHIZAKA). Changes of the optical rotation (increased levorotation) suggest structural changes (stretching? plastic deformation?) of the antibody molecule, by which probably the toxic biological effects are caused.

The conditions are more complicated in vivo. Considerable quantities of soluble antigen (e.g. bovine $S^{35}$-labelled serum-albumin in rabbits) were found in the liver at least one year after the injection (GARVEY and CAMPBELL). The antigen persists as a small polypeptide fragment about the size of an «antigenic determinant». These fragments of the original antigen molecule are bound to soluble ribonucleic acid (Ag + s-RNA) and probably play a decisive part for the further production of antibodies, more so because they carry some protein. Whereas the polypeptide fragments alone (= antigenic determinants) do not provoke a formation of antibodies, antigen fragments + RNA compound are highly immunogenic.

The effects of the antigen-antibody complex on cells and tissues (= biological activity) are the strongest if the antigens abound. Details of the mechanism are not known, it is supposed that serum reactions likely to activate enzymes and to form pharmacologically active substance take place (DIXON). This explanation remains unsatisfactory as injuries can be caused also to washed plasma cells containing antibodies (F. SCHMID, 1953). The site, size and duration of the antigen-antibody relations are of importance for the clinical effects; especially plasma cells, serous membranes, unstriated muscles and endothelia are sensitive.

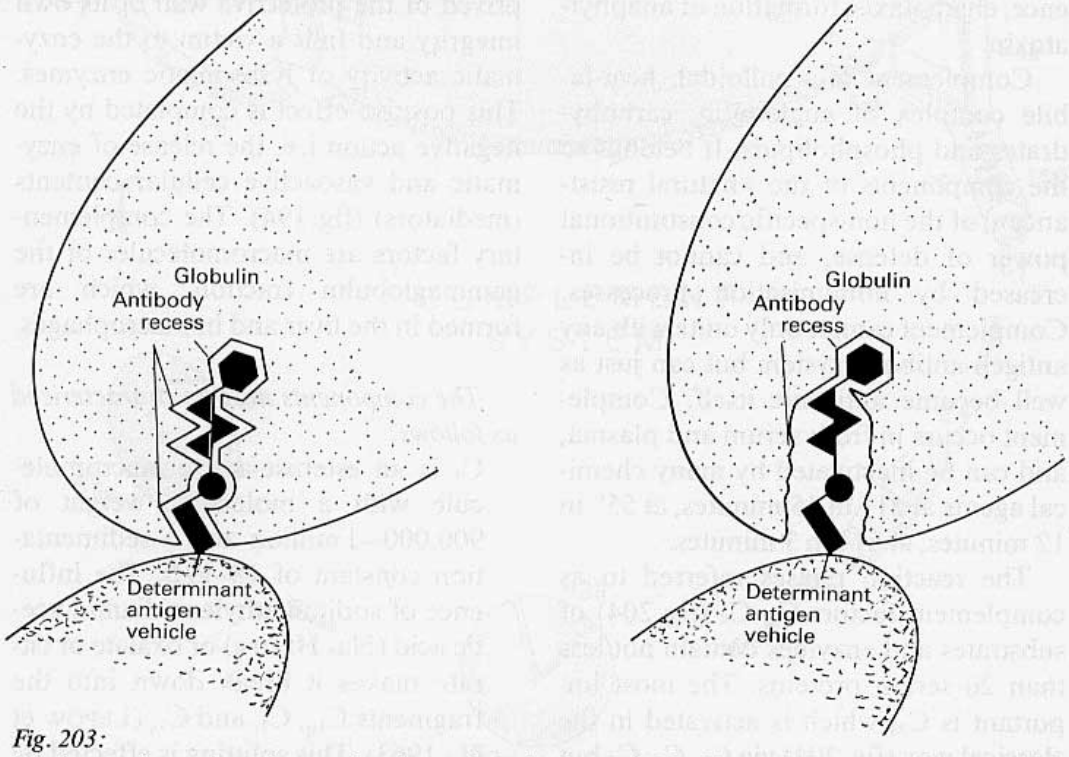



*Fig. 203:*
Plastic transformation of a complex determinant by the antibody (a); «enlargement» of the specificity. As the relief of the recess flattens, the antibody remains specific only for the terminal sugar molecule but can now respond also to all other antigens possessing such a terminal sugar ring.

## *The complement system*

*Besides the cellular synthetic system and the humoral transportation and distributing mechanisms, the complement system forms the third characteristic chain of reactions of the immune system;* cellular and humoral factors concur in a cascade-like chain reaction. As part of the antigen-antibody interrelations, the complementary system has a complex relay function. As the components are known, the former definition as «cytotoxic activity» of the serum has turned out to be a partial aspect, but there are more effects and secondary processes. Besides the cytotoxicity with subsequent immunocytolysis, the complement has the capacity of dissolving bacterial walls. Intermediary products and split fractions perform during the chain reaction essential immunobiological functions such as phagocytosis, immune adherence, chemotaxis, formation of anaphylatoxin.

Complement is a colloidal, heat-labile complex of euglobulin, carbohydrates and phospholipids. It belongs to the components of the «natural resistance», of the non-specific constitutional power of defense, and cannot be increased by immunisation processes. Complement cannot only unite with any antigen-antibody system but can just as well become antigenic itself. Complement occurs in fresh serum and plasma, and can be inactivated by many chemical agents at 51° in 35 minutes, at 55° in 12 minutes, at 61° in 3 minutes.

The reaction phases referred to as complement factors $C_1$–$C_9$ (fig. 204) of substrates and enzymes contain not less than 20 serum proteins. The most important is $C_3$, which is activated in the classical way (fig. 204) via $C_1$, $C_2$, $C_4$ but can just as well act through a short circuit. $C_3$ decomposes into the active component $C_{3a}$ and the component of continued activation $C_{3b}$. The latter has multidimensional effects: it promotes the integration of $C_5$–$C_9$ into the complex of cytolytic effects, but also activates the formation of serum proactivators and can split into the fragments $C_{3e}$ and $C_{3d}$, which are said to have the function of inactivators in the complement regulation. The enzyme activities $C_5$–$C_9$ can, in this completion, break defects of substance into the cellular and bacterial membranes and thus enable the cellular contents to extravasate into the extracellular fluid spaces.

