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- EDUCATION

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MILITARY PHARMACY AND MEDICINE

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Military Pharmacy and Medicine is quarterly interdisciplinary journal of Military Centre of Pharmacy and Medical Technique in Celestynów, Poland published in English on scientific, socio-professional and training issues of Military Pharmacy and Medicine.

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Article with published erratum:
Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide [published erratum appears in N Engl J Med 1979;302:322-5]. N Engl J Med 1979; 301: 1382-5.

Article in electronic form:
Drayer DE, Koffler D. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from: URL:*http://www.cdc.gov/ncidod/EID/eid.htm*

Article, no author given:
Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

Book, personal author(s):
Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Book, editor(s) as author:
Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Book, Organization as author and publisher:
Institute of Medicine (US). Looking at the future of the Medicaid program. Washington: The Institute; 1992.

Chapter in a book:
Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Conference proceedings:
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Infectious diseases

Rabies vaccine administered to soldiers of the Polish Army leaving for foreign missions

Radosław Ziemba

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Summary:

This work presents WHO guidelines on the treatment of rabies after exposure, taking into account the types of wounds and methods of treatment depending on the state of the animal – the rabies carrier. Situations and the method of administration of VERORAB vaccine within rabies-risk areas were described. Contraindications for its administration were also included.

Key words: rabies, exposure, serology testing, vaccination.

Rabies is a disease of viral etiology, an acute zoonotic disease of the central nervous system of mammals, always fatal for humans. The source of infection are usually wild animals such as bats, squirrels, foxes, deer and domesticated animals such as dogs, cats, cows.

Infection with rabies is possible almost anywhere in the world, although some places in the world are regarded as free of rabies. Antarctica, Japan, Scandinavia and Oceania are considered to be such places. Until recently, United Kingdom and Australia have been free of rabies infection, but the disease has been brought there by bats. A very large number of infections occur in China and India, where rabies risk is comparable to the risk of AIDS. About 100 000 people in the world die every year because of rabies, mostly in tropical countries. In Europe and Poland, fox is the main source of infection. Each species of animals has a biotype of the virus, so fox virus can be distinguished in this case.

Man does not have a separate biotype. Animals bitten by a fox with rabies may be a source of infection for humans. This refers mainly to cats and dogs, more often to other domestic animals. Small rodents such as mice or rats usually do not pose a threat of rabies to humans. Man does not become infected by small rodents, as their biotype cannot cause the disease. Poikilothermous animals do not transmit the virus.

One can get infected with rabies only directly through a bite or getting licked, but not by objects licked by such an animal, unless the contact occurred within a few minutes after this fact. So far, there have been no cases of infection caused by a patient with rabies, although the patients' saliva includes rabies virus. A man sick with rabies is not dangerous, because the passaged virus loses its virulence.

The most dangerous is a bite in the face above the nose, then the neck and bare limbs. Rabies virus is sensitive to X-rays and UV, to chemicals such as phenol and formaldehyde, as well as drying. At low temperatures, it can survive for up to several years, as it withstands cooling to -70 ° C.

Areas at risk of rabies

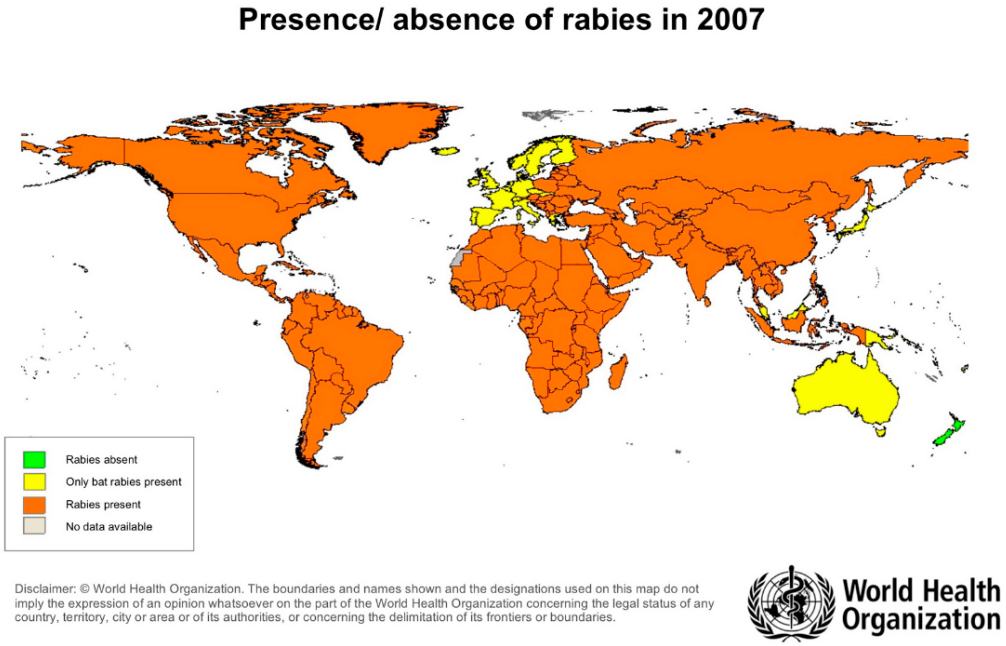

Figure 1: Presence/absence of rabies, at: http://www.who.int/rabies/rabies_maps/en/index.htm

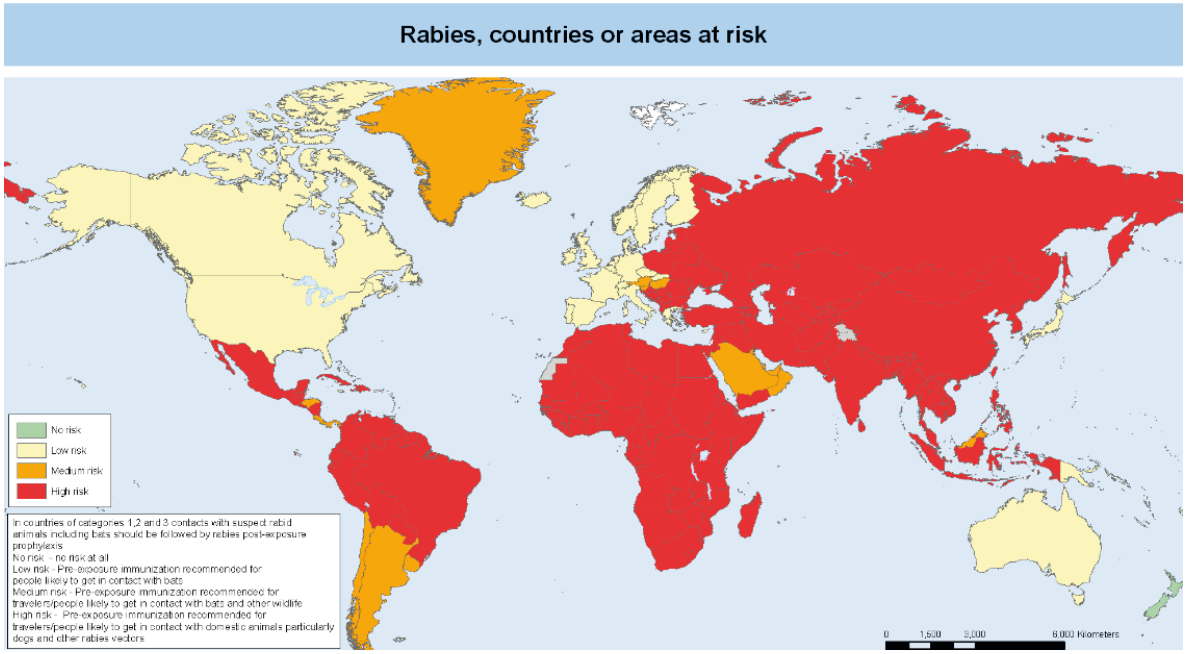

Figure 2: Rabies areas or areas at risk, at: http://www.who.int/rabies/rabies_maps/en/index.html

Composition

After reconstitution, 1 dose (0.5 ml) contains:

Active substance:

Rabies virus, Wistar Rabies PM/WI38 1503-3M strain (inactivated) not less than 2.5 IU, proliferated in VERO cells. The amount determined using the NIH test (National Institutes of Health test) in accordance with international standards.

Excipients:

Powder: maltose, human albumin.

Solvent: sodium chloride, water for injections.

Available packages:
1 vial of powder with 1 dose + 1 pre-filled syringe and needle with solvent of 0.5 ml - in a cardboard box;
5 vials of powder with 1 dose + 5 ampoules with solvent of 0.5 ml - in a cardboard box.

What is VERORAB and what is it used for?
VERORAB is a vaccine powder and solvent for suspension for injection. It is indicated for the prevention of rabies in children and adults. It can be used before and after exposure, as a primary vaccination or a booster.

Vaccination before exposure should be offered to persons at high risk of infection with rabies virus. Everyone who is constantly exposed to infection, such as employees of the diagnostic, R&D and manufacturing departments carrying out work with

Table 1: The procedure, depending on the status of the animal

Circumstances	Proceedings concerning		Remarks
	animals	patients	
The animal is not available. Suspicious or non-suspicious circumstances.		Transport to a specialist rabies treatment centre for therapy.	Treatment(b) is always full.
The animal is dead. Suspicious or non-suspicious circumstances.	Send the brain to be examined at an authorized laboratory.	Transport to a specialist rabies treatment centre for therapy.	Treatment is interrupted. if the test result is negative, otherwise it is continued.
The animal is alive. Non-suspicious circumstances.	Subject to veterinary observation(a).	The decision to postpone anti-rabies treatment.	Treatment (b) is administered depending on the result of veterinary observation of the animal.
Suspicious circumstances.	Subject to veterinary observation.	Transport to a specialist rabies treatment centre.	Treatment (b) is interrupted if veterinary observation showed no signs of rabies

Table 2: The procedure, depending on the status of the animal

Category of severity	Type of contact with a wild(a) or domestic animal with suspected or confirmed rabies or with an animal that cannot be subjected to observation	Recommended treatment
I	Touching or feeding animals. Licking of intact skin by an animal	Treatment is not to be used if reliable medical documentation is available.
II	Bitten exposed skin. Minor scratches or abrasions without bleeding. Licking of intact skin by an animal.	Administer vaccine immediately.
III	Single or multiple bites or scratches through the full thickness of skin, licking of mucous membranes by an animal	Administer immunoglobulin and rabies vaccine immediately.

rabies virus, as well as soldiers leaving for stabilization missions of the Polish military contingents should be vaccinated. Control serologic testing is recommended to be carried out every 6 months.

Vaccination **before exposure** should also be considered in individuals at risk of frequent exposures to rabies virus, such as:

- veterinarians and their assistants, and caregivers of animals;
- persons who, because of their profession or in their spare time, have contact with species such as dogs, cats, skunks, raccoons, bats or other species that potentially may have rabies. Examples of such people are foresters, hunters, forestry workers, speleologists, taxidermists;
- adults and children leaving or travelling to areas at risk of rabies infection;
- soldiers and civilian employees of the army leaving for stabilization missions of the Polish military contingents, including medical personnel.

In areas at low risk of rabies, veterinarians and their assistants (including students), animal carers and foresters are considered a group at risk of occasional exposure and they should receive a primary vaccination against rabies.

Serological tests for antibodies against rabies should be carried out at regular intervals depending on the degree of exposure of individuals.
Booster doses should be administered consistently depending on the degree of exposure of individuals.

Prevention of rabies **following exposur**e (vaccination after exposure): if there is the slightest risk of infection with rabies, vaccination should be administered immediately. In some countries, vaccination must be submitted in specialized rabies treatment centres.

Treatment after exposure includes topical, nonspecific wound treatment, passive immunization with immunoglobulins (RIGs) and vaccination, depending on the type of wounds and the condition of the animal (Table 1 and 2).

Do not use VERORAB vaccine:
Before exposure in the case of:

- fever or acute illness. Vaccination should be postponed;
- hypersensitivity to the active substance, any of the excipients, polymyxin B, streptomycin or neomycin.

Following exposure: there are no contraindications to vaccination after exposure because rabies infection always causes death.

Take special care with VERORAB vaccine:

As with all injectable vaccines, appropriate treatment should be readily available in the event of an anaphylactic reaction immediately after vaccination, especially in the case of post-exposure vaccination of persons with known hypersensitivity to polymyxin B, streptomycin or neomycin.

Do not inject into the buttock, since lower levels of neutralizing antibodies were observed after administration in this part of the body.

It is necessary to perform regular serological testing. Such serological tests are carried out by confirmation of total neutralization of the test virus, using fluorescence inhibition. This examination should be performed every 6 months for people at continuous risk of exposure and every 2-3 years after each booster dose in persons from groups at risk of periodic exposure. If antibody levels are lower than the protective level, i.e. 0.5 IU/ml, a booster dose should be given.

In case of administration of the vaccine in individuals with immunodeficiency or immunosuppressive disease caused by the ongoing immunosuppressive therapy (such as corticosteroids), serological antibody levels in these individuals should be determined after 2-4 weeks following vaccination. When the determined level of antibodies is lower than that considered protective, i.e. 0.5 IU/ml, an additional dose should be given.

In pregnant women.
Because of the severity of the disease, the vaccination schedule cannot be altered due to pregnancy. If a woman becomes pregnant during the vaccination course, medical attention should be sought immediately, only a doctor may adjust the vaccination schedule to the situation.

Breastfeeding.
This vaccine may be used during breastfeeding. A doctor should be consulted before taking any medicine.

Driving and operating machinery.
Dizziness was often reported after vaccination, which may temporarily affect the ability to drive and use machines.

Use of other vaccines and drugs.
A doctor should be informed if a patient is taking medicines, even those without a prescription. Corticosteroids and other immunosuppressive drugs may adversely affect the production of antibodies and make the vaccination ineffective.

Immunoglobulin must be given at a different location than the vaccine (opposite side).

How to use VERORAB?

Before reconstitution, the powder is uniformly white. In order to reconstitute the vaccine:

- remove the cap from the vial;
- inject the solvent from the vial or pre-filled syringe into the vial with powder;
- shake gently to obtain a homogeneous suspension. The reconstituted vaccine is a clear liquid;
- immediately draw 0.5 ml of the suspension;
- inject.

Do not inject intravascularly. Before vaccination, make sure that the needle is not in a blood vessel.
Do not administer subcutaneously.
The reconstituted vaccine should be used immediately, as it contains no preservatives.

Any unused product or waste material should be disposed of in accordance with local regulations.
Vaccination schedule should be adapted to the circumstances of the indications for vaccination and immunization of persons against rabies.

Vaccination before exposure.
Three doses of VERORAB vaccine (0.5 ml) should be given on days 0, 7 and 28 or 21.

Booster doses of vaccination before exposure.
Booster dose of VERORAB (0.5 ml) should be given after one year following vaccination.

Recommendations for primary vaccination and booster doses are presented in Table 3.

Table 3: Recommendations for primary vaccination and booster doses

Primary vaccination	3 injections	On day 0, 7 and 28
Booster dose	1 year later	
Booster doses	Every 5 years	

Injection on day 28 can be done on day 21.
VERORAB vaccine can be given as a booster dose after primary vaccination against rabies with vaccine prepared in cultures of human diploid cells or VERO cells.

Vaccination after exposure.
First aid, local treatment of wounds.
All bites and scratches should be washed immediately with soap and water or detergent. This may enable effective removal of rabies virus from the site of infection. Then 70% alcohol or iodine solution or 0.1% solution of quaternary ammonium base can be used (provided soap was not left in the wound, because the products neutralize one another). Depending on the severity of injury, it may be necessary to provide anti-rabies immunoglobulin (RIGs) simultaneously with the vaccine.

If necessary, treatment may be supplemented by anti-tetanus prevention and (or) antibiotic therapy.

Fully immunized persons.
Two booster doses of VERORAB vaccine (0.5 ml) should be given on day 0 and 3. In this case, the administration of rabies immunoglobulin (RIGs) is not necessary and should not be done because the booster dose is always followed by an immune response associated with immune memory. Previously vaccinated persons should be able to document:

- use of the full course of vaccination before or after exposure with a vaccine produced in cell culture or
- titer of antibodies against rabies virus > 0.5 IU/ml

If in doubt or if more than 5 years have passed since the last vaccination, or if it was incomplete, the patient should not be considered as sufficiently immunized and full treatment should be started after exposure.

Recommendations for vaccination against rabies after exposure, depending on prior vaccination, are presented in Table 4.

Table 4: Recommendations.

Vaccination within the last 5 years (vaccine against rabies produced in cell culture)	2 injections on day 0 and 3
Vaccination earlier than 5 years ago or incomplete vaccination	5 injections on day 0, 3, 7, 14 and 28 with RIG immunoglobulin, if necessary

Non-immunized persons.
Five doses of VERORAB vaccine (0.5 ml) should be given on day 0, 3, 7, 14 and 28.

Rabies immunoglobulin (RIGs) should be given simultaneously with the first dose in case of severe injury. Horse or human rabies immunoglobulin can be used simultaneously with VERORAB vaccine.

Internationally recognized RIG immunoglobulin dosage is as follows:
Human rabies immunoglobulin: 20 IU/kg of body weight

Horse rabies immunoglobulin: 40 IU/kg of body weight
RIG immunoglobulins may partially suppress production of antibodies and therefore should not be used in a dose higher than recommended.
Vaccine and RIG immunoglobulin should be administered to different sites on the body, on the opposite side.

In areas at risk of rabies, it may be justified to give two doses of vaccine on day 0 in case of very serious injuries or if their location is close to the nervous system, or in case of a patient with immunodeficiency, or if a patient has not reported for a medical consultation immediately after exposure.

Method of administration:

VERORAB vaccine is given only intramuscularly, in the deltoid muscle in adults, and in the anterolateral part of the thigh in infants and young children.

Adverse reactions after vaccination with VERORAB.
Like all medicines, VERORAB vaccine can cause side effects. Mild adverse reactions at the injection site: pain, redness, swelling, itching, and induration at the injection site.

General side effects: mild fever, chills, malaise, fatigue, headache, dizziness, joint and muscle pain, gastrointestinal disorders (nausea, abdominal pain).
Very rarely: cases of anaphylactic reactions, urticaria and rash.
In infants born prematurely (at 28 weeks gestation or earlier) longer intervals between breaths may appear within 2-3 days after vaccination.

VERORAB vaccine should be stored out of the reach and sight of children, at 2°C - 8°C (refrigerator). Do not freeze. After reconstitution, the vaccine should be used immediately.
Do not use the vaccine after the expiry date stated on the packaging.

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Biochemistry

The internal structure of binary liquid mixtures DMSO + water

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Summary:

The review of literature concerning the internal structure of dimethyl sulfoxide, water and their mixtures was presented in this paper. At the same time, results of own research connected with the analysis of intermolecular interactions in liquid mixtures of DMSO + water were discussed.