The main function of the complement is «to break holes into the membranes» i. e. membranes foreign to the body (bacteria) or endogenic, antibodies carrying cell membranes. With the cell membrane lost, the bacterium (or the cell) is deprived of the protective wall of its own integrity and falls a victim to the enzymatic activity of lysosomatic enzymes. This positive effect is completed by the negative action i. e. the release of enzymatic and vasoactive cellular contents (mediators) (fig. 194). The complementary factors are macromolecules of the gammaglobulin fraction, which are formed in the liver and in macrophages.

*The components may be characterized as follows:*

$C_1$ is an esterase-active macromolecule with a molecular weight of 900,000 – 1 million and a sedimentation constant of 18–19 S. The influence of sodium ethylene diamin acetic acid ($Na_3$ HEDTA) or oxalate or citrate makes it break down into the fragments $C_{1q}$, $C_{1r}$ and $C_{1s}$ (LEPOW et al., 1963). This splitting is effected by uniting with calcium ($Ca^{++}$); the 3 fragments can be recombined only

by the intervention of calcium. $C_1$ unites with an antibody molecule of the cellular surface.

Activated $C_1$ has the function of an activated esterase, which starts up the components $C_4$ and $C_2$. The acting factor is the fragment $C_{1s}$, the substratum is $C_4$. With the essential participation of magnesium ($Mg^{++}$), $C_2$ is formed. $C_2$ disintegrates rapidly and initiates the complement-fixation reaction to $C_9$. $C_2-C_4$ set a complex enzyme of $C_3$ convertase, which catalyses the adsorption of $C_3$ to the cell membrane.

The $C_3$ component consists of at least 4 fragments: $C_{3b}$, $C_{3c}$, $C_{3e}$, $C_{3f}$. $C_3$, $C_5$, $C_6$ and $C_7$ form a thermostable intermediary product, the membranolytic effect comes on only with the completion by the factors $C_8$ and $C_9$. The terms $EAC_{1a,4,2a,3}$, which are used frequently, mean complement erythrocyte complex (E = erythrocytes of sheep; A = antibody; C = activated complementary factors), whose reaction product is $EAC_{1a,4,2a,3,5,6,7}$.

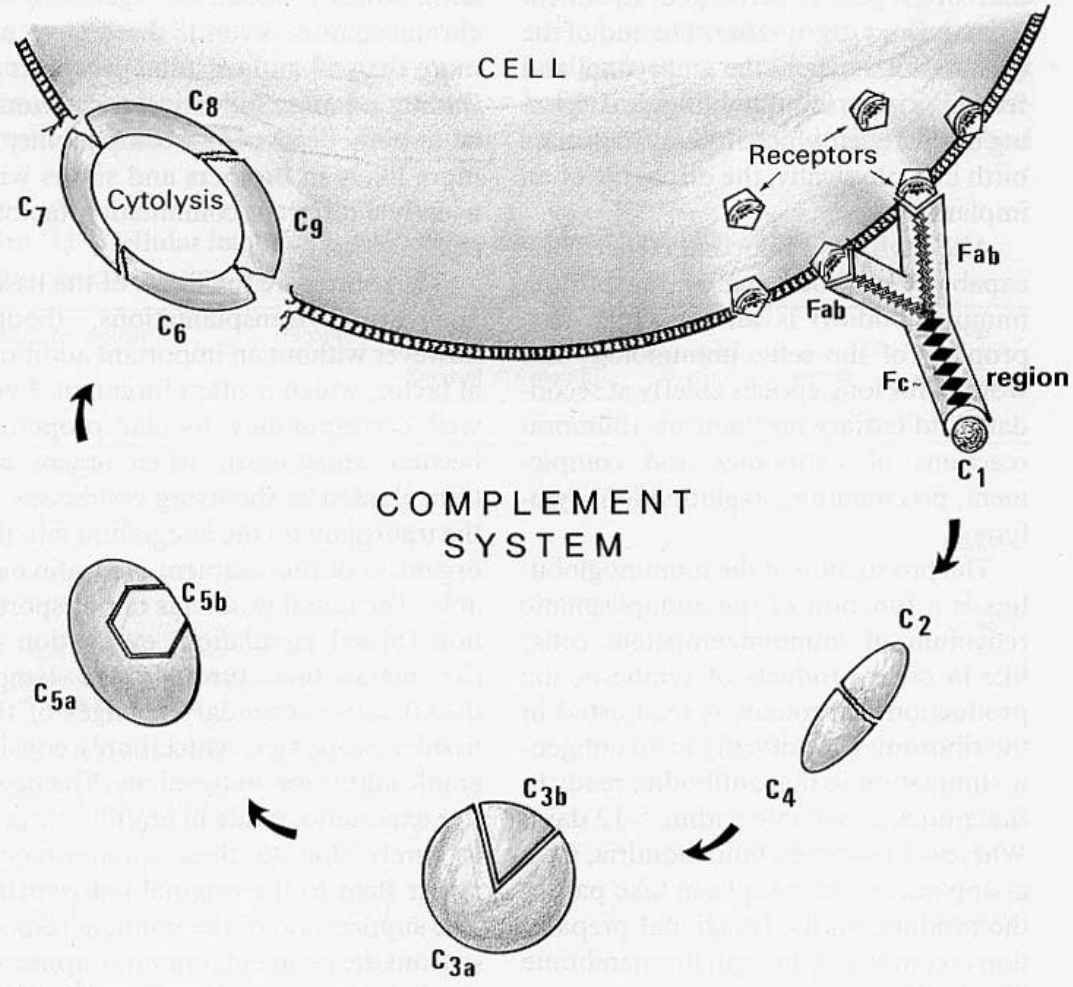



*Fig. 204:*
Complement system (for particulars see text)

## *Immun-deficiencies*

Immunobiological mechanisms serve for the preservation of the biological character and integrity, and therefore are obligatory properties of independent life. Rudiments of a cellular immunity occur in the human fetus after the 10th week of pregnancy, humoral antibodies about the 20th week of pregnancy, immunological maturity is reached about birth till 9 days thereafter. Physiologically, the fetus (which consists of maternal and paternal tissular structures and is regarded as a foreign implant according to immunological cliché interpretations and ought to be discharged) is tolerated and even gets a privileged treatment from the host, the mother. The end of the immunotolerance in the embryonal and fetal time is the immunobiological ripening of the fetus, which is likely to initiate birth i. e., physically, the discharge of an implant.

Although immunocompetence (the capability of producing or transporting immune bodies) is an autochthonous property of the cells, immunology has worked for long epochs chiefly at secondary and tertiary mechanisms (humoral reactions of antibodies and complement, precipitation, agglutination, cytolysis).