Key words: dimethyl sulfoxide, water, intermolecular interactions.

The advances in natural science follow two inseparably interrelated paths: experimental and theoretical. Accumulation of an appropriate amount of experimental data allows drawing generalized conclusions, deriving appropriate formulas and formulating laws that govern the studied phenomena. This leads to the possibility to predict and program expected effects for practical use.

Obviously, such a research cycle requires, particularly in solution chemistry, the theoretical results to be verified by experimental results.

However, in theoretical and physical chemistry, such a verification proves to be difficult.

Calculations (e.g. calculations of the internal solution structures) are based on the principles of quantum mechanics, which can be currently applied only in an approximate manner to small unit systems. It is hard to imagine a complete structural description (based on such calculations) that would take into account all possible types of intermolecular interactions, e.g. in solvent mixtures. On the other hand, experimental results are obtained for molecular systems as described above, located in actual environment, which often has a decisive effect on both the course of the observed phenomena and the properties of studied objects.

Another problem is determination of appropriate research methods. This is associated with the need to select such measurable physicochemical parameters, for which changes caused by the effects of interest might provide important information on the behavior of the entire system in the particular environment.

Such problems appear when analysis of intermolecular interactions and assessment of internal structures of liquid one-, two-, and multicomponent systems are being attempted.

The subject of analysis of intermolecular interactions and assessment of internal structures of liquid solvent mixtures is important to every chemist who carries out homophasic chemical reactions or heterophasic electrode processes in these solvents. This is due to the fact that ion-solvent molecule, ion-ion or solvate molecule-solvent molecule interactions are inseparably linked to physicochemical properties of the solvent. These properties are, in turn, a function of intermolecular interactions within the solvent. Several excellent monographs were published on the subject, such as I*ntermolecular Interactions* by H. Ratajczak, published in 1982, or *Solvents and Solvent Effects in Organic Chemistry* by Ch. Reichardt, published in 1988 [1, 2].

The review of the literature data suggests that in different research sites, a wide range of spectral methods, thermochemical methods and studies of intensive macroscopic properties of solutions (such as density, viscosity, relative electric permittivity, surface tension, etc.) in different temperatures were used to analyze the internal structures of liquid solvent mixtures [3]. Obviously, when attempting to assess the structure of a two-component solvent mixture, one needs to know the properties and structure of its components. Therefore, before moving on to the attempted description of the internal structure of dimethyl sulfoxide (DMSO) – water mixtures, I am going to present a short review of data on the properties and internal structure of both components of this mixture.

The review of literature data shows that no scientific information on dimethyl sulfoxide had been available for nearly 100 years since it was discovered by Saytzeff in 1867 [4]. Only as late as in the 1960s, when the capability of this solvent to solubilize different types of chemical compounds insoluble in other solvents (among others, sulfamides) was observed, the interest in DMSO was revived. Another stimulus that greatly enhanced the interest in DMSO was the studies published in the late 1960s, suggesting a great potential for the use of this solvent in pharmacology and medicine [5-15]. Since that time, the interest in chemical and physical properties and the structure of liquid dimethylsulfoxide and its solutions has been unrelenting. This can be proved by more than ten thousand articles published to date, indicative of a great interest in this solvent in all areas of chemistry, physicochemistry, biology, pharmacology and medicine. In recent years, a large number of articles has been published regarding the use of DMSO in cryopreservation processes, more precisely regarding the replacement of 5-10% aqueous solutions of glycerol used in this process with aqueous solutions of DMSO. The mechanisms of cryopreservation are not fully studied. It is assumed that upon slow freezing, glycerol leads to cell dehydration, which prevents formation of ice crystals. Aqueous solutions of DMSO have similar properties while additionally chelating protein metals upon slow freezing, thus preventing protein denaturation.

DMSO is a very hygroscopic liquid (e.g., at a temperature of 293.15 K, under pressure of 1 atm and at a relative humidity of 65-70%, it is able to absorb the amount of water that is equal to its own mass [12]), miscible with water in any ratio and dissolving, in wide concentration ranges, lower alcohols, aldehydes, ketones, ethers, esters, heterocycles and aromatic compounds, as well as macromolecular compounds (e.g. polyacrylonitrile, nitrocellulose and cellulose acetate [16]).

From the standpoint of chemical structure, it is a very interesting feature of DMSO that while the C–S bond may be treated as a regular covalent single bond, the nature of the S–O bond has not been fully explained. An interpretation that explains well the physical properties and reactivity of DMSO is presenting DMSO molecule as a hybrid between two resonance structures:

Figure 3: Resonance hybrid structures of DMSO.

The first structure is characterized by a polarized single S–O bond, while the other features a double bond [17].

DMSO is characterized by high polarity, as evidenced by relatively high values of its electric permittivity and dipole moment (ε = 48.9, μ= 4.3 D). These properties are responsible, among others, for good DMSO solubility of many types of chemicals insoluble in other solvents.

From the standpoint of structural studies, a high boiling point (189°C), evaporation entropy (123,85·J deg^{-1}·mol^{-1}) and cryoscopic studies in benzene suggest strong intermolecular associations within liquid DMSO. $(DMSO)_n$ associates may be formed via bridge bonds [18, 19]:

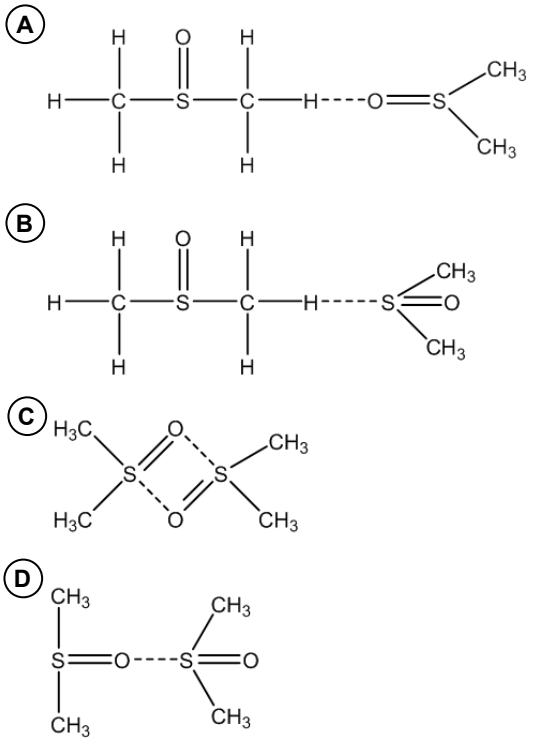

Figure 4: Example $(DMSO)_n$ associates formed via bridge bonds.

However, most authors believe that due to low autoionization constant of DMSO k = $5 \cdot 10^{-18}$ [20]), the probability of formation of associates (1) or (2) is very low. According to studies conducted by Szmant *et al.*, DMSO molecules are associated by the so-called *oxygen-sulfur bridges* S–O [18]. Szmant observed, that for the absorption band of $\nu_{S\text{-}o}$= 1060 cm^{-1}, the Lambert-Beer's law is fully met only for solutions of DMSO in CC14 at concentrations of less than 0.08 M. Thus, only monomers are present within this concentration range. Upon increasing the concentration of DMSO in $CC1_4$ from 0.08 M to 0.3 M, cyclic dimers (3) become prevalent, as evidenced by the presence of new absorption bands of $\nu_{S\text{-}o}$= 1100 cm^{-1} . Linear dimers (4) should generate at least three distinct bands $\nu_{S\text{-}o}$. Further increase in DMSO concentration (c > 0.3 M) destroys cyclic dimers and leads to formation of macromolecular chain associates of type (4), with structures as described above.

Most researchers believe that the main reason for the lack of C–H···O bonds in liquid DMSO is the low acidity of C–H groups (as a C–H acid, DMSO is ca. 10^7 weaker than triphenylmethane), while intermolecular S···O bonds are formed in liquid DMSO or in its aqueous solutions thanks to the significant contribution of specific electron donor-acceptor (EDA) interactions, enhanced by non-specific dipole-dipole interactions. It should also be mentioned that DMSO is a strong electron donor and a weak electron acceptor (electron donor and electron acceptor numbers of 29.8 and 19.8, respectively) [21].

It might seem that in case of water, all issues regarding its properties and internal structures should be well described. However, there is nothing more erroneous.

In his wide monograph [22], containing a review of literature data on the internal structure of liquid water, Guillot states that:

"*Water is the simplest compound of two most prevalent reactive compounds in the universe. Our body is composed of water in 2/3. Life or evolution would be impossible without water. Water is the most extensively studied solvent; it is therefore surprising, that its properties and behavior are still poorly understood, not only by general population, but, more importantly, by scientists who analyze its properties and internal structure.*"

Experimental results suggest that water molecules may be considered as a "rigid" system, in which the precisely calculated, experimentally determined O–H bond lengths are 0.9572 Å, and the H– O– H angle is 104.5°. Water molecule is also assumed to be an isotropic, polarizable sphere with a constant dipole moment of $6.3 \cdot 10^{-30}$ C·m.

In reality, this issue is much more complicated. This may be supported by the fact that one of the recent review articles on the subject presented 46 different models of water molecule [23]. All analyzed models were the so-called "rigid" water molecule systems. They assumed that the hydrogen-oxygen bond lengths and bond angles in the molecule are constant. "Flexible" structure models, which take molecular vibrations into account, resulting in variable bond lengths and angles (such as the central force (CF) model developed by Stillinger and Rahman [24] and the BJH model developed by Bopp, Jancso and Heinzinger [25]) have also been developed.

However, one should keep in mind that liquid water is not a set of isolated, independently moving molecules. Comparing e.g. the self-diffusion coefficient of water with self-diffusion coefficients of solvents characterized by much larger molecules reveals that the process of self diffusion in water is caused not only by correlated movements of connected molecules. Based on the analysis of values of this parameter, Narten and Levy [26] assumed that intermolecular aggregates are formed in liquid water, which must affect its internal structure and properties. These aggregates and structures are formed in liquid water due to short-range interactions between neighboring water molecules and formation of intermolecular hydrogen bonds. Of course, the simplest structure of this type is a dimer consisting of two water molecules. The more linear is the hydrogen bond formed between oxygen in one molecule and hydrogen in another molecule, the stronger it is. The energy of the hydrogen bond in such cluster is ca. 20 kJ/mol and thus it is much higher than the value of the k·T product. Therefore, one may suspect that the lattice of hydrogen bonds in water should be energetically stable. However, one must keep in mind that the internal structure of water (and any other liquid) is a ***flickering structure***. This means that the actual lattice of hydrogen bonds in water undergoes continuous rearrangement and new hydrogen bonds and, in consequence, new spatial configurations of internal structures are formed within picoseconds. This effect must have led to many different models of internal structure of liquid water being published in the literature.

In general, structural models may be divided into two categories:

- the so-called mixture models [27-29], developed from equilibrium mixtures of aggregates differing by the number of associated water molecules and the specific structural arrangement of these aggregates.

- The so-called *continuum* models [27-29], describing a continuous lattice of molecules connected by hydrogen bonds. Bending the hydrogen bonds in the lattice results in continuous distribution of hydrogen bond lengths, angles and energies.

Of course, models that constitute specific combination of bent hydrogen bond lattice with mixture model concepts are also published in the literature. This allows, among others, to interpret the experimental data describing the microscopic structure of water (diffraction analysis) using *continuum* models and the thermodynamic properties (such as compressibility or thermal capacity) by a model consisting of small internal, local structures.

It must be emphasized that all the discussed structural models assume molecular clusters of different sizes being present within liquid water. According to Walrafen [30], three structural components may be identified in liquid water: quadruply-, triply- and doubly-coordinated units of hydrogen bonds. Kim [31] postulates that water contains small water molecule clusters $(H_2O)_n$, where $4 \leq n \leq 8$. Arakova [32] presents a pentamer-momomer model, based on the assumption that liquid water is an equilibrium mixture of water molecules bound in tetrahedral arrangements (pentamers) and water monomers. Luu *et al.* [33] assumed that water contains cyclic pentamers, bicyclic octamers and tricyclic octamers of the following structures:

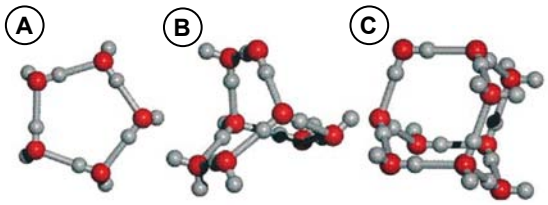

Figure 5: Spatial structure of cyclic pentamer (A), bicyclic octamer (B) and tricyclic octamer (C) [33].

These three small clusters are relatively stable and their mutual interactions lead to formation of larger clusters with icosahedral symmetry. These, in turn, bind one another to form a lattice of icosahedral $(H_2O)_{280}$ clusters [22, 23, 29].

It might seem that this diversity of literature structural data makes it impossible to develop coherent interpretation of energy changes (i.e. the assessment of the energy of intermolecular interactions) in liquid water. There is nothing more erroneous. The course of changes of the intermolecular interaction energy as the function of intermolecular distance in liquid water allows interpretation of not only the structural effects, but also explanation of many abnormal properties of water (change in density upon melting and solidification, abnormal viscosity at 4° C, specific heat or the Mpemby effect). This shows that hydrogen bonds between water molecules keep them at distances larger than in case of non-binding interactions. The conflict between these two effects and their dependence on external conditions (temperature and pressure) is responsible for the most of the aforementioned "unusual" (abnormal) properties of water [22, 23, 29].

Having at my disposal the above structural data relating to neat DMSO and water, I attempted to assess the internal structure of liquid DMSO + water molecules based on own research (densimetry, dielectrometry, viscosimetry, refractometry and ^{1}H-NMR and IR spectrometry [37-37]) and data published by other authors. Very important from the standpoint of issues under discussion were the spectral studies by Mierzecki *et al.* [38], consisting in Raman spectroscopic analyses of liquid DMSO-H_2O solutions. The results of these studies supported the concept of at least two intermolecular complexes being present in these liquid mixtures, i.e.: **DMSO·2H$_2$O** and **DMSO·H$_2$O**, with possibility of **2DMSO·H$_2$O** not being excluded. However, Mierzecki did not propose a way to relate the internal association between these complexes to the internal structures of studied liquid mixtures. Analysis of Raman spectra led those authors to the conclusion that in the **DMSO·H$_2$O** complex (formed in equimolar DMSO+H_2O) mixtures, only one electron pair in DMSO oxygen is engaged in complex formation. In more water-rich solutions, both electron pairs of DMSO's oxygen atom are connected with H_2O molecules with hydrogen bonds. However, it must be mentioned that relatively stable DMSO dimers were detected by the authors even in solutions containing significant excess of water. Drawing logical conclusions from Mierzecki's work, I arrived at conviction that aqueous solutions of DMSO, formed e.g. from combining equimolar amounts of both components, contain prevalently **DMSO·H$_2$O** complexes, accompanied by more water-rich complexes (**DMSO·2H$_2$O** and **DMSO·3H$_2$O**) as well as water-deficient complexes (**2DMSO·H$_2$O**). These solutions must also contain relatively water-resistant dimers $(DMSO)_2$. This argumentation leads to the following conclusion: If the extreme values of several studied physicochemical processes suggest a characteristic composition of the mixture, e.g. containing ca. 50% mol DMSO, this means that the internal structure of that solution has an averaged stoichiometry **$(DMSO·H_2O)_n$**. However, one must also remember that the structure contains intermolecular complexes with more water-rich or more DMSO-rich compositions. Thus, actual internal structures of liquid bicomponent DMSO + H_2O systems are mixed structures consisting of dominant DMSO·H_2O complexes with locally included complexes of other compositions.

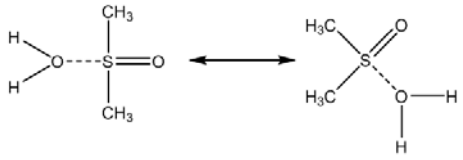

Figure 6: Spatial structures of intermolecular **DMSO·H$_2$O** complex proposed by Schott [39].

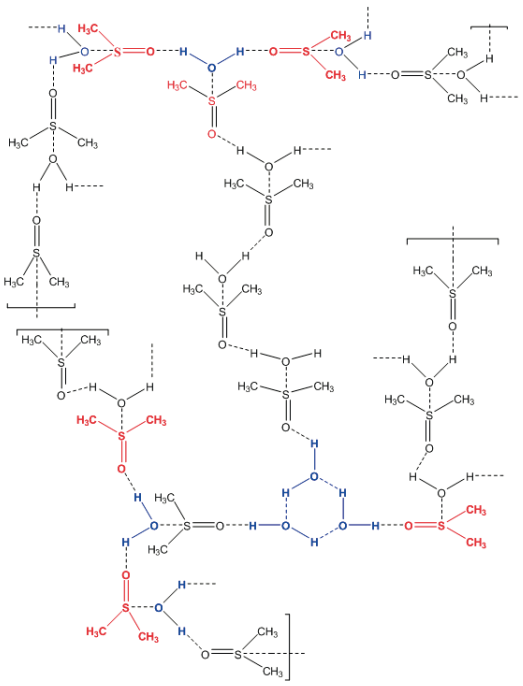

Figure 7: Proposed internal structure of liquid DMSO + H$_2$O mixtures with predominance of **DMSO·H$_2$O** complexes [37].

Here, one should also mention the papers by Schott [39], in which he assumed that water may be bound to DMSO not only via the hydrogen bonds, but also via interactions between the positively charged end of dipole S–O and negatively charged end of dipole O–H. Taking this into account, Schott proposed the following spatial structures of intermolecular DMSO·H$_2$O complexes:

Taking into account the above structural considerations, the following hypothetical internal structures

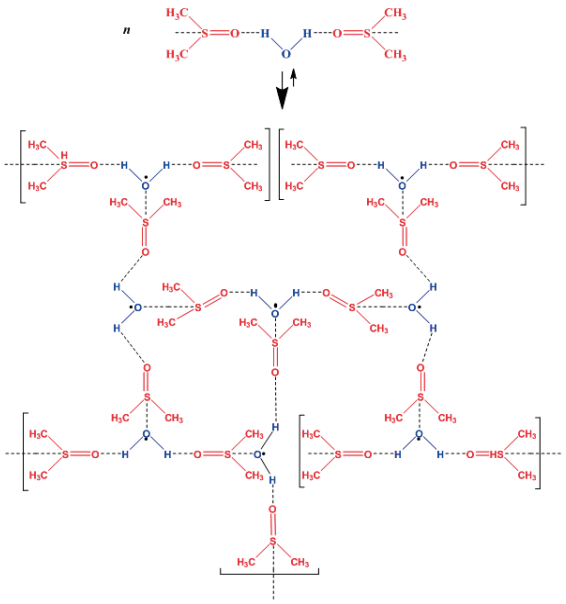

Figure 8: Proposed internal structure of liquid DMSO + H$_2$O mixtures with predominance of **2DMSO·H$_2$O** complexes [37].

of liquid DMSO + H$_2$O mixtures could be presented, containing predominant DMSO·H$_2$O complexes (Figure 5) and **2DMSO·H$_2$O** complexes (Figure 6) .