The production of the immunoglobulins is a function of the endoplasmatic reticulum of immunocompetent cells; like in other products of synthesis, the production of proteins is readjusted in the ribosomes specifically to an antigenic stimulation so that antibodies ready to function are available within 7–12 days. Whereas ribosomes, mitochondria, Golgi-apparatus and cytoplasm take part in the production, the functional preparation is completed through the membrane of cytoplasm.

The properties of the human blood-groups (A, B) are coupled to the membrane of the erythrocytes; here, foreign blood-groups are discerned, antigen-antibody reactions take place, as agglutination or as haemo- (better: erythrocyto-) lysis.

Other antigens are discerned and answered by the mononuclear cells (usually referred to simply as lymphocytes). Best known and characterized is the so-called HLA (human lymphocyte antigen) system. The most important of these more than 60 antigens known so far (D. NIETHAMMER, 1979) is the major histocompatibility complex (MHC system), which is coded on 4 genes of the chromosome 6. Even if there were not more than 60 antigens, the prospects of finding a donor of identical tissue would be extremely low. The compatibility is more likely in brothers and sisters with usually 4 different combination factors, best in twins.

These then are the limits of the tissue and organ transplantations, though however without an important additional factor, which is often forgotten. Even well corresponding tissular properties become antagonistic when organs are transplanted as the living conditions of the transplant till the integration into the organism of the recipient are unfavourable. The initial problems of transportation (blood circulation, evacuation of the metabolites through the lymph ducts) cause secondary changes of the tissular properties, which imply considerable additional antigenicity. The negative experience made in grafting surgery is surely due to these circumstances rather than to the original antigenicity. The suppression of the immune response from the recipient, immunosuppression, is a necessary though not the best conclusion from this situation.

*Forms of the cell implantations*

The clinical application of cell implantations in innate immunodefects has kept abreast of the development of theoretical knowledge. According to a survey by D. NIETHAMMER, 1979, implantations in 69 children with serious combined immunodefects had been conducted by that time. Table 13 contains a summary of the tissues used, complications and rate of survivals.

It appears that so far mostly HLA genotypically identical bone-marrow, HLA phenotypically identical bone-marrow, HLA-D-identical and non-identical bone-marrow, fetal tissue of the liver, of the thymus or of both were used. As far as can be judged from results obtained and from the discharging reaction, the compatibility of fetal tissues, which need not be identical, is not more unfavourable than in genotypically identical bone-marrow, and more favourable than in phenotypically identical bone-marrow and non-identical bone-marrow.

As the possibility of obtaining genotypically identical tissues from brothers and sisters, other members of the family or twins is rather restricted, the problem can be solved by means of fetal tissues from the liver and thymus. Recent experience has shown that the fetal tissues are tolerated the better the earlier the stages of fetal growth from which they originate.

*Immunobiological life-profile*

The physiological development of the immunocompetence in man is characterized by lacking or insufficient immunity before birth, by a maturing period of immunological defense during childhood

*Tab. 13:* **Cellular implantations in severe combined immunity defects** (after NIETHAMMER, 1979)

| Group/transplant | Transpl. | Transpl. | Graf-versus-host-reaction[a] Survival < 6 months 0–+ | Survival < 6 months +++–+++ | Survival > 6 months 0–+ | Survival > 6 months +++–+++ | Survival after 6 months |
|---|---|---|---|---|---|---|---|
| I HLA-genotypically identical bone-marrow (brothers and sisters, other relatives in inbreeding) | 16 | 18 | 1 | 3 | 8 | 2 | 10/16 = 63% |
| II HLA-phenotypically identical bone-marrow | 4 | 4 | 2 | 4 | 3 | 2 | 5/13 = 38% |
| III HLA-D-identical bone-marrow with incompatibility of the HLA-A and/or HLA-B-locus | 9 | 23 | | | | | |
| IV HLA-D-non-identical bone-marrow with/without incompatibility of HLA-A and/or HLA-B-locus | 19 | 27 | 3 | 7 | 1 | 0 | 1/19 = 5%[b] |
| V Fetal organs | 21 | 30 | 3 | 2 | 7 | 2 | 9/21 = 43%[c] |
| Fetal liver | 8 | 14 | | | | | |
| Fetal thymus | 11 | 14 | | | | | |
| both | 2 | 2 | | | | | |
| **Total** | 69 | 102 | – | – | – | – | 25/69 = 36% |

*Tab. 14:* **Primary Immun-insufficiencies**

| Type | Supposed location of the cellular defect in stem cells | B-cells | T-cells |
|---|---|---|---|
| Severe combined insufficient immunity | | | |
| a) autosomal-recessive | + | + | + |
| b) x-bound | + | + | + |
| c) sporadic | + | + | + |
| Insufficient immunity with generalised hematopoietic hypoplasia | + | + | + |
| Insufficient immunity with short-membered nanism | + | + | + |
| Insufficient immunity with thrombocytopenia and eczema (Wiskott-Aldrich-syndrome) | | + | + |
| Insufficient immunity with Ataxia teleangiectatica | | + | + |
| Insufficient immunity in thymoma | | + | + |
| Insufficient immunity with normo- or hyperimmunoglobulinaemia | | (+) | (+)(−) |
| Infantile X-bound agammaglobulinaemia | | + | |
| Selective lack of immunoglobulin (IgA) | | +(−) | |
| X-bound insufficient immunity with hyper-IgM | | +/− | |
| Transitory hypogammaglobulinaemia in babies | | + | |
| Thymus hypoplasia (Di George-syndrome) | | | + |
| Episodical lymphopenia with lymphocytotoxin | | | + |

up to a biological culmination in the 9th–12th years, by a slowly declining plateau in adults and a growing decrease in higher periods of life. This profile includes:

1. the immunotolerance in the embryo and fetus;
2. the insufficient immunity in the baby, which is compensated towards the end of the second year;
3. the immunological ripening and period of maturity;
4. the increasing senility beyond the 40th and 50th years of life;
5. the senile immunoparalysis at the end of biological existence.

*Division of the immunodeficiencies*

Only innate defects of the immunosystem are often denoted as immunodeficiencies. The acquired immunodebilities, however, are certainly not only more frequent but, practically, more important. To meet the plurality, the immunodeficiencies must be divided into the following groups:

*Immunodeficiencies*

1. physiological immunodeficiencies
2. innate immunodeficiencies
   a) primary
   b) secondary
3. transitory immunodeficiencies caused by
   a) nutritive influences
   b) infectious diseases
   c) chemical substances
   d) physical noxae (radiation).

A special group must be mentioned:

4. artificial immunodegradation (immunosuppression)

*Innate immunodeficiencies*

Innate immunodebilities can result from a universal insufficiency of the mesenchymal defense mechanism or selectively influence various components of the same.

*Tab. 15:* **Organismic mesenchymal weakness and decrease of immunity**

1. Immaturity of the mesenchyme (immature new-born, premature children)
2. General mesenchymal hypoplasia (general weakness of the connective tissue, Osteogenesis imperfecta, Down-syndrome)
3. Decrease of the volume of immunocompetent tissues (osteosclerosis, marble-bones, storage-reticulosis, systemic malignoma of the bone-marrow)
4. Runt's disease

Tab. 16: **Defective material for the formation of antibodies**

**1. Insufficient supplies**
Qualitative false nutrition or quantitative insufficient nutrition; dystrophy, atrophy, kwashiorkor, nutritional faults by overfeeding infants with carbohydrates, lack of vitamins

**2. Defective absorption**
a) by lack or absence of ferments (mucoviscidosis)
b) by inflammatory (enteritis, enterocolitis) or allergic (Coeliakia, intestinal allergy) alteration of the intestinal epithelium
c) by mechanic lesions of the intestinal wall in abnormalities (stenosis, atresia, megacolon)

**3. Disturbed intracellular metabolisation**
in enzymopathies and storage disorders, hypothyreosis, Diabetes mellitus

**4. Increased loss**
a) enteral syndrome of protein loss
b) loss of renal proteins (nephrosis)
c) loss of vascular proteins (extensive bleedings, subdural haematoma, transudates, Shwartzmann-Sanarelli syndrome, Waterhouse Friderichsen syndrome, haemolytico-uremic syndrome)

Selective innate insufficiency of the resistance to infection is due to an insufficient production or mobilisation of immunoglobulins. The stimulation of antigens provokes inadequate concentrations of antibodies in the immunocompetent cells or in the humoral system: either (a) through lacking or deficient cellular synthesis, or (b) through insufficient elimination from the cells.

Clinically, blood findings with leukopenia, anemia, thrombocytopenia suggest a general insufficiency also of the immunoapparatus, the deficiencies can be demonstrated by substantiating a deficit of humoral antibodies (IgG deficit) whereas the serum concentrations of IgM and IgA reflect only indirect the cellular deficiency.

The defense against infection (especially against extracellular microbes) is reduced, the surfaces exposed to the environment (respiratory passages, gastrointestinal tract, skin, urinary passages) tend to recurrent and, partly, serious and fatal infections. The degree of the lowered resistance to infection is decisive for the prognosis and thus for life expectancy.

The aspects shown in tab. 14 have been established according to a division of the primary innate immunoinsufficiency prepared by a WHO-committee. Corresponding to the modern immunological conception, the cellular defects are classified after the supposed site of the defect in the parent cells, B-cells and T-cells.

These primary innate immunoinsufficiencies should be regarded in contrast to the secondary immunoinsufficiencies. These forms summarized in tab. 15 are systemic dysfunctions of the vascular-connective tissue apparatus, and the de-

crease of the immunoresistance is, symptomatologically, unimportant but constitutes a partial symptom of the whole illness.

*Transitory immunodeficiencies*

*Nutritive influences*

The synthesis of immunoglobulins requires a hardly surveyable number of cellular metabolites, which partly go into the balance and become structural elements, in their majority have a temporary, but essential, importance as catalysts. Among them are nucleic acids (RNA), magnesium, calcium, iron, zinc and phosphorus compounds. Lack of these substances necessary for the formation of antibodies prevents a sufficient synthesis. A deficit, therefore, may result if the supply is insufficient, the absorption does not suffice, the intracellular metabolism is disturbed and excessive quantities of metabolites are lost. Tab. 16 gives a survey of the clinical forms.

*Infectious influences*

The immunoresistance, which depends on the age and individual properties, can be overstrained by casual infection or artificial infectional strain (inoculations). The result of such a coincidence of illnesses is transitory immunodebilities as incidental occurrences. Three basic constellations must be distinguished:

1. Intact systems of defense are overcharged by the coincidence of infections and become insufficient. The coincidence of a chronic disease (tuberculosis) with an acute infectious disease (e.g. measles, influenza, chickenpox) is the clinically most

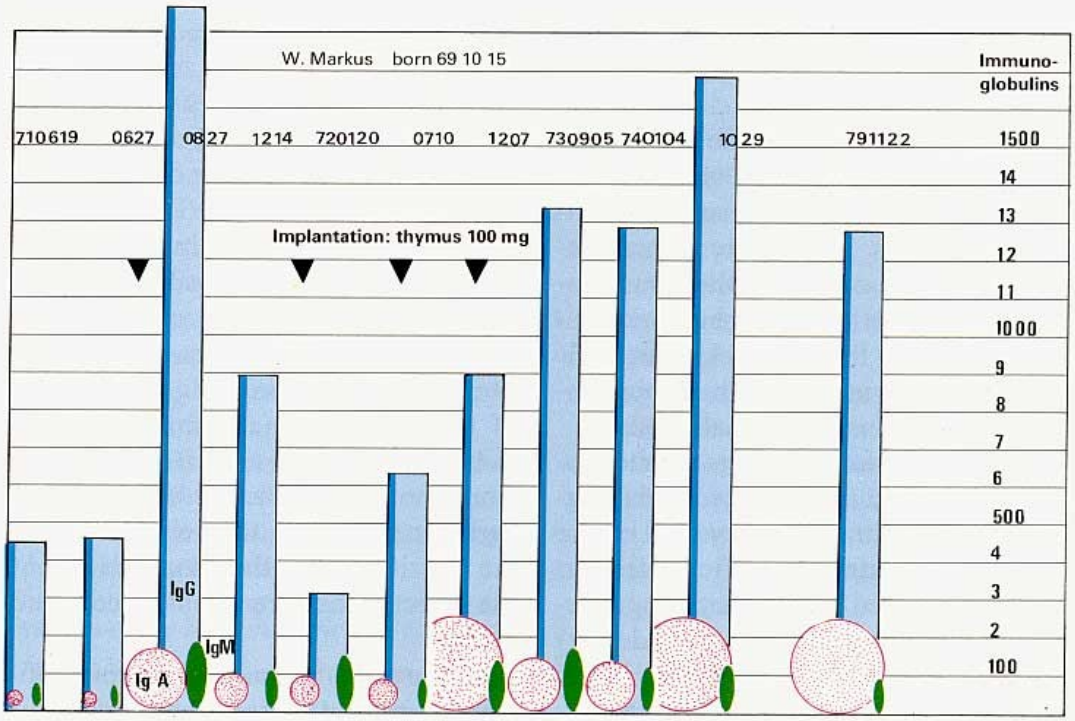



*Fig. 205:*
Syndrome of innate antibody-deficiency; development of the immunoglobulins after implantation of xenogenous, fetal, immunocompetent tissues. The antibody-deficiency is repaired by 3 series of implantations for many years. A subsequent control (800318) showed high values: IgG 2000, IgA 250, IgM 194.

conspicuous example. The resistance to infection by the chronic disease (e. g. miliary tuberculosis) may collapse.