Of course, the internal structures proposed here are purely hypothetical in nature. This is due to the fact that, as mentioned before, contrary to analogous solid structures, actual internal structures of liquid bicomponent systems are flickering structures [34-37]). This makes it impossible to determine their actual internal structure by means of semiempirical calculations or to determine the actual number n of molecules within the clusters **xDMSO·yH$_2$O** that form this structure at any given moment. However, one must realize that such types of studies give rise to interpretation mechanisms that allow to explain issues related to ion-ion, ion-solvent or solvent-solvent interactions in multicomponent liquid systems.

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Maritime & Tropical Medicine

The application of Individual Prophylactic and Therapeutic Kit by soldiers of the Polish military contingents

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Summary:

Due to the new experiences gained during stabilisation missions in Iraq and Afghanistan, new medical kits have been introduced to the Polish Army such as: a paramedic rucksack, a medic rucksack, Individual Prophylactic and Therapeutic Kit for a soldier and an observer, and individual medical package. The paper describes the application of Individual Prophylactic and Therapeutic Kit in the contemporary battle field. Various parts of the rucksack equipment have been depicted, illustrated and presented taking into account both its composition and the specific use of its components. The proposed kit involves providing first aid to one person (maximum two) by a casual rescuer.

Key words: first aid, Individual Prophylactic and Therapeutic Kit, first aid kit, military rescue, tactical rescue, rescuer training.

The concept of first aid means a fast organized action conducted by people or a person from the from the vicinity of the victim, who has sustained an unfortunate accident. Efficient and competent performance by trained medical personnel during first aid on the contemporary battlefield is very often decisive for the outcome of further treatment – it often determines the life of the victim. First aid is usually granted at the accident site and these first steps to prevent loss of life and health in the area of combat operations are granted by the soldiers involved in the Polish military contingents in the world. Although providing first aid is possible based on a complete improvisation with fortuitously available resources, but prophylactic preparation of even minimal emergency equipment (first aid kit) may facilitate the operation and greatly improve its effectiveness.

The first criterion for selection of rescue equipment are our needs, from car kits to sophisticated specialist rescue equipment.

The second criterion is the preparation of a rescuer. We supply ourselves in the equipment and measures that can be safely used. Specialized equipment such as resuscitation equipment, drugs, or evacuation equipment require additional (usually complicated) training. Therefore, in the basic first-aid kit it is particularly risky to place drugs or specialist equipment. The package of the first-aid kit should satisfy the conditions of mechanical resistance, clear purpose, convenience (portability). Traditional storing of the first-aid kit in a cardboard box, plastic bag or in a locked office closet is excluded. There should always be the possibility of quick delivery of the first-aid it to the scene instead of moving the victim to the place where it is stored. In case of the factory first-aid kit it is better to have several easily accessible, simple dressing kits (prominently displayed in the 'critical' points of the building) than one large specialized set locked in the ambulatory or a storage.

A model basic first-aid kit should contain the following dressing materials and rescue equipment:

- instruction for first aid in case of emergency,
- torch or a disposable chemical flashlight,
- scissors of a knife,
- sterile gauze dressing (gauze compresses) – 4 packs,
- hydrogel burn dressing (WaterJel®) – 2 packs, 20 x 20 cm
- elastic bandage – 4 packs,
- scarf bandage – 2 pcs,
- codofix (elastic mesh dressing) – 2-3 sizes,
- safety pin – 4 pcs
- isolaide resuscitation device,
- rubber gloves – 3 pairs,
- thermal insulation foil silver-gold (foil NRC) 1 – 2 pieces,
- 2 rolls of plain plaster,
- plasters with dressing (several sizes).

Proposed kit assumes providing first aid to one person (maximum two) by a casual a rescuer. Anticipating the eventual possibility of major accidents and losses, the number of the various content elements should be increased or preferably place there several sets.

The guidelines of first aid should be as simplified as possible (rather pictures than text) so that a casual rescuer without specialist training could safely use the content without making further damage to the victim of an accident. It should also contain a reminder of emergency telephone numbers, ambulance, fire brigade, etc., according to the needs and circumstances.

A torch can be used to call help and be essential in case of evacuation of endangered areas. An alternative to the usual torch is a disposable chemical emergency flashlight ('Safety Light'). Quite often, in order to provide assistance, it will be necessary to cut the car seat belts, clothing of the injured person, or dressings using a knife or scissors. Scissors with rounded ends (so-called dressing scissors) are convenient and safe checked for example by cutting a cardboard or a nylon tape.

The first layer of each dressing is usually constituted by a gauze dressing (not a cotton wool, lignin, toilet paper, oakum, etc.). A pack of sterilized gauze dressing is usually referred to as the 'compress gas'. An elastic bandage would be the best to attach the gauze to the wound (a bandage rather not gauze, which is usually torn during dressing). In addition, a roll of a bandage could be a roll pressing the pressure dressing, whereas two rolls may stabilise and seal a possible "foreign body" in the wound.

A scarf bandage (made of cotton canvas, interlinings, or foil) can be used for covering large injured surfaces, burns, attaching dressings on the head, temporary 'slings'.

Elastic mesh dressings of various widths (Codofix®, Elastofix®) are a convenient novelty among dressings. They can be used to attach dressings as elastic, mesh sleeve (stockings).

According to the standard adopted by the National Rescue-Firefightng System, hydrogel dressings should be a dressing of choice for all burns. According to current data, this dressing significantly reduces pain and complications.

Safety pins are used for temporary slings made of jacket tails, to pin a slit clothe or the ends of a dressing. Contrary to previous military guidelines safety spins are no longer used to pin wounds or to pin a tongue to the chin of the victim in order to restore the patency of the respiratory tract.

Usual sticking plaster is used for sealing and attaching a dressing or to secure a wound. An ordinary, linen one instead of paper and foil plasters. In chemical rescue a plaster may be used to seal the tears of evacuation overalls.

Small plasters are sufficient for minor scratches, cuts or grazes. Their application is more for hygienic and aesthetic matters than actual rescue in emergency cases. Simultaneously, it is the most commonly used item of first-aid kits in the plants.

Providing first aid at body damage and injuries is always associated with the risk of contact with blood. For protection against the infection it is advised to use rubber protective gloves (not necessarily a sterile pair, but rather not those made of foil, because they tear during putting them on). According to the recommendations for the National Rescue-Firefightng System, nitrile rubber gloves have optimal parameters.

Disposable masks for resuscitation (isolaide resuscitation device or Resusci Face Shield®) were introduced in a similar purpose as the gloves. It is a piece of foil with plastic mouthpiece and valve or filter that allows a possible substitute resuscitation using mouth-to-mouth technique.

The last essential item found in the first-aid kit is a thermal foil (NRC). The injured are often exposed to considerable heat loss, while waiting for medical assistance and transport to the hospital. A screen of silver and gold foil NRC, which reflects about 80% of infrared radiation and is windproof and waterproof, can provide effective protection against heat loss. The injured should be wrapped with the silver side of the foil. A typical foil (220 x 160 cm) is usually sufficient to secure an adult. NRC foil can also serve as a protection against overheating – in such case its silver side should be turned to the sun so that it would constitute a mirror reflecting the sunlight.

The proposed first-aid kit does not contain cotton wool, a piece of rubber (stasis, tourniquet), medicines and disinfectants. As it was previously mentioned, cotton wool should not be use to dress wounds, as it is extremely difficult to remove the its fibres during change of a dressing and it may hinder the healing of wounds or cause purulence. Cotton wool can only be a possible lining for stiffening dressings in case of fractures. A wide tape like a belt or a tie (reduced risk of local tissue damage) is suggested to temporally staunch bleeding from limbs wounds rather than narrow rubber tube (stasis). Tourniquets are generally used in case of mass accidents or trauma amputation.

It not recommended to place disinfectants in the first-aid kit. Open wounds, burns should not be disinfected (recommendation does not apply to the specific field conditions). The reason is that if someone suggested with the old way of dealing with burns will pour a second degree burn with e.g. salicylic alcohol, he will cause a series of complications including severe pain shock, additional tissue burn with alcohol, severity of the inflammation, damage to the nerve endings by the alcohol and neurotoxic salicylic acid. Iodine i.e. alcohol iodine solution in potassium iodide apart from the effects of alcohol causes uncontrolled absorption of iodine into the body. Gentian would act in the same way as it is also an alcohol solution. Moreover, it should be noted that there are people allergic to iodine or gentian. Dyes also make the surgical assessment of the injury impossible.

Hydrogen peroxide solution is too unstable as for the purposes of first-aid kit in the factory, and its possible preparation of perhydrol carries a risk of preparing to concentrated caustic solution.

The kit does not contain other agents such as rivanole and potassium permanganate, requiring troublesome dissolution before use.

Drugs are deliberately not included in the first-aid kit. Drugs typically placed in the kit are usually drugs requiring oral administration (swallowing), so the pharmacological effect can be expected after some time from the ingestion – in typical conditions after 20-40 minutes. Usually, we do not have such a luxury during first aid. Moreover, the injured in shock has relatively ischemic gastrointestinal tract what greatly hinders the absorption of the drug and significantly increases the risk of choking, nausea and vomiting, and irritation of the gastric mucosa. In injuries it would be desirable to administer analgesics, however the pain medications available in pharmacies without the prescription are too weak or are in the form impeding administration (oral - excluded, suppositories - controversial in the application). Moreover, leaving any drugs in generally accessible first aid kit factory creates the risk of abuse and accidental poisonings (which is not included in the group insurance contract). The person placing the first aid kit in the workplace is responsible for their content. Placing medical carbon for treatment in case of poisonings can be taken

Figure 1: A) The bag of Individual Prophylactic and Therapeutic Kit. Model Soldier. B) The bag of Individual Prophylactic and Therapeutic Kit with equipment. Model: PKW Soldier Asia/Summer

DESCRIPTION: A bag made of Condura material intended for storing and transporting of drugs and medical materials. The inside is divided in the way enabling generic placement of the equipment.

into consideration, because even though requiring large quantities. it is safe, passive medication.

First-aid kit should contain self-expanding bag for substitute breathing (Ambu, Laerdal, VMB), military individual dressings, eye rinsing glass, a collar for stabilisation of the cervical spine (may be disposable) and evacuation sheet or a rescue board.

Individual Prophylactic and Therapeutic Kit, introduced in 2006, serves for providing fist aid to the soldiers usually in form of self-aid.

The individual prophylactic and therapeutic kit for soldiers leaving to the area of combat operations, particularly in the region of Asia and Africa consists e.g. of miniature suction pump for removing ticks and venom of other venomous animals. It is related to as Aspivenin, Extractor or Anti-tick.

The device acts as a suction pump. It is used for suction (aspiration) of the venom after bites of insects (mosquitoes, wasps, bees, hornets, etc.), vipers and scorpions. The device is also used to remove ticks from the human body. Vacuum created at the end of the pump causes 'sucking' a tick off the body without leaving any of its parts. It is perfect for the needs of the first aid. In more complex cases, consultation with a physician is required. Due to the very tight, the rubber seal, the efficiency of the pump is guaranteed for a very long time.

Directions for use:

1) Apply as soon as possible after the bite or noticing a tick on the body.
2) To prepare the device for use, press the rubber plunger until it stops.
3) Place the ending of the device to the body to the area of the introduction of venom (where the tick has clung). A bite should be located in the central part of the position of the ending.
4) Press the device against the body and thus keeping the pressure gradually, slowly pull the plunger to the correct position.
5) Hold in this position for 10-15 minutes. Repeat the procedure if necessary.
6) Disinfect the bite site with disinfectants.
7) Wash the ending of the device with soap and water and then disinfect with a disinfectant

Contraindications:
Do not use the device on wounded skin around the eyes and the external genital organs. The device should not be applied in children below 3.

One-minute use of the device may prevent serious consequences of bites by:
- hornets,
- wasps,
- bees,
- mosquitoes,
- horseflies,
- ants,
- blackflies,
- indigenous spiders.

Figure 2: A pump removing ticks and venom. Model: Aspivenin.

DESCIPTION: ASPIVENIN® produced by the French company ASPIR® is a miniature suction pump generating negative pressure of 0.75 At and thus non-invasively and painlessly removes all the venoms and toxins. Regardless of its basic function of sucking toxins, ASPIVENIN® produces an additional effect i.e. generated negative pressure stops the blood circulation in the local net of capillaries and prevents the further spread of the toxins in the body. This device, thus, serves as a tourniquet without causing adverse effects associated with its long-term use while waiting for medical assistance in more severe cases.

Two-minute use sucks off the entire tick. Three-minute use prevents the effects of bites of:
- vipers
- spiders (e.g. Southern black widow, tarantula),
- venomous fish (e.g. stingray, Trachinus)
- scorpions.

Another component of the individual prophylactic and therapeutic kit is a gel used to disinfect the skin and mucous membranes as well as in treatment of infected wounds, carbuncles, abscesses, mixed skin inflammations. The gel is called **Rivel**.

Figure 3: RIVEL 0,5% gel 30g.
DESCRIPTION: Rivel gel is used for skin and mucous membranes disinfection and for the treatment of infected wounds, carbuncles, abscesses, mixed skin inflammations (bacterial and mycothic)

Action: RIVEL is a convenient, gel with rivanol mainly used in the treatment of skin inflammations and wounds. Active ingredient of the preparation acts on the skin surface and also penetrates deeper, acting as disinfectant and preventing infectious agents from penetrating into the wound. As a result, redness and swelling subsides, a sensation of warmth or pain disappears, the inflammation is reduced and the wound heals faster. The preparation does not irritate the skin and mucous membranes.

Indications: disinfecting of skin and mucous membranes, disinfecting of superficial skin damages (lacerations, harms, skin abrasions), disinfecting of wounds, furuncles, abscesses, mixed skin inflammations (bacterial and mycothic), on insects bites.

Contraindications: diagnosed hypersensitivity to ethacridine lactate, acridine derivatives or other auxiliary ingredients.

Dosage: Apply a thin layer of gel on the affected skin or mucous membrane 2-3 times a day (more often if necessary). The gel can also be used under the dressing.

Composition: Active ingredient 1 g of gel contains 5 mg of ethacridine lactate (Rivanolum 0.5%). The other ingredients: Macrogoli 7 glyceroli cocoas, triethanolamine, Eumulgin B3, Nipaguard MPA, polyacrylic acid, purified water.

Malarone

Malarone as a very important drug included in the individual prophylactic and therapeutic kit

It contains two active ingredients, atovaquone and proguanil hydrochloride, having biocidal effect on the agamonts of Plasmodium falciparum parasite present in the blood and liver.

Malarone is used for:
- prevention of malaria caused by Plasmodium falciparum
- treatment of acute, uncomplicated malaria caused by Plasmodium falciparum.

Because Malarone is effective against infections caused by the strains of Plasmodium falciparum susceptible and resistant to other drugs, it is recommended for the prevention and treatment of malaria caused by Plasmodium falciparum strains that may be resistant to other antimalarials.

Composition: each pill of Malarone contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride; other ingredients: poloxamer 188, microcrystalline cellulose, hydroxypropyl cellulose, povidone K30, sodium starch glycollate (Type A), magnesium stearate, hypromellose, titanium dioxide (E171), iron oxide red (E172), macrogol 400 and polyethylene glycol 8000.

Possible side effects: in the doses used for malaria prevention and treatment, possible adverse reactions caused by Malarone are usually mild and transient. Side effects that may be caused by Malarone and various ingredients include: abdominal pain and diarrhoea, headache, anorexia, nausea and vomiting, coughing.

1) Vascular and lymphatic system: anaemia, neutropenia (reduced numbers of white blood cells), pancytopenia (a decrease in all types of blood cells) in patients with severe renal failure.
2) Endocrine system and metabolism: anorexia, hyponatraemia (low levels of sodium in the plasma).
3) Digestive system: abdominal pains, nausea, vomiting, diarrhoea, gastric disorders, oral mucosa inflammation.

Dosage and further information: daily dose of Malarone should be taken at the same time.

To prevent malaria: Preventive administration of Malarone should begin 24 or 48 hours before coming to the endemic area with the incidence of malaria. Treatment should be continued throughout the period of residence in an endemic area, but for no longer than 28 days. Administration should continue for 7 days after leaving the endemic area. The recommended dosage of Malarone is one tablet once a day.

To treat malaria: The usual dose for adults is 4 tablets once a day for 3 days. For children the dose depends on their bodyweight:
- 11-20 kg - 1 tablet once a day for 3 days
- 21-30 kg - 2 tablets once a day for 3 days
- 31-40 kg - 3 tablets once a day for 3 days
- over 40 kg - dose as for adults.

Package: 12 tablets of Malarone

Contraindications: hypersensitivity to atovaquone or proguanil hydrochloride, or any other auxiliary ingredient and in the prevention of malaria caused by P. falciparum in patients with severe renal failure.

Loperamide

Loperamide is another drug in the individual prophylactic and therapeutic kit. It is an organic chemical compound, opioid antidiarrhoeal medication. It is one of the opioid substances, but it does not pass completely through the blood brain barrier, and thus there is no typical opioid effects on the nervous system what allowed its free use in medicine without the consequences of addiction. In medicine, it is the most widely distributed under the trade name - Laremid.

INDICATIONS: Symptomatic treatment of acute and chronic diarrhoea of various origins (with the exception of acute bacterial diarrhoea).

Dosage: Oral. Adults and children over 12 years of age: acute diarrhoea - two tablets initially, followed by one tablet after each loose bowel movement., the maximum dose is 8 tablets a day, chronic diarrhoea

Figure 4: LOPERAMID WZF 2mg pills, a'30

DESCRIPTION: Strong acting antidiarrhoeal medication. The effect of a reduction in the incidence and number of bowel movements. The effect is maintained for approximately 24 hours. Medical use: in the symptomatic treatment of acute and chronic diarrhoea occurring in functional disorders or inflammatory bowel disease, in patients with external fistula of the ileum (ileostomy) after colectomies or extensive resection of intestines to reduce the volume of eccrisis.

- initially 1 tablet 2 times a day, increase the dose to 4 tablets, if necessary (up to 6 tables a day). In chronic diarrhoea loperamide should not be used longer than 10 days. Children aged 6 to 12: 1 tablet after each abnormal bowel movement (Do not administer more than 2 tablets in children aged up to 8 and 3 tablets in children aged below 10 in any 24 hour period). This medicine is not recommended for children under 6 years old. While the use of loperamide adequate amounts of water and mineral salts should be taken. In the case of no improvement within 48 hours, discontinue treatment and contact a physician. Familiarize yourself with the properties of the medicine described in the leaflet before use. Before using this medicine, check the expiry date stated on the label. Do not use after expiry date. Keep the medication in a tightly closed container, out of reach and sight of children and as required by the manufacturer.

Possible side effects: skin rash, abdominal pains, flatulencies, nausea and vomiting, constipation, drowsiness, dizziness, dry mouth, loss of appetite. Side effects may include tiredness, dizziness or drowsiness. Therefore, it is advisable to exercise caution when driving or operating machinery. When a person is allergic to loperamide or to other ingredients when a person takes opioid analgesics, or if you are or think you are pregnant and when breastfeeding preparation should not be used during pregnancy unless your doctor decides otherwise. It should be used with caution in nursing mothers.

Panko

The individual prophylactic and therapeutic kit consists also of preparation Panko, which is an effective preparation against bites of mosquitoes, ticks and many other insects including blackflies. It ensures 8-hour protection. Application of this preparation consists of the exact application of the preparation to the bare body parts and clothing (except for leather clothing and synthetic materials). Apply indirectly on the face and neck – first spray hand, and then gently spread.

Fig. 7

Figure 5: Panko – Spray against mosquitoes and ticks, 75ml.

DESCRIPTION: it is an effective preparation against bites of mosquitoes, ticks and many other insects including blackflies. It effectively deters insects, sooths the bites and ensures 8-10 hour protection. Panko contains DEET – the most effective repellent.

Radiosun

Figure 6: RADIOSUN Sunburns cream; 100 ml tube.

DESCRIPTION: Radiosun is a soothing and calming cream with a complex action. It can be used in all types of burns: UV, thermal, and also in radiation-induced reaction of the skin after radiotherapy.

Its soothing and soothing action owes to unique composition formulation (Aqua, Olive oil, Myristal Myristate, Olive, Glicerin, Reynoutria japonica extract, panthenol, SQUALENE, Sylibum marianym Extract, Carbomer, Suttocide, Parfum Mentha).

The cream is efficient to use, easy to spread and leaves a soft protective layer on the skin. Very well absorbed. It soothes, softens skin burns occurring after exposure to UV and thermal burns, alleviates sensation of tension and itching of the skin, reduces heat and burning sensation, redness, soothes, smoothes and firms the skin. It effectively nourishes and lubricates the skin, neutralizes free radicals, and helps the skin barrier function.

Dermatological and application studies have not confirmed any irritating and allergenic action of the preparation. Moreover, Radiosun® is appreciated by specialists who recommend it to patients suffering from radiation-induced reaction of the skin after radiotherapy, because it soothes and calms the skin so that patients can feel comfortable. To obtain satisfactory results on the irritated skin, gently spread the cream several times a day.

Figure 7: MED. PLUS, UV protecting cream-emulsion 75 ml

DESCRIPTION: Cream provides effective, high protection of the skin of each type, prevents sunburn, SPF 30UVA + UVB.

Figure 8: Dermaplast Universal. Sticking plaster.
DESCRIPTION: Hypoallergenic sticking plaster made of a waterproof foil protecting from dirt is ideal for fast and hygienic dressing of small wounds. Apply to dry and clean skin.

Individual package includes:
- 4 pcs Ø 22 mm;
- 6 x 9 mm x 38 mm;
- 8 x 16 mm x 57 mm;
- 12 pieces of 19 mm x 72 mm;
- 10 pieces of 25 mm x 72 mm.

Figure 9: Cha-ha 0,2% on-irritating antiseptic fluid; 75 ml.
DESCRIPTION: Diluted solution ready for use, intended for the general hygienic skin disinfection. The active ingredient in Cha-ha is chlorhexidine. Fluid has a broad spectrum and long duration of antibacterial activity. It does not contain alcohol and does not irritate and sting the skin, even when the skin is particularly sensitive with damaged epidermis, or injured. It does not dry skin. and stain. Preparation can be used as an antimicrobial agent, effective in disinfecting and cleansing the skin of hands and body. Designed for external use only.

Figure 10: Anida, glycerine – aloe vera hand cream with vitamin A, E, 75 ml
DESCRIPTION: The content of aloe vera extract soothes irritations. Ideal moisturizer. It protects and regenerates skin exposed to the adverse external conditions.

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Biochemistry

Biosynthesis and characteristics of anti-inflammatory proresolving derivatives of omega-3 and omega-6 polyunsaturated fatty acids

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Summary:

Anti-inflammatory pro-resolving mediators are endogenous lipid-derived compounds that are actively engaged in the resolution phase of acute inflammation. These mediators derive from polyunsaturated fatty acids (PUFA): lipoxins from omega-6 (ω6) arachidonic acid (AA), oxylipins from ω6 docosapentaenoic acid (DPA-ω6), resolvins series E from ω3 eicosapentaenoic acid (EPA), and resolvins-D, protectins and maresins all from ω3 docosahexaenoic acid (DHA). The formation of anti-inflammatory pro-resolving mediators occurs in a process called transcellular biosynthesis in which two types of interacting cells participate, present in the region of inflammation, i.e. neutrophilic granulocytes and other cells, such as epithelial cells, platelets, endothelial cells, or monocytes. Enzymes contributing to the biosynthesis of pro-resolving mediators include lipoxygenases (LOX-5, -12, -15) and cyclooxygenases (COX-2 and aspirin-triggered acetylated enzyme, i.e. ASA-COX2), as well as monooxygenases of the cytochrome P450 family. Some chemical reactions taking part in the biosynthesis of pro-resolving mediators, such as epoxidation or hydrolysis, may be enzyme-dependent or enzyme-independent. Pro-resolving anti-inflammatory mediators exert their biological activities in a receptor-dependent manner. Of their various biological effects, the most important include inhibition of leukocyte mobilization and traffic through endothelial or epithelial layers, suppression of pro-inflammatory cytokines release by different cells present in inflamed tissue, and stimulation of the phagocytic activity of monocytes/macrophages. This article presents the current knowledge on the mechanisms responsible for and conditions underlying the formation of pro-resolving mediators, describes their functional characteristics, and depicts new trends on a possibility of their use in therapy.

Key words: anti-inflammatory pro-resolving mediators, polyunsaturated fatty acids, arachidonic acid, 6-docosapentaenoic acid, eicosapentaenoic acid, docosahexaenoic acid, lipoxins, resolvins, protectins, maresins, oxylipins.

Introduction

The involvement and role of lipid mediators such as leukotrienes, prostaglandins, thromboxanes and platelet activating factor in the course of inflammation is part of the canon of the patophysiology of this process. The three first listed groups represent a numerous family of compounds known as eicosanoids, derived from arachidonic acid – a polyunsaturated fatty acid of the omega-6 series, which is a constituent of membrane phospholipids. Platelet activating factor (PAF) is in fact a family of many factors, derivatives of glycerophosphocholine. All these group of compounds are inflammatory mediators, involved in propagation of inflammatory reaction [10, 27, 35, 53].

Biosynthesis of eicosanoids is preceded by the release of arachidonic acid from membrane phospholipid pool upon the action of phospholipase A_2 (Fig. 1). Only the free acid becomes the substrate for the two types of oxygenases: cykloxygenase (COX) and lipooxygenase (LOX). Enzymes of the COX family initiate the arachidonic acid →//→ prostaglandins/thromboxanes transformation pathway, while the enzymes of the LOX family initiate the transformation pathway leading, among others, to leukotrienes. Although studies on the biological properties of the listed eicosanoids, particularly inflammatory mediators, are being continued, their general characteristics and mechanism of action are well known and included in university textbooks (e.g. [27, 53]); therefore, they will not be discussed in this study.

The subject of this study will include mediators of anti-inflammatory potential: lipoxins, oxylipins, resolvins, protectins and maresins, formed from both arachidonic acid and other polyunsaturated fatty acids (PUFAs) present in plasmatic membranes, representing lipids of both omega-6 (ω6), and omega-3 (ω3) series. The listed classes of mediators represent a numerous group of anti-inflammatory pro-resolving mediators. An overview of the role of these mediators in acute inflammation has been presented in the previous work of the current author [35] and in other studies [3-5, 34, 36, 52].

Currently, we shall focus on biosynthesis and conditions for formation of these lipid compounds. In addition, detailed characteristics of these mediators shall be presented. According to the latest concepts regarding the course of acute inflammatory reaction [5, 35, 52], fast and inconsequential resolution of this process requires active contribution of "agonist" mediators, such as pro-resolving mediators. They are generated locally, i.e. at the inflammation site, and exert specific actions which – as is currently believed – are required for the acute process not being transformed into a chronic one, often constituting a platform for the development of pathologies which may last for many years, sometimes throughout the remaining lifetime, often posing a hard-to-cure medical problem.

Anti-inflammatory arachidonic acid derivatives

Lipoxins

Lipoxins (LXs) are metabolites of a**rachidonic acid** (AA; C20:4-ω6) with anti-inflammatory and immunomodulatory properties. The history of lipoxins, dating back to early 1980s, is relatively long in comparison to the history of anti-inflammatory derivatives of omega-3 PUFAs, i.e. resolvins, (neuro)protectin and maresins, which spans the period of several recent years. Back at that time, a group of researchers led by the Nobel Prize winner of 1982, Bengt Samuelsson, described a new arachidonic acid transformation pathway, consisting in double transcellular oxidation catalyzed by lipooxygenases (LOX) and leading to formation of unstable 15*S*-epoxytetraenic acid and, subsequently, to two other structures, named lipoxins, as in words: ***lipox****ygenase* and ***inf****lammation* [41, 46]. Two lipoxins were identified: **LXA4** and **LXB4**, and their full names are respectively: 5*S*, 6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid and 5*S*,14*R*,15*S*-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid.

Ten years after the discovery of lipoxins, a collaborator of B. Samuelsson, Charles N. Serhan showed that leukotriene LTA_4 might also be a substrate for the lipoxin synthesis [41, 43]. Several years later, Claria and Serhan reported formation of two lipoxin epimers [13].

The discovery of **15-epi-LXA4** and **15-epi-LXB4** was made in an *in vitro* experimental system, in which two types of human cells: human umbilical vein endothelial cells or epithelial (A549) cells were coincubated with neutrophils in the presence of acetylsalicylic acid (ASA). The studies involving the use of ASA (popular aspirin) led to two observations. The first one was easy to foresee and due to suppression of COX activity (which led to inhibition of the synthesis of proinflammatory prostaglandins and was associated with anti-inflammatory activity of the drug), and the other was unexpected, but associated with important consequences. It turned out that acetylated COX-2 (ASA-COX2), although incapable of promoting the synthesis of prostaglandins, inhibited another metabolic pathway of arachidonic acid, i.e. its transformation into 15-epi-lipoxins. The described biological system: coincubation of two types of cells in the presence of ASA, was subsequently used in numerous further experiments, in which another lipid mediators were discovered.

Synthesis of lipoxins

The synthesis of lipoxins from arachidonic acid (AA), although theoretically possible to occur in a single cell, usually occurs sequentially in two types of cells. Such a process is defined as transcellular biosynthesis; it is an example of cell-specific processes. Thus, biosynthesis of lipoxins requires cooperation of various types of cells present at the inflammation site, where said cooperation consists in transferring byproducts for further transformations.

Enzymes and/or chemical reactions (such as non-enzymatic processes) involved in lipoxin synthesis may differ depending on the type of cells involved in their formation. Fig. 1 presents metabolic pathways leading to formation of various signaling compounds, including lipoxins. Of note is the fact that the first stage determining further transformations is excision of AA from membrane phospholipids by means of the enzyme phospholipase A_2 (PLA_2). Free AA is a substrate for many enzymes of lipooxygenase (LOX) and cyclooxygenase (COX) families, as well as monooxygenases of the cytochrome P450 family. Action of these enzymes leads to formation of compounds of varied biological activity, such as prostaglandins, thromboxanes and leukotrienes. In contrast to these compounds, most of which are characterized by proinflammatory activity (prostaglandins, leukotrienes), lipoxins have an anti-inflammatory effect. Thus, the discovery of the AA →//→ lipoxins metabolic pathways changed the universal claim that the derivatives of the polyunsaturated omega-6 fatty acid, arachidonic acid (AA) are inflammatory mediators. Beyond doubt, lipoxins do not belong to this category.

There are at least three pathways to form lipoxins in different cell systems (Fig. 2), such as:

- **Epithelial cells – neutrophils**; the system involves sequential action of two types of lipooxygenases, i.e.: 15- and 5-LOX. First, the action of these enzymes leads to formation of 15*S*-hydro(peroxy)-eicosatetraenic acid, which is further transformed into intermediate 15*S*-hydro(peroxy)-5*S*, 6*S*-epoxytetraenic acid and next to lipoxins A_4 (LXA_4) and B_4 (LXB_4);

- **polynuclear neutrophils – platelets**; the system involves the sequence of 5-LOX and 12-LOX – the intermediate compound along this pathway is leukotriene A_4 (LTA_4);

- **neutrophils – vascular endothelial cells** or **epithelial cells** or **monocytes**; these systems involve COX2 and 5-LOX, where the former must be present in its acetylated form, as is the case in presence of acetylsalicylic acid (ASA). The action of ASA-COX2 leads to formation of 15*R*-hydroxy-ETE (15*R*-HETE), while the action of 5-LOX leads to 5*S*, 6*S*, 15*R*-epoxytetraenic acid. The final products of the aforementioned cell systems are 15*R*-epimers of lipoxins, i.e. 15-epi-LXA_4 and 15-epi-LXB4, commonly referred to as 15-epi-lipoxins or 15-epi-LXs or identified using other acronyms: AT-LXA_4 and AT-LXB_4, which underline the necessity of ASA; AT stands for aspirin-triggered. Both lipoxins are commonly referred to as ATLs. One must note that the biological activity of lipoxins and AT-lipoxins is similar. A proof for the formation of ATLs in humans was demonstrating the presence of ATL in the urine of healthy volunteers after administration of aspirin at the dose of 100 mg/day for ≥ 8 days, and in plasma following 8 weeks of treatment with low ASA doses [39].

Inactivation of lipoxins

Inactivation of lipoxins and AT-lipoxins in the inflammation region is important as it eliminates biologically active structures, thus contributing to termination of their effect. Studies showed that LXA_4 is a substrate for two enzymes: 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and multifunctional eicosanoid oxidoreductase (EOR), including enzymes with affinity to both prostaglandins (PGR, prostaglandin reductase), and leukotrienes B_4 (LTB_4DH – LTB_4 dehydrogenase); sometimes, the lipoxin-inactivating enzymes are referred to using the common acronym PGR/LTB_4DH. These enzymes act on LXA_4, which leads to the formation of inactive compounds: 15-oxo-LXA_4 and 13,14-dihydro-15-oxo-LXA_4; the latter may be further transformed into 13,14-dihydro-LXA_4 [14]. Thus, the listed reactions include oxidation at position C15 and reduction of the C13=C14 bond. More recent data mention an additional lipoxin metabolic pathway, consisting in hydroxylation at position C20 [38]. One should mention that 15-epi-LXs are more resistant to inactivating enzymes than LXs, owing to which their body levels are higher and their effects are stronger.

During inflammation, multiple active compounds are synthesized; initially, they include inflammatory mediators, e.g. prostaglandins and leukotrienes, and later, they include also anti-inflammatory compounds, such as lipoxins, as well as resolvins and maresins (see below). Local inactivation of these compounds, similar to their inactivation in the inflammation area, fundamentally affects the course and outcome of inflammation. Thus, the role of enzymes degrading inflammatory mediators will be as important for the course of the inflammatory reaction as the role of mechanisms responsible for their formation and "supply".

Biological effects of lipoxins

Lipoxins, or, in particular lipoxin A_4 (LXA_4) and its 15-epi-LXA_4 – since it is these two compounds that are considered to be main representatives of the series (to date) – exert their action by inhibiting the receptor known as ALX [12]. Despite the fact that lipoxins A and B are structurally similar, LXB_4 and 15-epi-LXB_4 do not act via the ALX receptor. As suggested by functional test results,

there is most probably a B_4 lipoxin-specific receptor waiting to be discovered.

The ALX receptor was studied at the molecular level in the early 1990s [21]. It belongs to a numerous family of G protein-coupled receptors (GPCR); it consists of 351 amino acid residues and coded by a gene found in humans in chromosome 19q. ALX receptors are present in different cells, with particularly large numbers observed on leukocytes and in somewhat lower amounts on eosinophils, monocytes/macrophages, basophils, T-cells, dendritic cells, fibroblasts, renal mesangial cells, endothelial and vascular smooth muscle cells and hepatocytes.

The biological effects of stimulation of the ALX receptor are varied and location-dependent, i.e. cell-specific. For instance, in case of **neutrophils**. inhibition of chemotaxis, adhesion and transmigration can be observed, as well as reduction in degranulation, adhesion to the endothelium and homotypic aggregation, as well as reduction in IL-1β and IL-8 levels, expression of CD11b/CD18 (adhesion proteins). In case of **eosinophils**, inhibition of migration and degranulation, as well as eotaxin and IL-15 production. In case of **monocytes/macrophages**, intensification of: chemotaxis and adhesion to laminin as well as phagocytosis of apoptotic polynuclear leukocytes, and inhibition of IL-8 production, NF-κB activation and formation of the reactive oxygen radical: superoxide nitrate. In **T-cells** – inhibition of secretion of TNF-α, and in **dendritic cells** – reduction in IL-12 production; in **epithelial cells** – inhibition of IL-8 secretion and in **vascular endothelial cells** – enhanced expression of the tissue factor (TF) and heme-a oxygenase, formation of prostacylin (PGI_2) and reduction of: VEGF-dependent proliferation, adhesion and migration as well P-selectin expression.

The diversity of the effects of stimulation of the ALX receptor, and thus of the biological activity of LXA_4 and its 15-epimer (several of the above biological effects of LXA_4 can also be exerted by LXB4), makes lipoxins being considered as strong endogenous anti-inflammatory factors. The "disadvantage" of these compounds is that they undergo rapid enzymatic inactivation *in vivo* [38]. This makes exogenous lipoxins incapable of being used as anti-inflammatory drugs. However, the attempts to use synthetic and metabolically stable analogs of lipoxins and AT-lipoxins are continued with good results, which is a cause for optimism.