2. A temporarily not fully efficient defence system against infection is exhausted even by «trivial» infections. Lack of protein, malnutrition, avitaminosis, accumulated infections, diseases of the haematopoietic system and extended neoplasms may cause such depressions of the immunological potency.
3. Vaccinations meet with an organism already overloaded by infections (see 1) or not fully efficient owing to other causes (see 2). This may lead to «inoculating complications» in the form of
   a) insufficient formation of immunoglobulins against the inoculated antigen,
   b) provocation of acute infections,
   c) exacerbation of a chronic or latent basic disease (e. g. tuberculosis)
   d) an abnormal sequence of inoculations increased to an «vaccination disease».

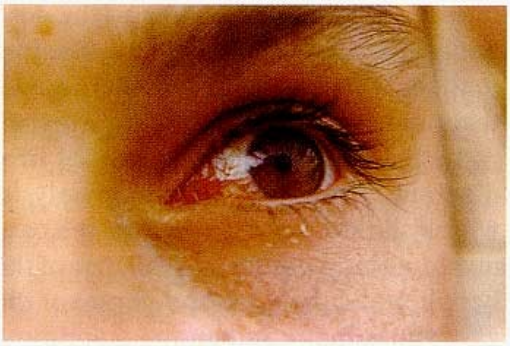
*Immunodepressions by chemical substances*

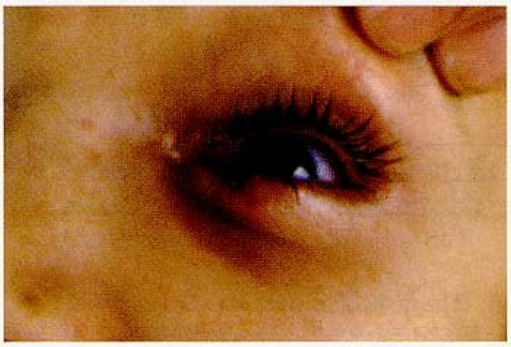
External influences on the cells of immunocompetent tissues can diminish or even abolish the capability of synthetising immunoglobulins. As the formation of antibodies on the basis of RNA takes place in the immunocytes, an immunodepression is effected by processes that

a) change the biochemical qualities of the cell, specially to RNA metabolism,
b) inhibit the mesenchymal proliferation of the cell,
c) bring about a non-physiologically enhanced cytolysis.

Corresponding noxae are provoked by many chemical substances, drugs and physical influences (radiation).

Immunoinhibitory effects of chemical substances have been detected first in alkalizing substances (benzene, toluene, 1916; dichlorethylsulphide, 1916). The





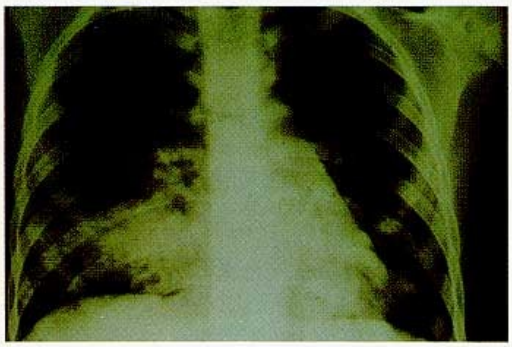


*Fig. 206:*
*Ataxia teleangiektatica (Louis-Bar syndrome)* as a typical example of a mesenchymal-epithelial insufficiency: IgA deficiency, dysfunction of thymus, infections of the respiratory passages, cerebellar ataxia; here a) typical dilation of the conjunctival vessels; b) chronic herpes of the lower eyelid; c) bronchiectasis.

formation of antibodies was suppressed by these substances if they were administered together with the antigen or 4 days earlier. On this principle depend now several groups of substances with immunoinhibitory effects (tab. 17).

Most of the antibiotics (the wider the spectrum of therapeutic effect the more distinct) influence strongly not only the bacterial but also the nucleic acid metabolism of cells; this property is a prerequisite for the effect on microorganisms that also consist of nucleic acids but applies just as well to the cells with a high synthetising activity such as the immunocytes. For the duration and dosage of antiphlogistic drugs, antirheumatics, cortisone derivatives, phenothiazines, antihistamin products, certain sedatives and antiepileptics, this immunoinhibitory effect on the formation of antibodies ought to be taken into account same as for the dosage and duration of broad-spectrum antibiotics.

*Tab. 17:* **Immunodepressory chemical substances**

| | |
|---|---|
| **1. Alkylising substances** (e.g. *trenimon, endoxan, honvan, myleran)*<br>**2. Antimetabolites**<br>a) folic-acid antagonists (aminopterin; *methotrexate*)<br>b) purin antagonists (6-mercaptopurin; *purinethol,* and others)<br>c) pyrimidin antagonists (5-fluoruracil) | **3. Mitotic poisons and blockers of mitosis** (colchicine, vincaleukoblastin, podophyllotoxin)<br>**4. Antibiotics** (actinomycin C and D; mytomycin C)<br>**5. Antiphlogistic medicaments** (antirheumatics, cortison derivatives, antihistamines) |

*Artificial immunosuppression*

For excessive immunizing reactions, the therapy uses increasingly the so-called immunosuppression; the same principle is applied in cases of unwelcome immunizing reactions. In such cases, specially the above chemical substances and physical insulti (rays) are used.

*Immunological effects of irradiation*

The effects of ionizing irradiation on immunobiological processes depend not only on the dose but also on the volume of influence (irradiation of part of the body or whole-body irradiation). Whole-body irradiation influences the production of antibodies according to the dose and stage. Doses up to 400 r are sublethal, those between 400 and 900 r are lethal, and those over 1000 r supralethal.