Soon, the treatment of inflammations, particularly acute inflammations, may include pro-resolving drugs, which would constitute a qualitatively novel strategy of treating these conditions. Lipoxin analogs currently studied for their potential used as drugs in humans include ATL analogs, e.g. 15(*R/S*)-methyl-LXA_4 ($ATLa_1$), 15-epi-16-(*para*-fluoro)-phenoxy-LXA_4 ($ATLa_2$; the compound is present as a methyl ester – *in vivo*, the ester is rapidly hydrolyzed by plasma and liver esterases into the free acid, which is the active compound), 3-oxy-15-epi-LXA_4 (ZK-994), o-[9,12]-benzo-ω6-epi-LXA_4 or 16-phenoxy-LXA_4 [15, 23, 26, 37, 38]. The synthesis of stable lipoxin analogues takes into account the fact that interaction of LXA_4 with the ALX receptor is highly stereospecific and requires certain structural and conformational arrangements being maintained, including the 5*S*,6*R*-orientation of hydroxyl groups and the presence of the C11=C12 double bond in *cis* position.

New and particularly interesting – particularly for ophthalmologists – is the fact that the stable analog of AT-lipoxin, ATLa, showed pro-resolving effects in acute inflammatory reactions in ocular tissue and effectively blocked corneal neovascularization – phenomena induced in mice by administration of micropellets containing IL-1β and/or VEGF-A [22].

Summarizing the effects of lipoxins and AT-lipoxins, one may conclude that these compounds, as well as their metabolically stable analogs, exert anti-inflammatory action by active contribution at the active inflammatory reaction resolution phase [40]. *In vivo*, the anti-inflammatory effect is a resultant of multidirectional effects of lipoxins in several types of cells involved in the inflammatory process. The most important effects of lipoxins (characterized by anti-inflammatory and pro-resolving properties) include, on one hand, reduction/inhibition of neutrophil function and transmigration through "barriers" of epithelial and endothelial cells, and on the other hand, suppression of the release of pro-inflammatory cytokines by T-cells and stimulation of phagocytic activity of monocytes and macrophages.

Attempting to classify the biological effects of lipoxins into classical anti-inflammatory and pro-resolving effects, the division may be as follows: the group of anti-inflammatory effects would include the effects dependent on specific signals generated by neutrophils, i.e. the reduction of: CD11b/18, production of reactive oxygen species, activation of NF-κB, secretion of pro-inflammatory cytokines/chemokines and the increase of production/enhancement of the activity of anti-inflammatory cytokines/chemokines. The group of pro-resolving effects (dependent on specific „signals" generated by monocytes/macrophages) would include: the increase/enhancement of Ca^{2+} ions mobility, adhesion and chemotaxis, as well as

stimulation of macrophages to phagocytize apoptotic neutrophils in the area of inflammation.

Finally, it has to be mentioned that the spectrum of biological effects (both anti-inflammatory and pro-resolving) of lipoxins may be wider than that presented above, as there are premises indicating that these compounds may enter interactions with receptors other than ALX, such as $CysLT_1$ (antagonistic effects observed in macrovascular epithelial cells and mesangial cells → suppression of the effects of leukotriene LTD_4) and nuclear aryl hydrocarbon receptor AhR (*aryl hydrocarbon receptor*), which is a ligand-activated transcription factor controlling the expression of different gene sets; LXs are direct agonists of this receptor → anti-inflammatory effects) [12, 23, 39]. In terms of the overall effect of lipoxins, of importance may be also the inhibitory effect of signals generated by ALX and $CysLT_1$ receptors on the function of growth factor receptors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) or connective tissue growth factor (CTGF) – such interactions may lead to suppression of processes dependent on these factors, such as angiogenesis, proliferation and fibrosis [12, 23, 39].

Anti-inflammatory derivatives of omega-3 polyunsaturated fatty acids

Resolvins - the name is derived from words ***resol****ution* and ***in****teraction*, referring to the *cell-cell interaction* required for the synthesis of the compound or **in**flammation, as in case of lipoxins. Resolvins are a family of derivatives of eicosapentaenoic acid (E series) and docosahexaenoic acid (D series).

Resolvin E series – eicosapentaenoic acid derivatives (EPA)

The discovery of resolvin E series dates back to the year 2000 [1]. At that time, an observation was made regarding unexpected, albeit resembling the case of lipoxins, effect of the acetylsalicylic acid (ASA) on COX-2 in human vascular endothelial cells (exposed to TNF-α in order to stimulate COX-2 expression) and the capability of the acetylated enzyme (ASA-COX2) to catalyze the transformation of **eicosapentaenoic acid** (EPA; C20:5-ω3) to 18R-hydro(peroxy)-eicosapentaenoic acid, or 18*R*-H(p)EPE. After being uptaken by neutrophils present in the culture, 18*R*-H(p)EPE was transformed by the action of neutrophil-derived 5-LOX into 5*S*-hydro(peroxy)-18*R*-hydroxy-EPE, or 5*S*-H(p)-18*R*-HEPE, then to 5*S*(6)-epoxy-18*R*-HEPE and finally to 5*S*,12*R*,18*R*-triHEPE (Fig. 3). The last structure is that of **resolvin-E1** (**RvE1**), or 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8E,10*E*,14*Z*,16*E*-eicosapentaenoic acid [1] (Fig. 3).

Resolvin-E2 (**RvE2**), or 5*S*,18*R*-diHEPE (5*S*,18*R*-dihydroxyeicosapentaenoic acid) was found to be formed simultaneously with RvE1. RvE2 is a product of the reaction of peroxidation of 5*S*-H(p)-18*R*-HEPE, which is also an intermediate in the synthesis of RvE1 (Fig. 3).

Formation of resolvins of the E series resembles the process of lipoxin formation and is a result of the process described as transcellular synthesis. These qualitatively novel EPA metabolites showed anti-inflammatory activity in different cell systems and inflammation models. The activity consisted in activation of the process of resolution of acute inflammatory reaction. The biological activity profiles and strengths of RvE1 and RvE2 are similar, although some differences can be observed. According to data available to date, the range of RvE1 effects is wider than that of RvE2. RvE1 and RvE2 regulate (inhibit) infiltration– transendothelial migration of neutrophils into the inflammation area, stimulate macrophages to phagocytize apoptotic neutrophils and reduce the release of pro-inflammatory cytokines (Table 1). Resolvins promote the stage of inflammation healing, i.e. katabasis or resolution [19]. The strength of both resolvins is similar after intravenous (i.v.) administration; however, following intraperitoneal (i.p.) administration, the effect of RvE1 is stronger than that of RvE2. In addition, RvE1 affects: thrombocytes (disturbing thromboxane-dependent platelet aggregation), T-cells (enhances the expression of the chemokine receptor CCR5), dendritic cells (inhibits IL-12 migration and production) and eosinophils (inhibits allergen-dependent mobilization of eosinophils). In addition, RvE1 alleviates colitis and prevents osteoclast-dependent bone destruction [1, 2, 19, 44].

Comparison studies showed that in some biological systems, the anti-inflammatory effects of RvE1 were stronger that these of aspirin, and even these of dexamethasone [1, 44].

RvE1 exerts its biological action by the ChemR23 receptor, showing 36% structural similarity to the ALX receptor [2, 19]. Stimulation of the ChemR23 receptor activates a series of signaling processes, including MAP kinase cascade. ChemR23 is also activated by the peptide ligand – chemerin, which has anti-inflammatory properties [11]. RvE1 may also interact with the leukotriene LTB_4 receptor BLT1, expressing an interaction profile characteristic for that of a partial agonist. This interaction led to suppression of the LTB_4→BLT_1 signal in neutrophils [2].

Human neutrophils synthesize larger amounts of RvE2 compared to RvE1. However, RvE2 does not interact with the ChemR23 receptor, and thus the

molecular mechanism of receptor signaling induced by this resolving remains unknown [56].

It is assumed that resolvins are formed in the final stage of acute inflammation as a result of interactions between two types of cells (transcellular biosynthesis). However, studies in healthy volunteers receiving fish oil (containing 1 g of EPA and 0.7 g of DHA) with aspirin (160 mg), revealed presence of RvE1 in plasma samples in the amounts of 0.1-0.4 ng/mL, suggesting that biosynthesis of resolvins may take place in healthy humans, without any inflammation process detected [1].

Resolvin D series – docosahexaenoic acid derivatives (DHA)

Resolvins of the D series, i.e. compounds derived from **docosahexaenoic acid** (DHA; C22:6-ω3), were detected in the exudate from mice with chemically induced inflammation receiving DHA and aspirin [47]. Reactions of **AT-RvD** and **RvD** formation were essentially similar to these involved in the synthesis of resolvins of E series (transcellular biosynthesis), with the difference consisting in a larger number of resolvins being formed (four compounds per series): RvD1–RvD4 and AT-RvD1–AT-RvD4. In case of AT-RvD resolvins, the starting metabolite of DHA (formed as a result of ASA-COX2 action) is 17R-H(p)DHA, which is next transformed, via 7*S*-hydro(peroxy)- and 7*S*(8)-epoxy- forms, into AT-RvD1 and AT-RvD2. Transformations of 17R-H(p)DHA → 4S-hydro(peroxy)-derivatives → 4S(5)-epoxy-derivatives lead to formation of resolvins D3 and D4, i.e. AT-RvD3 i AT-RvD4 (Fig. 4).

LOX-LOX-dependent pathways of transformation of DHA into D1-D4 resolvins (RvD1, RvD2, RvD3 and RvD4) are shown in Fig. This figure also contains full chemical names of the compounds. According to a recent publication by Calder [8], there may be more resolvins in the D series: in his work, author suggested two new compounds, resolvins D5 and D6, but did not present the mechanism of their formation.

Inactivation

Inactivation of RvD1 and resolvins of E series involves the same enzymes as lipoxins, i.e. 15-PGDH and EOR; however, catalytic capacity of these enzymes is slightly lower in case of resolvins (reactions are slower). The aforementioned enzymes catalyze transformation of resolvins into 8-oxo- and 17-oxo-derivatives. An interesting observation was made in the comparison studies of metabolism of RvD1 and AT-RvD1 (the latter differs from RvD1 only with the configuration of the 17-hydroxyl group – 17*R*), which showed that only the first compound, i.e. RvD1 was rapidly inactivated [54].

Biological effects

In contrast to numerous known biological effects of resolvins of the E series, information regarding resolvins of D series is relatively scarce and describes mostly the use of resolvin D2 in animal models. First observations revealed the capacity of these compounds (administered to mice by intravenous route) to inhibit mobilization and infiltration of leukocytes in the mouse dorsal air pouch inflammation model [15] caused by TNF-α and in zymosan-induced peritonitis [47]. Protective effect of resolvins of the D-series was also reported with respect to renal damage or function loss due to hypoxia and following reperfusion [20].

Recent reports [51] have stated the protective effect of RvD1 when injected at very low doses of 0.01-10 ng *i.v.*, in inflammation caused by oxidative stress; peritonitis in mice was induced by *i.p.* administration of a cytotoxic and pro-inflammatory aldehyde, i.e. 4-hydroxynonenal (HNE), which is formed *in vivo* in the peroxidation of lipids, including numerous polyunsaturated fatty acids. Suppression of leukocyte infiltration was proportional to the RvD1 dose being used and was between 30 and 70% [51]. Table 1 Presents the effects of resolvins on different cells participating in the inflammatory process.

RvD1 has also inhibited IL-1β expression in microglial cells [25] and reduced vasoobliteration and neovascularization in retinopathy [16]. Recent reports extended the range of ocular effects of RvD1 and RvE1, which inhibited the pro-inflammatory signaling generated in choroid endothelial cells and leukocytes as well as transmigration of leukocytes through the endothelium *in vitro* [55].

(Neuro)Protectin – a docosahexaenoic acid derivative (DHA)

First observations showing the capacity of the central nervous system (CNS) tissues, including retina, to transform docosahexaenoic acid (DHA) upon catalysis with lipoxygenases (LOX) date back to the year 1984. The results of further studies showed a "beneficial" effect of the fatty acids of the omega-3 series (EPA and DHA) within the CNS. As early as in these times, that is more than two decades ago, the role of diet rich in these acids (especially DHA) in maintaining proper brain function was underscored. However, at that time nobody expected that certain metabolites of DHA, such as compounds of the type of hydroxydocosanoids might have unique

protective properties that would justify naming them protactins or neuroprotectins.

Biosynthesis of (neuro)protectin

The substrate for the synthesis of **protectin** is **docosahexaenoic acid** (DHA; C22:6-ω3). At the first stage of biosynthesis, LOX transforms DHA into 17*S*-H(p)DHA – a structure that next undergoes enzymatic epoxidation to form 16*S*(17)-epoxydocosatriene. Finally, the docosatrienoic compound is transformed by enzymatic hydrolysis into 10*R*,17*S*-dihydroxy-docosa-4*Z*,7*Z*,11E,13E,15*Z*,19*Z*-hexaneoic acid, i.e. **protectin D1** (**PD1**); the suffix D1 presents the nature of the compound: D provides information about the origin, i.e. DHA, while 1 stands for the first compound in the series. If biosynthesis takes place within the CNS, the generated compound is called **neuroprotectin D1** (**NPD1**); if biosynthesis takes place outside the CNS, the compound is called PD1. Fig. 6 presents the DHA transformation pathways with emphasis on the pathway leading to protectin generation.

In physiological conditions, biosynthesis of neuroprotectin takes place mostly in the structures/organs containing large amounts of DHA. The CNS, and particularly the retina, belong to this group of organs; It is the DHA content that makes the retina a unique organ in the animal and human system [32, 33]. The specific and effective DHA transport system within mammal bodies ensures high supply of DHA from the gastrointestinal tract into the retinal pigment epithelium (RPE) and photoreceptors [31]. It should be noted again that polyunsaturated fatty acids, particularly those of the omega-3 series (EPA, DPA, DHA, and, to a large extent, the precursor of these compounds, i.e. α-linolenic acid, C18:3-ω3), belong to the so-called essential fatty acids (EFAs), which cannot be synthesized in sufficient amounts in the human body, and which thus must be introduced with food or as diet supplements. The presence of this most unsaturated, fatty acid, containing six double bonds, in plasmatic membranes of photoreceptors and, in particular, their external segments (containing visual pigments responsible for absorption of light photons), is essential to maintain both the functional "plasticity" of the cell/plasma membrane and the compartmentalization of processes associated with perception of visual sensations. In contrast to other lipid membrane components, DHA present in the membranes of the RPE-photoreceptor complexes shows high mobility and dynamics, also with regard to generation of NPD1.

Although the reactions of NPD1/PD1 biosynthesis are well known, initiation of the process of neuroprotectin generation is not fully understood; it is uncertain whether actual inflammatory process with cell influx into the inflammation area is necessary for the synthesis, as discussed in other articles by the authors [34, 35]. This type of doubts are justified by the fact that cultured human RPE cells (ARPE-19 – spontaneously transformed RPE cells), or human brain cells are capable of synthesizing NPD1 e.g. under conditions of hypoxia, oxidative stress and the presence of cytotoxic bis-retinoid A2E, as well as in the presence of IL-1β and calcium ionophore A23187 [24, 28, 29]. Docosanoid formed in these conditions showed neuroprotective properties, e.g. preventing cell apoptosis caused by oxidative stress and induction of COX-2 stimulated by the presence of pro-inflammatory cytokine. These and other observations were decisive for the 10R,17*S*-dihydroxydocosahexaenoic acid being called "neuroprotectin" (NPD1) [6, 24, 28, 29, 45].

It cannot be excluded that the DHA→//→NPD1 transformation is a kind of defensive reaction occurring in threat situations, e.g. in inflammation or neurodegeneration (according to the most recent concepts, chronic inflammation and microglia are crucial as the factor inducing and maintaining neurodegeneration). It should be mentioned that some well known endogenous factors are capable of stimulating biosynthesis of NPD1 in RPE cells; they include, for example, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), leukemia inhibitory factor (LIF), and even anti-angiogenic pigment epithelium-derived factor (PEDF). It was also reported that the presence of NPD1 leads to upregulation of the expression of anti-apoptotic and downregulation of the expression of proapoptotic proteins of the Bcl-2 family, resulting in a drop in proapoptotic activity of caspase -3 and suppression of the apoptotic process [6, 24].

To date, no specific receptor of NPD1/PD1, through which the protectins might exert their biological effects, was identified. However, the concept of receptor-dependent nature of the mechanism of action of (neuro)protectin is predominant. Extensive research is currently conducted to find such receptors within the retina and the brain.

It is assumed that the lack of (neuro)protectin may contribute to the acceleration of the development of degenerative pathologies such as age-related macular degeneration (AMD) or Alzheimer's disease [6, 24].

NPD1/PD1 exert many effects in line with their classification as pro-resolving factors, e.g. inhibition of expression of genes encoding

proinflammatory compounds such as IL-1, COX-2 and B94 (a pro-inflammatory element induced by TNFα) and cytokine exodus protein-1 (CEX-1, an inflammatory response and oxidative stress marker); other effects of (neuro)protectins are listed in Table 1.

Maresins – *docosahexaenoic acid derivatives (DHA)*

Maresin – the name is derived from three words: ***ma***crophage, ***res***olution and ***in***flammation.

Maresins are the most recent component of the family of endogenous pro-resolution mediators of the acute inflammation phase. An article published in January 2009 presented the results of recent research by Serhan *et al.*, suggesting a novel pathway of docosahexaneoic acid (DHA) transformations [49]. Using the advanced, complex techniques of lipid analysis (mediator lipidomics) allowing to isolate, extract and identify various (including stereospecific) metabolites of polyunsaturated fatty acids, including DHA, the Serhan's group managed to identify hitherto unknown DHA metabolites produced in exudates collected from mice with peritonitis (induced by zymosane) and by macrophages present in the exudates.

The researchers demonstrated that besides the already known metabolites, such as 17*S*-hydroxy derivatives of DHA (a precursor of the synthesis of D-series resolvins and protectins), hitherto unknown 14*S*-hydroxy derivatives of DHA were also present. After adding DHA or synthetically obtained 14*S*-H(p)DHA to the activated macrophage-containing suspension, presence of qualitatively new DHA metabolites containing two hydroxyl groups and characterized by biological activity similar to that of resolvin E1, originating from EPA (RvE1, containing three hydroxyl groups in positions 5*S*, 12*R* i 18*R*) and of protectin D1, originating from DHA (PD1, with two hydroxyl groups in positions 10*R* and 17*S*) was revealed. The newly identified compound turned out to be 7*S*,14*S*-dihydroxydocosa-4*Z*,8,10,12,16*Z*,19*Z*-hexaneoic acid, i.e. **7S,14S-dihydroxy-DHA** or 7*S*,14*S*-diH-DHA, or 7*S*,14*S*-diHDHA – all notations relate to **maresin** (**MaR1**). Of note is the lack of stereochemistry indications at positions 8, 10 and 12, which might, but does not have to represent 8*E*, 10*Z* and 12*E* configurations. It turned out that double oxidation of DHA, leading to formation of MaR1, was sequentially catalyzed by two enzymes: 12- and 5-LOX (Fig. 7).