Lethal and supralethal doses of irradiation provoke immunoparalysis, whose clinical effects constitute the panmyelophthisic syndrome (collapse of the lympho-reticular zone of defense) or the gastrointestinal radiation syndrome (collapse of the epithelial protective surfaces) (tab. 18).

*Tab. 18:* **Radiation syndromes**

| | |
|---|---|
| **1. Syndrome of panmyelophthisis** (bone-marrow syndrome); by eliminating universally the areas of haematpoesis, a «haematological death by radiation» is caused. | **2. The gastrointestinal syndrome** caused by destruction of the epithelial protective surface of the gastrointestinal tract.<br>**3. The neurological radiation syndrome** |

For the sublethal radiation area in the whole-body irradiation and irradiation of part of the body (including most of the diagnostic and natural irradiation insulti) the moment when the rays meet with a formation of antibodies is of importance. Whereas the initial phase of forming the antibody is very radio-sensitive, irradiation during the first days after supply of antigens can even enhance the production of antibodies. The strongest stimulation sets in 60 hours after the administration of antigens.

In animals that got whole-body irradiation by doses of 200 r, the dropping of granulocytes in the peritoneal exudate attained the low mark after 36 days, at 400 r after 30 days, at 800 r already within the first week. The normal cell population in surviving animals reappears after 3 months (90–120 days).

## *Clinical data on immunizing reactions*

Clinically, 4 forms of immunizing reactions are distinguished after the modern classification:

| | | |
|---|---|---|
| *1st type* | *I reaction:* | *immediate anaphylactic reaction of the reagin type* |
| *2nd type* | *II reaction:* | *hypersensitiveness of the cytotoxic type* |
| *3rd type* | *III reaction:* | *immediate reaction of the Arthus type* |
| *4th type* | *IV reaction:* | *cellular immunizing reactions of the «retarded type».* |

*The immediate anaphylactoid reaction*

Through the intervention of IgE, a few minutes after the contact with antigens circumscribed vasculo-capillary reactions in the form of erythema, urticaria (wheals) or rush will be seen. The reaction reaches a maximum after 20–30 minutes and will subside after 1–2 hours without leaving any injured tissue. With the help of the IgE molecules, the antigens bridge the barriers of cell membranes and release contents of mast-cells over the complement bridge (fig. 204). The released *«mediator»* or *«liberator»* substances *histamin, serotonin, bradykinin* and *SRS-A (slow*-reacting-substance-anaphylaxis) dilate vessels, increase the permeability of the capillaries and contract the unstriated muscles.

Clinical sequelae of these morphological elementary processes are (tab. 19):

*Hypersensitivity of the cytotoxic type*

Antigen-carrying cell membranes combine with the corresponding antibodies through their Fc-part or by the mediation of complement, either from complexes or provoke cytolysis by rupture of membranes. A prototype of this form of reaction is erythrocytolysis in Rhesus-incompatibility and other hemolytic diseases. Drugs ments such as chloropromacine and phenacetine may cause in this way haemolytic anaemia, pyramidon and quinine lead to leukopenia, sedormid to thrombocytopenia (H. SCHNEIDER). Rapidly supplied antilymphocyte globulin may provoke equal reactions, and still more phenomena of autoimmunization can certainly be associated with this type of reaction.

*Immediate reaction of the Arthus type*

The structures of antibodies acquired after contact and circulating in the serum are changed by repeated contact with antigens; thus substances leading to «serum disease» are relased at the Fc-end of

*Tab. 19:* **Clinical symptoms and therapy of anaphylactoid reactions.**

| Localisation | Symptoms | Therapy |
|---|---|---|
| Skin<br>Mucosa | Local erythema<br>Flush-rush<br>Urticaria<br>Oedema<br>Cyanosis<br>Salivation<br>Sweating<br>«Goose-flesh» | 1. Dose corresponding to age<br>*Suprarenin*<br>or<br>noradrenalin<br>Aludrin<br>Alupent<br>Norphen<br>subcutaneous<br>or as inhalation for<br>symptoms of respiratory<br>passages |
| Heart<br>Circulation | Tachycardia<br>Fall of blood-pressure<br>Precapillary constriction<br>of the arterial vessels<br>Tissular hypoxia<br>Tissular acidosis<br>Circulatory arrest<br>Respiratory-arrest | 2. Dose corresponding<br>to age of an<br>*antihistamin preparation*<br><br>3. *Glucocorticoids*<br>oral, intramuscular<br>or intravenous<br>1–2 mg/kg of body-weight<br>works after lapse of<br>20–30 minutes! |
| Respiratory<br>passages | Stridor<br>Throat irritation<br>with mucous discharge<br>Spasm of the bronchi<br>Dyspnoea | 4. *Calcium* |
| Digestive tract | Vomiting<br>Rectal tenesmus<br>Intestinal colic<br>Diarrhea | 5. Substitutions of volume<br>and catecholamines<br>Strophantin for<br>volume shock |
| Subjective<br>disorders | Nausea<br>Sickly feeling<br>Headache- and back-pain<br>Paleness<br>Anxiety or<br>heat-feeling | 6. For seizures:<br>phenobarbital<br>chloralhydrate<br><br>7. For clotting disorders:<br>heparin 150–200 U/kg<br>of body-weight,<br>in case substitution<br>of clotting factors |

the antibody molecules. This clinical picture has become known chiefly through the use of antidiphtheritic serum in recent decades. After injection of heterologous antidiphtheritic serum (from horses or other animals), antibodies are produced. Between the 6th–12th days after the injection, the serum disease will appear under the following aspect: erythema to urticaria to generalized oedema; fever, nausea, vomiting; generalized lymphonodulitis; arthritis, nephritis, myocarditis.

The morphological basis is an immu-

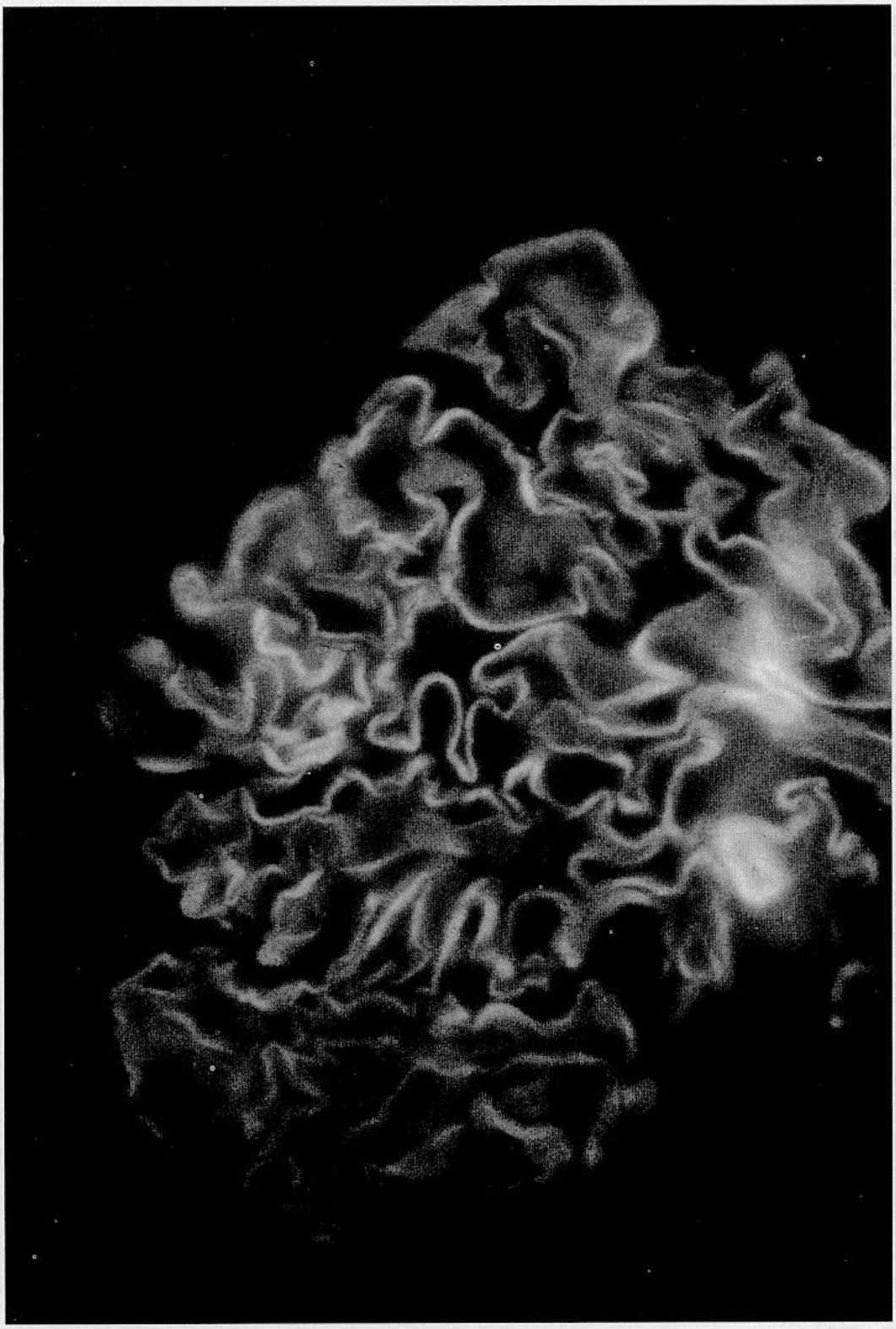


*Fig. 207:*
Sedimentation of immunocomplexes in the capillary loops of a renal glomerulus for Goodpasture syndrome. Immunofluorescence (SCHNEIDER H., BRUNNER P. and MEINL M.).

no-complex vasculitis, which, in contrast to the anaphylactoid reaction (type I), can cause and maintain lasting injuries to tissues. The intravasal antigen-antibody complexes clot and damage cellular constituents. Specially, aggregations of thrombocytes release substances damaging the vascular walls. Soluble immunocomplexes get into the elastica interna of the vascular walls or the basal membrane of the renal glomeruli (fig. 207). Here concentrated immunocomplexes bind complement, and the released anaphylatoxin $C_{3a}$ may in addition affect the permeability and favour the formation of edema and vasodilation. This vicious circle is worsened by immigrating granulocytes with polymorphous nuclei, the lysosomal contents of which affect the vascular walls as their pH is low.

The inflammatory reaction subsides only after the elimination of the immunocomplexes. As the numbers of antigens grows steadily, the lack of antibodies will cause chronic diseases. Examples are «chronic glomerulonephritis» after infections with beta-hemolytic streptococci of group A and the extended alterations of tissue in Lupus erythematodes disseminatus.

*Reaction of the retarded type*

After preliminary sensitisation, certain antigens and haptenes elicit a retarded inflammatory reaction of the so-called «tuberculin type» . In this phenomenon, described by R. KOCH and