Biological activity of MaR1 involves multidirectional interactions leading to restriction of accumulation of polynuclear leukocytes in inflammation area due to stimulation of phagocytic activity of macrophages (Table 1). Since MaR1 appears in the inflammatory reaction resolution phase, it is another proresolving mediator. MaR1 is thought to exert its biological activity via a specific receptor different from the receptor for resolvins and protectins, and remaining to be identified.

Anti-inflammatory derivatives of omega-6 docosapentaenoic acid (DPA-ω6)

The idea of searching for novel resolvins not associated with the omega-3 acids is related to recent observations, gathered since 2007 and focusing on the anti-inflammatory potential of oil produced by *Schizochytrium sp.* microalgae. The oil contains 40% DHA, 2.5% EPA and 15% DPA-ω6. The product is commercially available under the name of DHASCO-S (DHA-S™), derived from DHA Single Cell Oil (Martek Biosciences Corporation). In contrast to another oil product from Martek, known as DHASCO-T (DHA-T™), produced by microalgae *Crypthecodinium cohnii* and containing 40% of DHA (with trace amounts of other polyunsaturated fatty acids), DHASCO-S showed stronger anti-inflammatory effect in the rat inflammation model (hind paw edema caused by administration of mucous polysaccharide present in red algae – carrageenan induction test) [30].

Direct comparison of the relative strength of anti-inflammatory activity of individual polyunsaturated fatty acids present in the studied oils showed the following results: DPAn-6 (DPA-ω6) > DHA > EPA, while the studies of biological effects of combinations of ethyl esters of these acids: DHA + EPA and DHA + DPAn-6 (DPA-ω6), both in carrageenan test and in the test of *in vitro* migration of neutrophils and other phages stimulated by the chemotactic factor *N*-formyl-Met-Leu-Phe (fMLP) suggested that DPAn-6 (DPA-ω6) has high anti-inflammatory potential, either by itself, or via its metabolites [30].[1]

Detailed studies of the biological activity of DPA-ω6 and its various derivatives in two animal models of acute inflammation (mice, rats) [17] and in the murine model of delayed hypersensitivity [18] showed that the active compounds of high anti-inflammatory potential are two oxylipid derivatives formed from DPA-ω6 upon treatment with 15-LOX, i.e. 17*S*-hydroxydocosa-4Z,7Z,10Z,13Z,15E-pentaenoic acid (**17*S*-hydroxy-DPAn-6** or **17*S*-HDPAn-6** or 17***S*-DPA-ω6**) and

[1] In their work [30], Nauroth JM et al. consequently use the abbreviation DPAn-6 for the docosapentaenoic acid of the omega-6 series, while in this study, this acid is referred to as DPA-ω6; both abbreviations are equivalent.

10S,17*S*-dihydroxydocosa-4Z,7Z,11E,13Z,15E-pentaenoic acid (**10*S*,17*S*-diHDPAn-6** or **10S,17*S*-HDPA-ω6**). Due to their activity in the final phase of acute inflammations, these compounds were nicknamed **DPA-ω6 resolvins**. The popular name of these resolvins is oxylipins. Of note are particularly the data showing the anti-inflammatory activity *in vivo* in the delayed hypersensitivity model, where 17SHDPA-ω6 resolvin at doses as low as 5 μg/kg body mass caused statistically significant effect comparable to the effect of dexamethasone at the dose of 500 μg/kg body mass [18].

Formation of DPA-ω6 resolvins (oxylipins) was demonstrated both in *ex vivo* conditions, with DPA-ω6 incubated in the environment containing fresh whole human blood, and *in vivo*, where rats received DPA-ω6-enriched diet for 19 days. In the first model the main identified metabolite was 17*S*-HDPA-ω6, while in the second model, presence of 17*S*-HDPA-ω6 was detected in blood, bronchi, heart and, in smaller amounts, in small intestine, lungs and kidneys. Other studies showed that under *in vivo* conditions, formation of oxylipins from DPA-ω6 was higher than formation of DHA-derived resolvins. It should be mentioned that DPA-ω6 resolvins (oxylipins) were not detected in biological systems in which the ω6-precursor had not been used [17].

The aforementioned studies revealed yet another important observation of potential practical importance. It turned out that the metabolic stability of DPA-ω6 resolvins (oxylipins) and, for comparison, the 17-hydroxy derivative of DHA (all compounds were incubated at a concentration of 10 μM in microsomal human liver extract) was the highest for 10,17-HDPA-ω6 and 17-HDPA-ω6. Thus, the DPA-ω6 derivatives are metabolically more stable, which is a parameter of high importance when designing potential drugs. Finally, another practical hint was the fact that supplementation with DPA-ω6-containing products led to *in vivo* synthesis of pro-inflammatory oxylipins, which may interfere with the course of the inflammatory process.

Conclusion

When analyzing biosynthesis and properties of anti-inflammatory pro-resolving mediators, it is finally worth turning our focus to their precursors, i.e. the polyunsaturated fatty acids. They are commonly referred to as PUFAs or LCPUFAs, as in long-chain PUFAs. These acids are prevalent in living organisms, both vegetable and animal, starting from the simplest, single-cell organisms and ending at the most complex ones, including the human. They are nearly ubiquitous and indispensable for both normal cell structure and normal course of numerous physiological processes. PUFAs are integral components of plasmatic membranes, playing numerous roles [32, 33]. Despite PUFAs being so important, not all living organisms are capable of synthesizing them in sufficient amounts – therefore, they must be supplied from the outside. Humans are one of such organisms.

The function of fatty acids is determined by their chemical structure (having or not having double C=C bonds between carbons in the hydrocarbon chain) and spatial conformation (*cis* or *trans* forms), which is associated with the presence or absence of such bonds. The number of C=C bonds is decisive of the degree of unsaturation of each PUFA, while location of the last C=C bond (starting at the carboxyl end) in relation to the last carbon labeled by the Greek letter omega (ω, Ω), regardless of the length of the structure, decides whether the compound belongs to the omega-3, omega-6 or even omega-9 series. In other words, the last C=C bond may be treated as the first double bond in relation to the omega carbon; if it is present at position 3 → omega-3 (ω3) acids, position 6 → omega-6 (ω6) acids, position 9 → omega-9 (ω9) acids [32, 33].

Arachidonic acid, often mentioned in this study and a precursor of numerous both pro- and anti-inflammatory mediators (the latter including lipoxins), is a fatty acid of the omega-6 series; the series is started with linolic acid (C18:2ω6), having two double C=C bonds. Transformations of the lipid compounds of the omega-6 series are completed with docosapentaenoic acid (C22:5ω6), having 5 C=C bonds and known under the acronym DPA-ω6 (to differentiate from DPA-ω3, i.e. docosapentaenoic acid of the omega-3 series). Pro-resolving mediators – oxylipins – are formed from DPA-ω6. Transformations of omega-3 fatty acids, including three precursors of numerous pro-inflammatory mediators as discussed in this work: EPA→DPA-ω3→//→DHA, are started with α-linolenic acid (C18:3ω3), containing 3 C=C bonds, and completed with the already mentioned docosahexaenoic acid (DHA; C22:6ω3), characterized by six double C=C bonds. Reactions leading to increase in the number of double bonds and elongation of the hydrocarbon chain are catalyzed by enzymes known as desaturases and elongases, respectively, with the last stage of transformations in both series being the so-called β-oxidation, requiring translocation of appropriate substrates from endoplasmic reticulum to peroxisomes. The presence or absence of particular desaturases or elongases is decisive whether the particular cell/tissue or organ/organism is

capable of producing the particular acid. In addition, insufficiency of formation of certain acids may be due to the fact that the same enzymes take part in transformations of lipids in the omega-3, omega-6 and omega-9 series, competing for substrates. For instance, increased supply of omega-6 or omega-9 acids (common in popular vegetable oils), would cause reduction in production of omega-3 acids. And, in reverse, intensive intake of fish rich in omega-3 acids with simultaneous reduction in the supply of vegetable products would disturb the omega-3/omega-6 equilibrium in favor of the former. Proper omega-3/omega-6 ratio should be in the range of 1/2-4. Fig. 8 presents a scheme of transformations of omega-3 and omega-6 fatty acids (arrows at appropriate acids indicate their capability of being further transformed into compounds of high biological activity, including pro-inflammatory mediators).

First reports turning attention to the possibility of new (as it was referred to at that time) transformations of arachidonic acid into lipoxins, 15-epi-lipoxins, as well as docosahexaenoic acid into (neuro)protectin were published over 25 years ago [7, 46]. At that time, only few researchers believed that these studies would point out a novel direction for research - important not only for the purposes of gaining new knowledge, but also for practical applicability. Studies on metabolically stable analogs of lipoxins and resolvins have recently crossed the border of experiments and laboratory trials and entered the phase of functional and clinical trials [3, 5, 8, 9, 35, 40, 50].

Capability of pharmacological control of inflammation, including the process known as parainflammation may contribute to satisfactory therapeutic success in case of many diseases of unfavorable course, especially of the chronic type, such as asthma, coronary disease or rheumatoid arthritis, as well as certain diseases of the organ of vision [35, 36]. Of note are dynamically expanding studies of the role of (neuro)protectins in the physiology and certain pathophysiological conditions, as well as promising attempts to use such mediators in animal models of neurological and psychiatric disorders, as well as in clinical practice of management of such disorders, including Alzheimer's disease, and ophthalmological disorders such as age-related macular degeneration (AMD), which may lead to blindness [6, 24, 36].

The importance of the problem of rapid and complete resolution of inflammatory reaction without pathomorphological and/or physiological traces may be proven by very dynamic and extensive research on anti-inflammatory pro-resolution mediators: lipoxins, resolvins, protectins, maresins and oxylipins. The number of experimental and clinical data on the effects of these mediators, either formed endogenously or administered externally (for therapeutic reasons) is growing rapidly, ensuring optimistic attitude among physicians and a wide group of patients with inflammatory diseases, which are not easy to treat. Unique and extensive studies, e.g. those led by the unquestionable leader in the area of lipid pro-inflammatory mediators, Charles N. Serhan (Harvard Medical School, Boston, MA), continuously provide new information [42, 48, 50], contributing to the expansion of knowledge of the course of inflammation, the resolution of inflammation and potential use of pro-inflammatory mediators in therapy.

The practical aspect of the cited works is associated with yet another fact, i.e. the potential to regulate the supply of the precursors of the pro-inflammatory mediators of interest, i.e. polyunsaturated fatty acids, by means of appropriately profiled diet or supplementation with PUFA-containing products [32, 33]. Many products containing fatty acids, both of the omega-3 and the omega-6 series, as well as combinations thereof, are available at the market. Reasonably taken, these products may prove very useful, if not as drugs, then surely as auxiliary agents in the treatment of many disorders. It should be kept in mind that many metabolites of these acids, particularly of these being of high interest to a large part of the society (EPA and DHA), include compounds of high biological activity and anti-inflammatory and (neuro)protective profile.

Acknowledgements:

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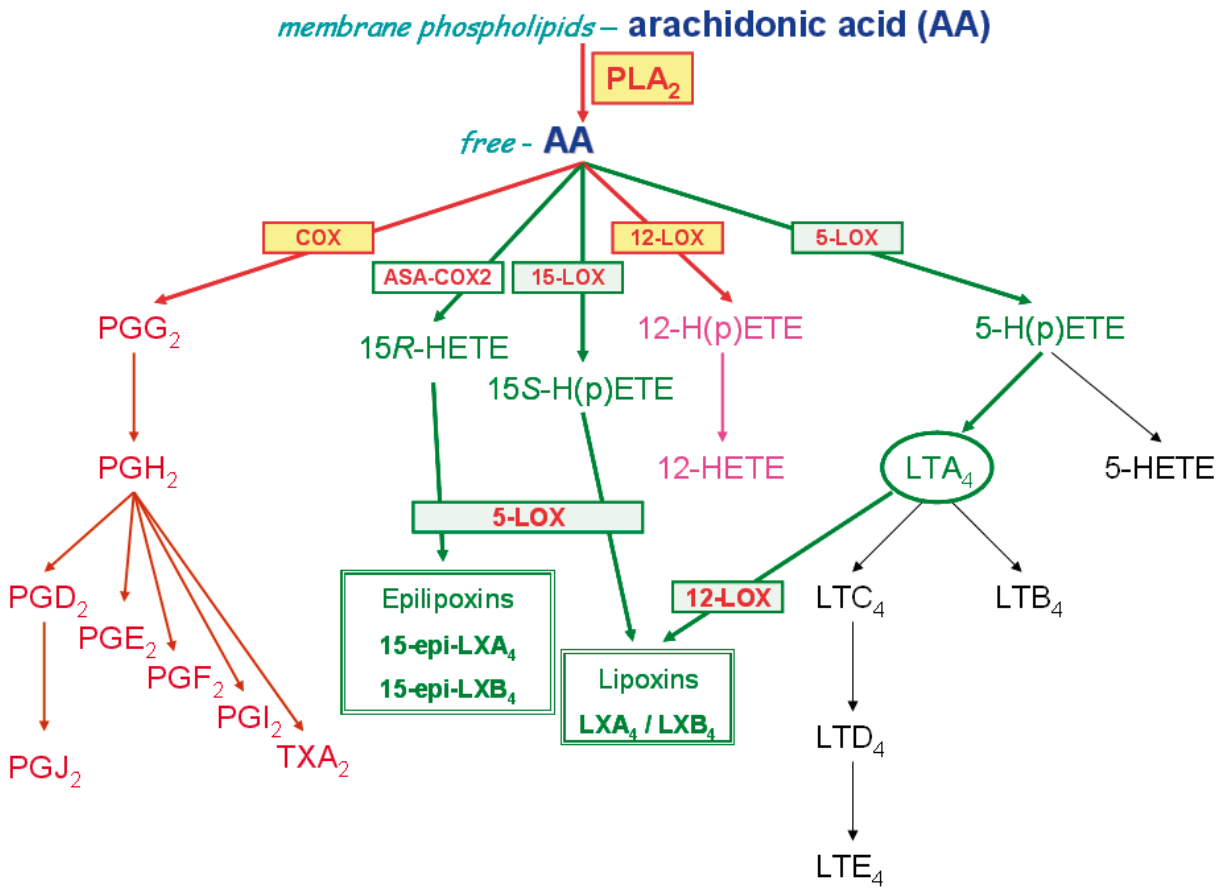


Figure 11: Metabolic pathways of a polyunsaturated omega-6 fatty acid, arachidonic acid (AA; C20:4-ω6). See text for explanations.

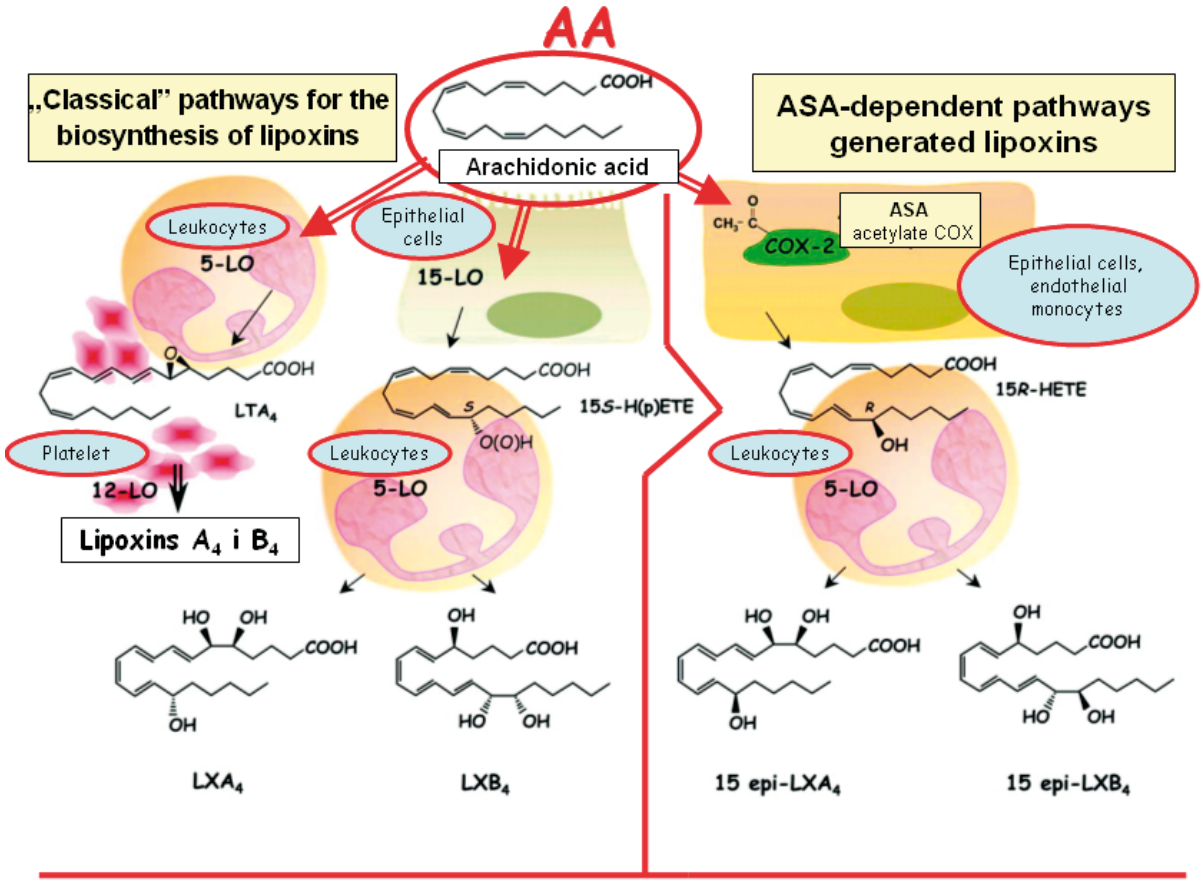


Figure 12: Transcellular synthesis of lipoxins (LXA_4 and LXB_4) and epilipoxins (15-epi-LXA4 and 15-epi-LXB_4)..