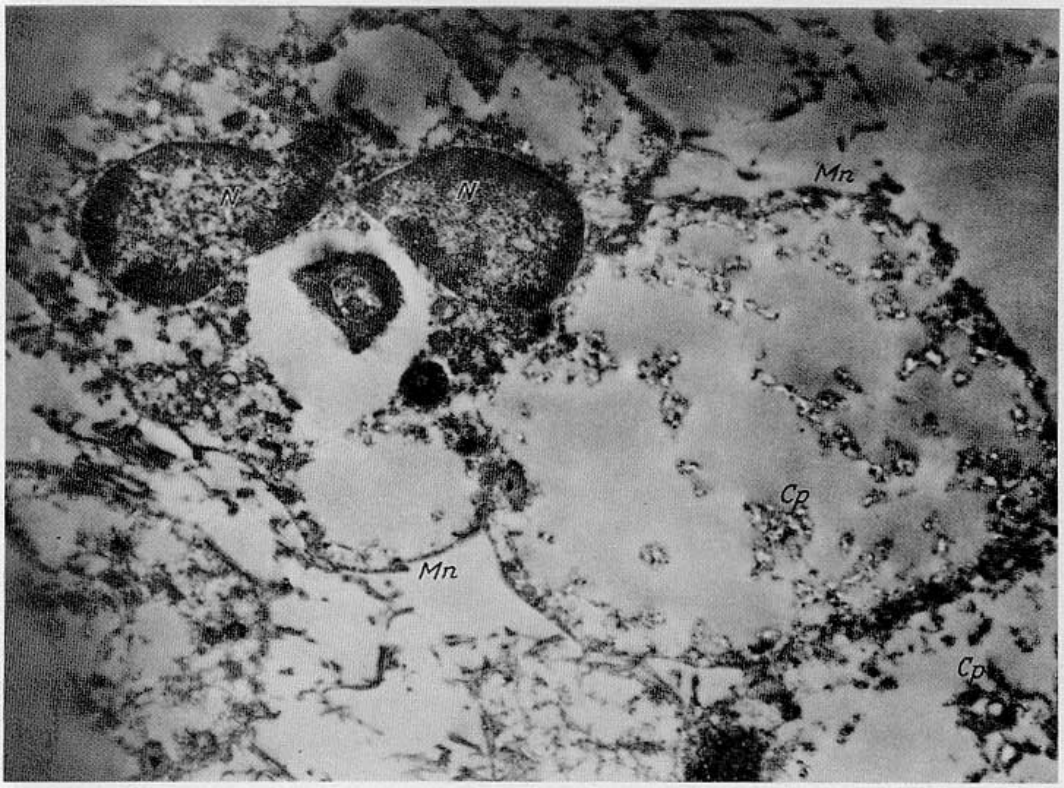



*Fig. 208:*
Explosive disintegration of a cell of peritoneal exudate (guinea-pig); shock elicited $88\frac{1}{2}$ hours after sensitisation. Fragmentation of the cytoplasm starting from the perinuclear space. N = nucleus, Cp = particle of cytoplasm, Mn = membrane.

*Tab. 20:* **Autoantibodies in human diseases** (after WARNATZ, 1979)

| Disease | Antibodies against | % positive |
|---|---|---|
| Immunothryreoiditis (HASHIMOTO) | Thyreoglobulin | up to 90 |
| | Microsomal thyroid antigen | 100 |
| | Border-cells | 32 |
| Primary thyreotoxicosis (long-acting thyroid stimulator [LATS]) | TSH receptor of the thyroid cell | 20–40 |
| Pernicious anaemia with chronic atrophic gastritis | Intrinsic factor | 70 |
| | Border-cells | 83 |
| Idiopathic Addison's disease | Cytoplasmatic Ag of the NNR cells | 50–70 |
| Male infertility | Spermatozoa | rare |
| Myasthenia gravis | Skeleton-muscles | 30–65 |
| | Thymus myoid cells | – |
| | Acetylcholine receptor | – |
| Pemphigus vulgaris | Desmosomes of the prickle-cells | up to 100 |
| Phacogenous uveitis | Lentil protein | – |
| Goodpasture syndrome | Basal membrane of the glomerulum capillaries | 100 |
| Immunohaemolytic anaemia | Erythrocyte antigens (mostly Rh-antigens) | 100 |
| Cold-agglutinin disease | Erythrocyte antigen (I-antigen) | 100 |
| Paroxysmal cold-haemoglobinuria | Erythrocyte antigen (P-antigen) | 100 |
| Active chronic hepatitis | Nucleoprotein | 20 |
| | Mitochondrial antigens | 25 |
| | Involuntary muscles | 70 |
| Primary biliary cirrhosis | Mitochondrial Ag | 90 |
| Colitis ulcerosa | Mucopolysaccharide of the colon cells | 50–100 |
| Lupus erythematodes disseminatus acutus (SLE) | Nucleoproteins | 100 |
| | DNA | 100 |
| | IgG (rheuma factor) | 35 |
| | Erythrocyte antigens | 15–20 |
| Mixed connective-tissue disease | Extractable nuclear antigen (enA) | 100 |
| Primary chronic polyarthritis = rheumatoid polyarthritis | IgG (rheuma factor) | 75 |
| | Nucleoprotein | 10 |
| Sjögren's syndrome | IgG | 75 |
| | Nucleoprotein | 55 |
| | Thyroid gland | 45 |
| | Epithelia of the salivary glands | – |

C. v. PIRQUET, an immunological cytolysis is at the beginning of the chain of reaction.

Cellular immunoglobulins M respond, after another supply of antigens, with a cellular antigen-antibody reaction, which entails the instantaneous explosion-like destruction of the cell (see fig. 156, 157, 208). In the tuberculin reaction, best explained of all, a haptene i. e. the tuberculin (tuberculoprotein fraction) evokes this reaction. According to quantitative relations, vasculitis, which via the fibrinoid conversion may even lead to necrosis, will develop. Vasculitis is characterized after 24–72 hours by a reddening and infiltration of mononuclear cells (lymphocytes, monocytes, epitheloid cells) round the damaged vessels. This process causes necrobiosis and the caseation in tuberculosis and other chronic diseases as mycosis, leprosy,

brucellosis, psittacosis and infection of echinococci. The contact dermatitis and the contact eczema rely on a similar mechanism.

*Common denominator*

Plausible though this division into 4 types of reaction may appear, it leaves many questions unanswered, many discrepancies remain dark. The common denominator of most of the reactions is the release of cellular contents by antigen-antibody relations. Intracellular substrates and enzymes, which have to perform metabolic special tasks in ecological areas surrounded by membranes (such as enzymes in lysosomes, transport substrates in vesicles) are suddenly released and cause destruction of the reactive, broad surfaces of contact of the terminal vessels. The pH necessary for the biochemical functions within the spaces delimited by membranes are probably of decisive importance because, suddenly set free into the fluidstream, they can exert destruction by acid-alkaline corrosion.

Different and specific though the causes of immune processes may be, the reactivities of the organism are quantitatively different, qualitatively virtually equal. They run form the reactive chain of biochemical lesions of the small vessels – vasodilation – increased permeability – extravasation of fluids and cells from the vessels into the surrounding tissue. From this uniform primary process, the aspect of inflammation, various clinical pictures develop by secondary processes, according to localization and quantitative conditions.

*Prophylaxis and therapy*

Owing to the non-specific, after all, response of the body to specifically induced processes, prophylaxis and therapy use for all forms of allergic reactions the same therapeutic principles: (1) Withdrawal of antigens (2) Blocking of antibodies (3) Inhibition of the inflammatory reaction.

The essential data of practical use are stated in tab. 19 and 21.

*Tab. 21:* **Prophylaxis of anaphylactoid reactions especially by repeated administrations of heterologous foreign tissues or sera**

1. 5 – 15 min. before injection:
   single dose, corresponding to age, of
   a) a glucocorticoid preparation
      (0,5 – 1 mg/kg of bodyweight prednisolon)
   b) *an antihistamin product*
      best of all a combined preparation
      (e.g. a measuring spoon or 1 tabl. of celestamines)
2. Immediately after injection (implantation):
   a single dose (corresponding to age) of a catecholamin by drops (*Novadral, Norphen, Effortil,* Artenerol, or similar prep.)