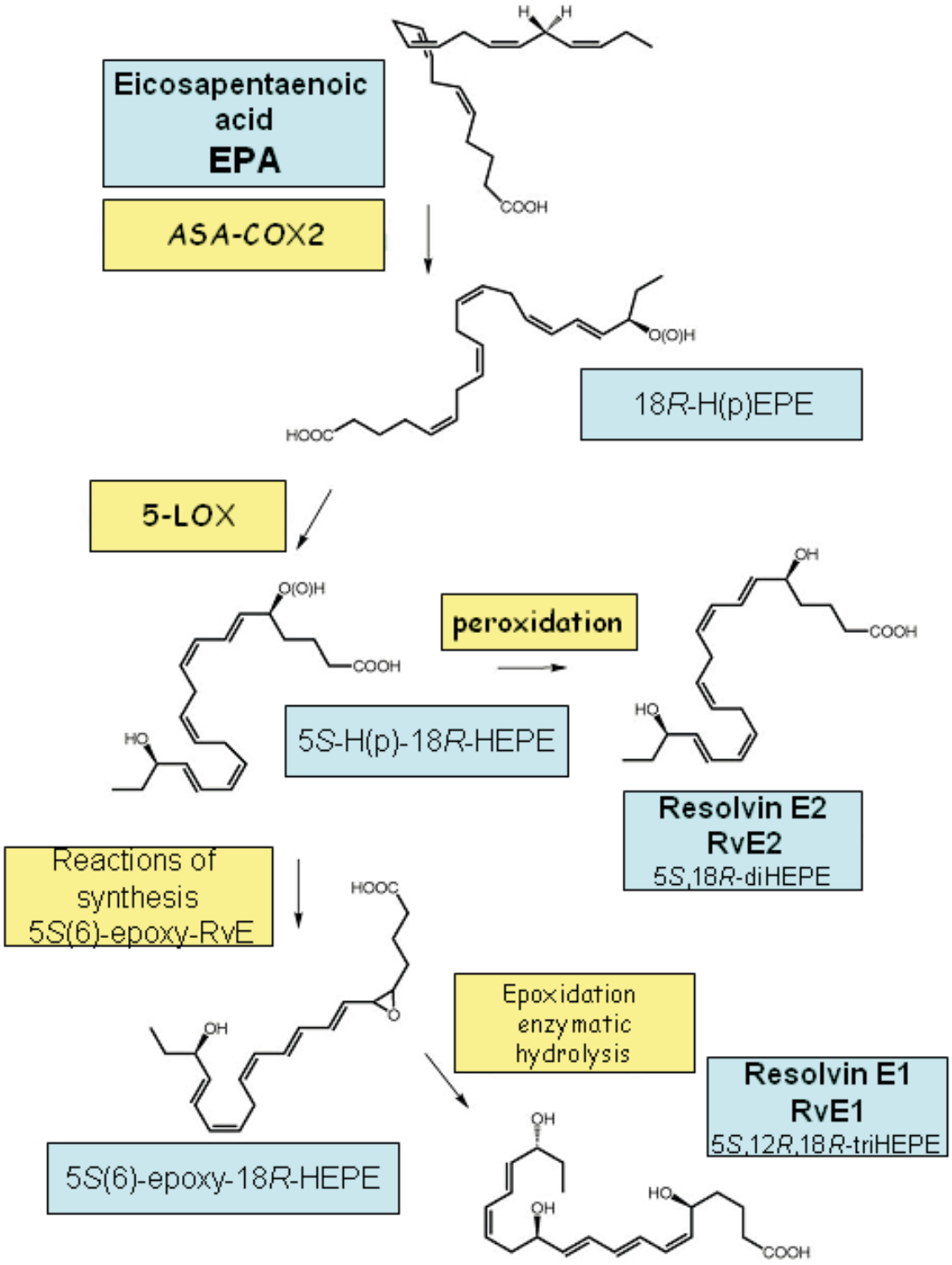


Figure 13: Pathways of biosynthesis of resolvin E series from eicosapentaenoic acid (EPA; C20:5-ω3).

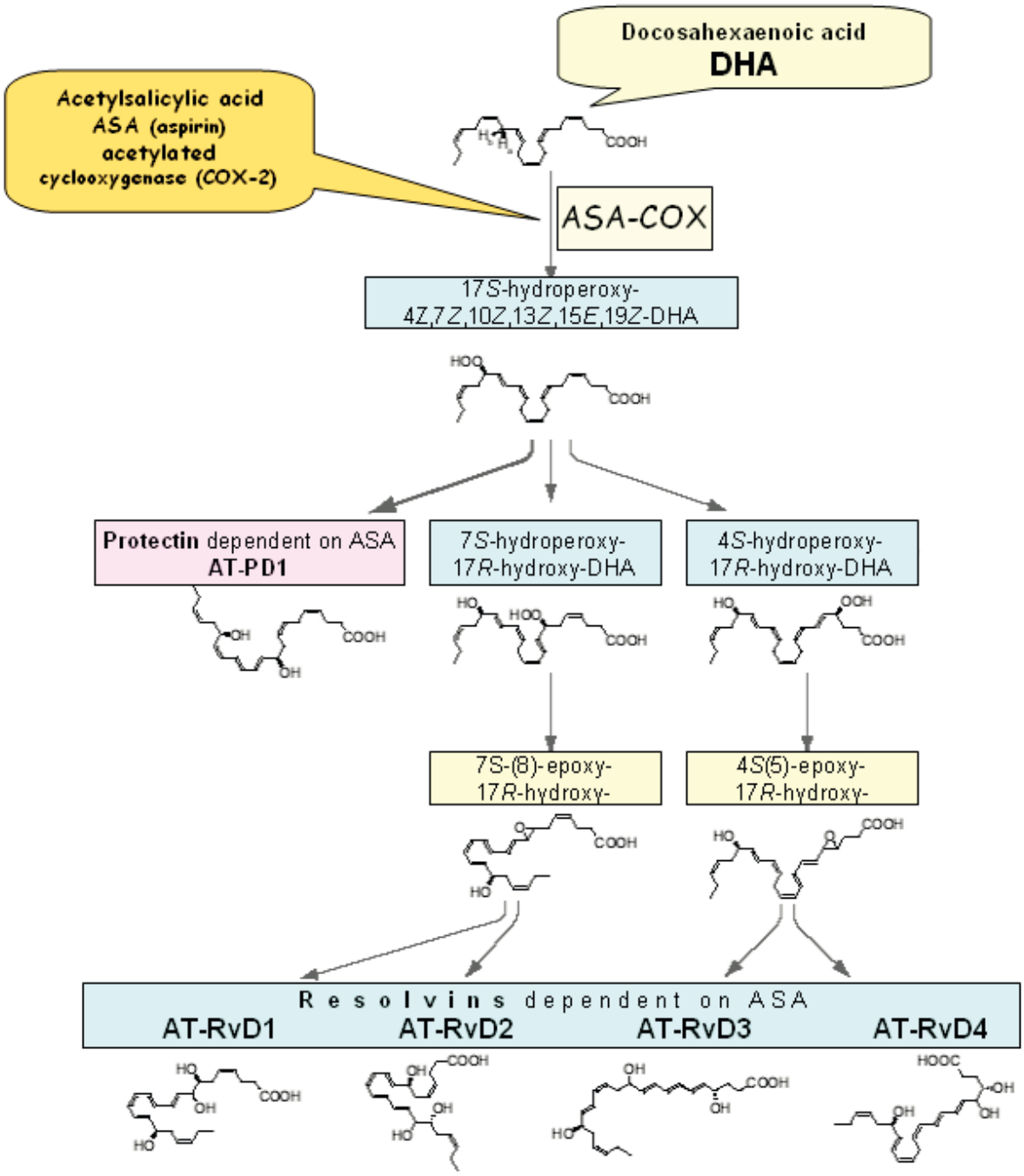
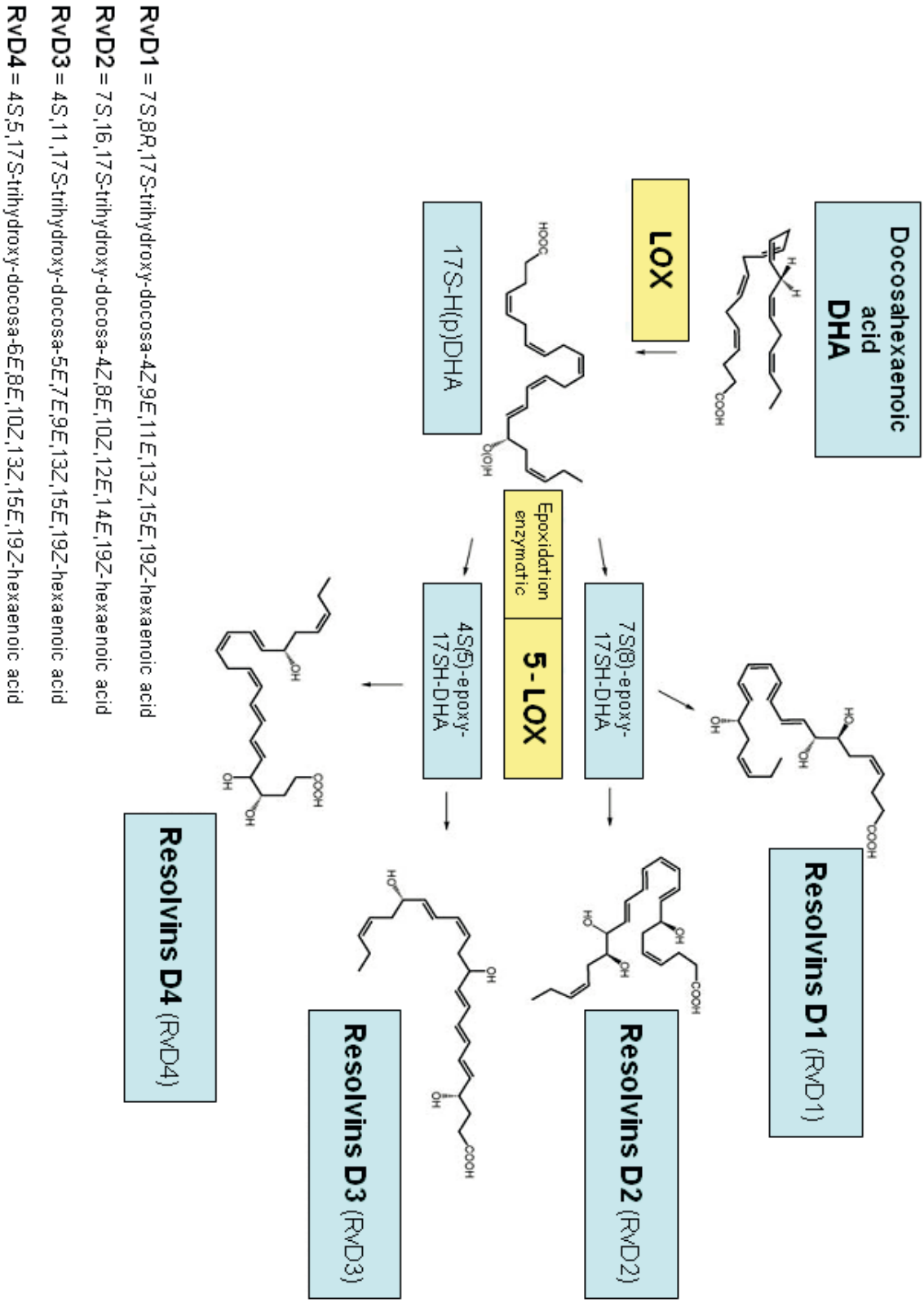


Figure 14: Pathways of biosynthesis of aspirin-triggered resolvin D series form docosahexaenoic acid (DHA; C22:6-ω3) with contribution from acetylated COX-2 (ASA-COX2).



RvD1 = 7S,8R,17S-trihydroxy-docosa-4Z,9E,11E,13Z,15E,19Z-hexaenoic acid

RvD2 = 7S,16,17S-trihydroxy-docosa-4Z,8E,10Z,12E,14E,19Z-hexaenoic acid

RvD3 = 4S,11,17S-trihydroxy-docosa-5E,7E,9E,13Z,15E,19Z-hexaenoic acid

RvD4 = 4S,5,17S-trihydroxy-docosa-6E,8E,10Z,13Z,15E,19Z-hexaenoic acid

Figure 15: Pathways of biosynthesis of resolvin D series from docosahexaenoic acid (DHA; C22:6-ω3).

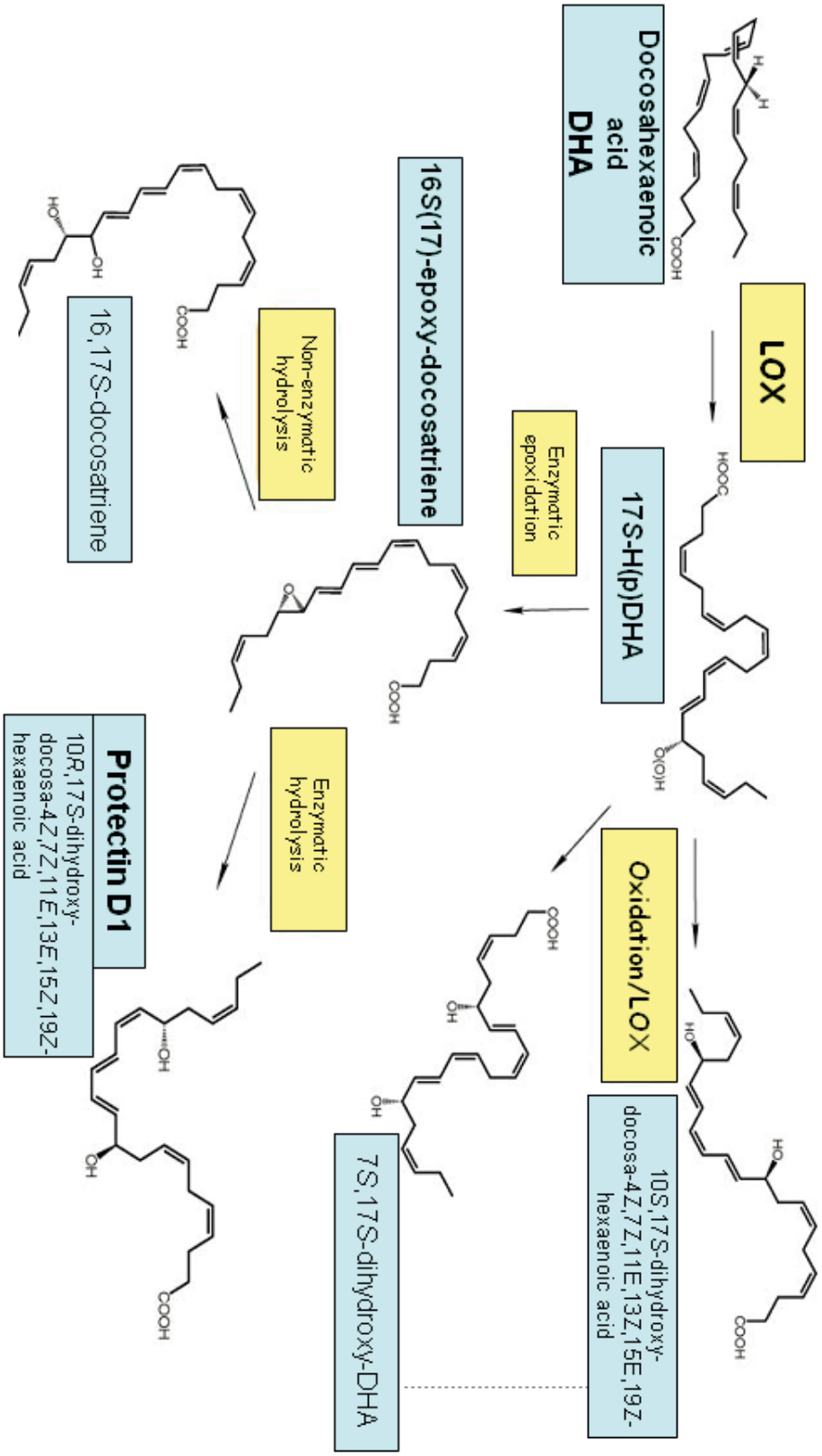


Figure 16: Pathways of biosynthesis of (neuro)protectin D1 from docosahexaenoic acid (DHA; C22:6-ω3).

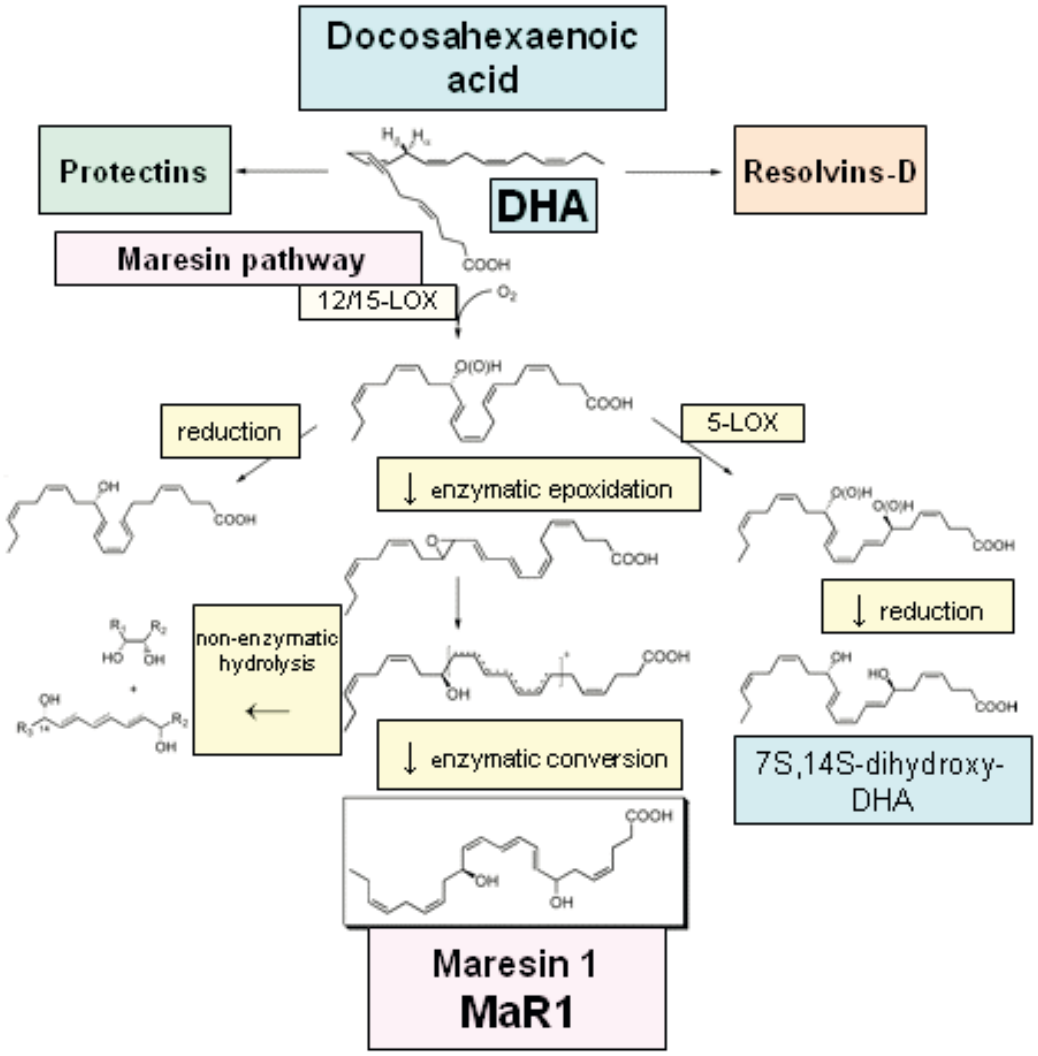


Figure 17: Pathways of biosynthesis of maresin from docosahexaenoic acid (DHA; C22:6-ω3). .

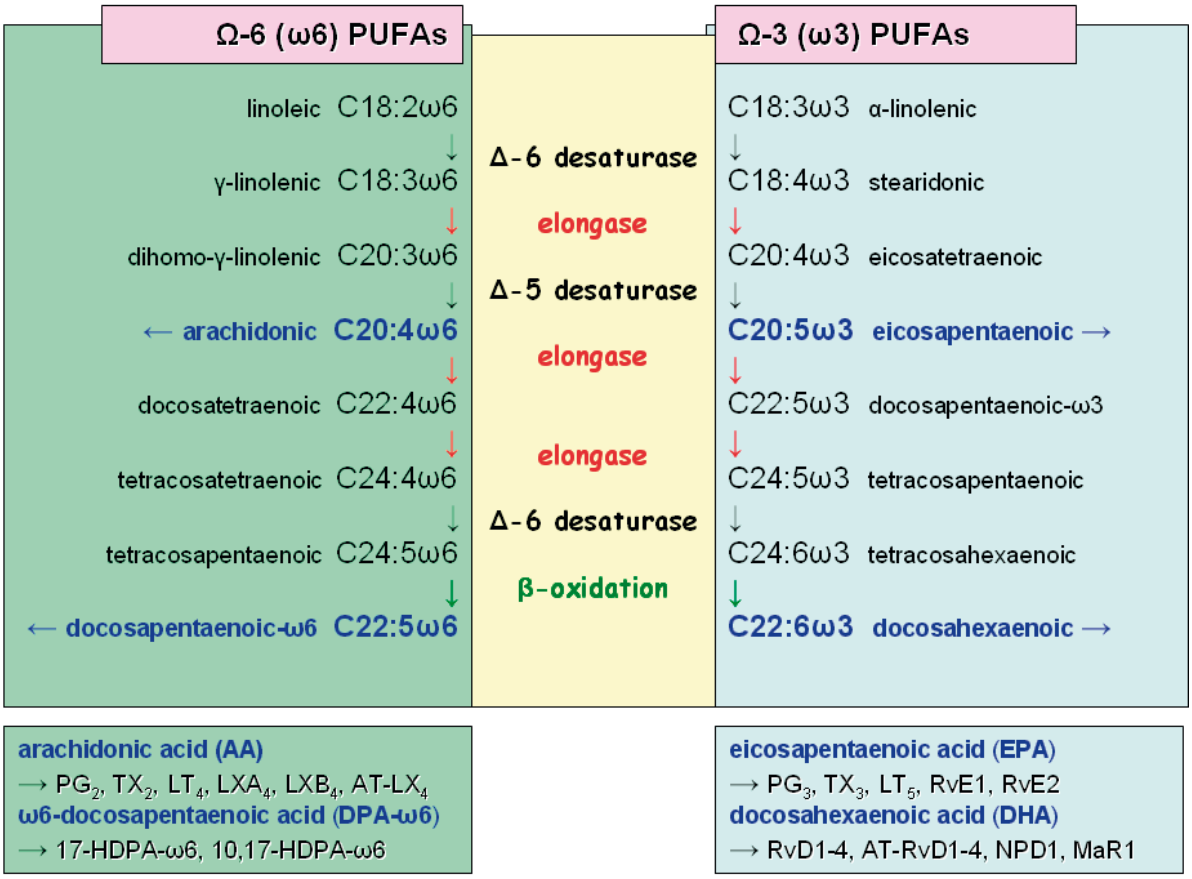


Figure 18: List of biological effects of anti-inflammatory pro-resolving mediators resulting from their impact on neutrophils, macrophages, dendritic cells, lymphocytes and thrombocytes. ↑ is for: increase, enhancement or activation; ↓ is for: drop, reduction or inhibition of activity.

Table 3: List of biological effects of anti-inflammatory pro-resolving mediators resulting from their impact on neutrophils, macrophages, dendritic cells, lymphocytes and thrombocytes. ↑ is for: increase, enhancement or activation; ↓ is for: drop, reduction or inhibition of activity.

Neutrophils	RvE1 / RvE2 / RvD1 / AT-RvD1 / PD1	↓ neutrophils mobilization
	PD1	↑ CCR5 expression; ↓ transmigration through the endothelium and epithelium; ↓ expression of L-selectin and CD18 in neutrophils and monocytes; ↓ leukocyte-endothelial interactions
	RvE1 / AT-RvD1	
	MaR1	↓ neutrophils migration; ↑ monocytes migration
Macrophages	RvE1	↑ phagocytize apoptotic neutrophils; ↑ phagocytes removal by the lymphatic system
	PD1	↓ release TNF through macrophages of bone marrow origin
	PD1 / RvE1	↑ phagocytosis stimulation of apoptotic thymocytes through macrophages; ↓ leukocyte-endothelial interactions
	RvD1	↓ release of pro-inflammatory cytokines by macrophages
	MaR1	↑ Zymosan phagocytosis stimulation by macrophages
Dendritic cells	RvE1	↓ IL-12 production by the dendritic cells; ↑ dendritic cells population development inducing apoptosis of T lymphocytes
Lymphocytes	PD1	↓ T-cells migration and ↓ secretion of TNFα and IFNγ
	RvE1 / RvD1	↑ CCR5 expression on T lymphocytes
Thrombocytes	RvE1	↓ platelet aggreagtion actvation ADP & receptor TBX dependent (but not aggregation initiated by colagen)

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Catastrophe Medicine

Strategies of dealing with stress among medical rescue workers

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Summary:

Medical rescue workers are subject to a wide range of stressors at their workplace. That is why this profession requires special mental predispositions. Resistance to stress and appropriate coping strategies are particularly important. We presented the results of a study among medical rescue workers examining their susceptibility to stress, experienced stress level and types of coping strategies for dealing with stress.

Key words: stress, coping strategies , medical rescue workers.

Introduction

Most concepts regarding stress at the workplace refer to the interaction between expectations encountered in the work environment and workers' resources determined by their mental capacity (11). These concepts are associated with the most popular psychological theory of stress by Lazarus, which defines stress as a "specific relationship between a person and its environment regarded by one as overwhelming or exceeding one's resources and threatening to one's well-being" (17). Subject's emotional reactions are immanent components of a stressful relation, very unpleasant and tempestuous at times. A stressful situation provokes actions toward improvement of this interaction, i.e. restoration of balance between the expectations posed by the environment and individual's capabilities, as well as an improvement of the emotional state. This pattern of activity is defined as coping with stress (15, 9, 10).

Carwer, Scheier and Weintraub referred to the Lazarus' theory and to the model of behavioral self-regulation when they proposed fifteen coping strategies classified into three general styles of coping with stress: problem-oriented, emotion-oriented and avoidance-oriented. Such strategies as: *Active Coping, Planning, Suppression of Competing Activities, Restraint Coping and Seeking Instrumental Social Support* are considered problem-oriented. On the other hand, strategies such as: *Seeking Emotional Social Support, Positive Reinterpretation and Growth, Turning toward Religion, Acceptance and Denial* authors consider emotion-oriented. The remaining strategies (*Focus on and Venting of Emotions, Mental Disengagement, Behavioral Disengagement, Alcohol/Drug Use and Humor*) are classified as avoidance-oriented (1, 2).

Research studies indicate that personality traits, susceptibility to stress in particular, also influence the level of stress perception. The concept of distressed or type D personality was first introduced to literature in 1995 by J. Denolett (3). According to the author, there are two main components of type D personality regarded as relatively permanent personality traits, i.e. negative affectivity and social inhibition. Negative affectivity is expressed

as individual's tendency to experience strong emotions such as fear, anger, irritation or hostility. Social inhibition, on the other hand, relates to the avoidance of threats to one's social interactions and refers to restraint in expressing negative emotions and behaviors consistent with those emotions (6, 4).

The following are characteristic for type D personality:

- tendency to worry and experience tension in difficult situations,
- low sense of security, pessimistic perception of the world,
- discomfort in the presence of other people, especially strangers,
- shyness, weak bonds with other people, keeping distance from others and poor inclination to share emotions (4).

Moreover, type D personality is associated with such symptoms of psychological stress as susceptibility to depression, difficulties in benefiting from social support, depressed mood, low self-esteem, low level of satisfaction with life and the sense of exhaustion. Type D is considered to be at the extremity of personality dimensions that form its structure while remaining within the psychological norms (5).

Hypotheses and the goal of this work

Medical rescue workers in particular are exposed to the influence of various stressors at their workplace. Overworking, performance under pressure of time, shift system, night on-calls, responsibility for the life and health of others, contact with death and suffering, dangerous situations, difficult work conditions and often lack of environmental support make the work of rescue workers highly stressful (19, 12, 7). Because of that, this profession requires special psychological predispositions and resistance to stress is particularly necessary (19). As many research studies have shown, working under conditions of excessive burden may have negative consequences, both health-related and psychological (8, 18, 14). The negative consequences of stress at the workplace result not only from the burdens associated with work itself but also from the deficiency or depletion of resources necessary for effective coping (16). The aim of this research project was to assess the level of stress perceived by medical rescue workers, to establish the type of personality (stress-susceptible or stress-resistant) predominating in their work environment and to identify strategies of coping with stress they use at their workplace. In this study we also attempted to establish the relationship between perceived stress intensity and an adopted coping method.

Materials and methods

There were 45 rescue workers from the Warsaw rescue teams enrolled in our study. A Perceived Stress Scale (PSS-10) was used to measure stress levels. The questionnaire measures person's own evaluation of the stressfulness of life situation in the past month. Stress coping strategies were measured using a Multi-dimensional Coping Inventory - COPE (13). The type of personality was assessed using a Type D Personality Scale - DS-14 (6, 20). Computer software SPSS (version 18.0.0) was used for statistical analysis of the results. A Kołmogorov-Smirnov (K-S) test was used to check for normal distribution. U Mann-Whitney or Kruskal-Wallis tests were used to check for the differences between means. Statistical dependence between variables was assessed using Spearman's rank correlation coefficient.

Study results

1. Study group characteristics

There were 38 (84.4%) men and 7 (15.6) women in the study group (table 1).

Table 4: Table 1. Study group characteristics[1]

Sex	n	%
Women	7	15.6
Men	38	84.4
Age		
20-29	26	57.8
30-39	13	28.9
40-49	6	13.3
Education		
Secondary	29	64.4
Undergraduate (Bachelor's degree)	10	22.2
Graduate	6	13.3
Years of work experience		
1-10	35	77.8
11-20	6	13.3
21-30	4	8.9

[1] Abbreviations used in table 5.1: n – number, % - percentage of all responses

The majority of subjects were in the 20–29 age group (57.8%). People aged 30–39 years comprised a less numerous group (28.9%) and the smallest group consisted of people 40–49 years old (13,3%).

Most of rescue workers in the study had secondary education (64.4%). The second-largest group consisted of people with undergraduate education (22.2%). The least numerous group included graduate degrees (13.3%).

A great majority of our study population consisted of people with less than 10 years of experience (77.8%). The second-largest group of subjects had between 11 and 20 years of work experience (13.3%) and the least numerous group contained workers with more than 20 and less than 30 years of experience (8.9%).

2. Strategies of coping with stress. Type D personality.

Mean values of particular variables assessed using the Perceived Stress Scale and Multi-dimensional Coping Inventory - COPE as well as the DS-14 questionnaire are presented in table 2.

Acquired data indicate that coping strategies most commonly used by medical rescue workers are: *positive reinterpretation and growth, planning and active coping*. Least commonly used are the following: *denial, alcohol/drug use, turning toward religion and behavioral disengagement*.

Table 5: Table 2. Arithmetic means and standard deviations of analyzed variables[2]

Variables	M	SD
Perceived Stress Level (global score)	**15.44**	**4.81**
- low	3.63	0.62
- medium	5.56	0.51
- high	7.27	0.47
Strategies of Coping with Stress		
Active coping	10.47	2.20
Planning	10.82	2.98
Seeking instrumental support	9.78	2.76
Seeking emotional support	8.98	2.90
Suppresison of competing activities	9.80	2.54
Turning toward religion	6.07	2.86
Positive reinterpretation and growth	10.82	2.18
Restraint coping	8.91	1.88
Acceptance	9.53	2.69
Focus on and venting of emotions	8.51	2.86
Denial	5.73	1.90
Mental disengagement	7.27	2.90
Behavioral disengagement	6.07	2.13
Abuse of alcohol or other psychoactive substances	5.87	3.04
Humor	8.38	2.28
Type D Personality		
- negative affectivity	9.07	5.61
- social inhibition	7.40	5.40

[2] Abbreviations used in tables 5.2; 5.4 – 5.7: M – arithmetic mean; SD – standard deviation;

The mean results of Type D Personality Scale – DS-14 testing in the study group were respectively: 9.07 (SD = 5.61) for *Negative Affectivity* and 7.40 (SD = 5.40) for *Social Inhibition*. A score of 10 and higher for both dimensions, indicating type D personality (i.e. stress-susceptible personality), was noted in 24.4% of rescue workers in the studied group. The percentage distribution of studied subjects is presented in table 3.

Table 6: DS-14 scores

Type of personality	Frequency	Percentage
Type D	11	24.4%
Type other than D	34	75.6%
Total	45	100%

Perceived stress level and coping strategies

Acquired data indicate that the majority of medical rescue workers present with perception of workplace stress of medium intensity; 33% of the studied group is characterized by low stress levels and the least numerous group consists of people with high-level stress perception (table 4).

Table 7: Percentage distribution of study subjects with respect to the perceived level of stress.

Perceived stress level	Frequency	Percentage
Low	15	33.3
Medium	19	42.2
High	11	24.4

Correlation coefficients presented in table 5 indicate significant correlation between low intensity of perceived stress and such coping strategies as: planning, seeking instrumental (social) support, positive reevaluation and growth and sense of humor. Obtained correlation coefficients show that the more frequently subjects use above mentioned strategies,

the lower the perceived stress level. Simultaneously, results obtained in the study demonstrate poor correlation between perceived level of stress and avoidance or emotion-orientated strategies.

Table 8: Correlation coefficients for perceived stress levels and strategies of coping with stress.

Strategies of coping with stress	Level of perceived stress			
	Low	Medium	High	General score
Active coping	0.35	0.26	0.57	-0.217
Planning	0.54*	0.17	0.14	-0.169
Seeking instrumental support	0.65**	-0.15	0.46	-0.048
Seeking emotional support	0.27	-0.06	0.23	-0.059
Suppression of competing activities	0.36	0.24	0.59	-0.071
Turning toward religion	0.34	-0.02	0.21	0.235
Positive reevaluation and growth	0.60*	0.43	-0.17	0.119
Restraint coping	0.16	-0.11	0.53	0.114
Acceptance	0.33	0.06	0.30	0.130
Focus on and venting of emotions	0.27	0.08	-0.10	0.230
Denial	0.36	-0.04	0.20	0.040
Mental disengagement	0.10	-0.03	0.52	-0.066
Behavioral disengagement	-0.23	-0.31	0.26	0.058
Use of alcohol and other psychoactive substances	0.14	0.01	0.35	0.154
Humor	0.61	0.01	0.35	-0.036

Type D personality and strategies of coping with stress

In this study, we tested the correlation strength between type D personality and its two dimensions, i.e. *negative affectivity* and *social inhibition*, and strategies of coping with stress. According to the data presented in table 6, *negative affectivity* is associated with such strategies as: *restraint coping, focus on and venting of emotions, mental disengagement and use of alcohol and other psychoactive substances*, while the following strategies significantly correlate with *social inhibition: suppression of competing activities, turning toward religion and also use of alcohol and other psychoactive substances*. In case of *suppression of competing activities* and t*urning toward religion*, this relationship is negative, meaning that the greater the intensity of features comprising this dimension, the lower the frequency of using mentioned strategies.

Type D personality (without dividing it into two separate dimensions) significantly correlates with such coping strategies as: *suppression of competing activities, positive reevaluation and growth, restraint coping and use of alcohol and other psychoactive substances*. There is a negative correlation in case of *suppression of competing activities* and *positive reevaluation*.

It follows that people with type D personality and high intensity of features comprising its dimensions rarely use these coping strategies. However, they more often apply avoidance strategies of coping with stress, i.e. *behavioral disengagement* and *use of alcohol and other psychoactive substances* as indicated by a positive correlation.

No significant relationship was noted between remaining coping strategies and type D personality or its dimensions.

Table 9: Table 6. Correlation coefficients for type D personality and coping strategies.

Variables	Negative Affectivity	Social Inhibition	Type D Personality
Active coping	0.040	0.001	-0.063
Planning	-0.057	-0.137	-0.170
Seeking instrumental support	0.077	-0.018	-0.012
Seeking emotional support	0.235	-0.038	0.146
Suppression of competing activities	-0.201	-0.419**	-0.312*
Turning toward religion	0.155	-0.298*	-0.013
Positive reevaluation and growth	-0.048	-0.265	-0.394**
Restraint coping	0.369*	0.181	0.228
Acceptance	0.100	0.057	0.018

Variables	Negative Affectivity	Social Inhibition	Type D Personality
Focus on and venting of emotions	0.467**	0.153	0.163
Denial	0.176	-0.070	0.047
Mental disengagement	0.325*	0.142	0.189
Behavioral disengagement	0.167	0.186	0.307*
Use of alcohol and other psychoactive substances	0.481**	0.312*	0.412**
Humor	0.089	0.024	0.137

Discussion

Analysis of obtained results indicates that people experiencing ordinary levels of workplace stress comprise the largest group among medical rescue workers, while those with high stress levels belong to the smallest group. It is undoubtedly influenced by the fact that most rescue workers do not possess the stress-susceptible type D personality. Moreover, the majority of studied subjects prefer problem-orientated strategies of coping with stress. Most often applied coping strategies, as demonstrated in studies by Ogińska-Bulik (19), are the following: active coping, seeking instrumental support, suppression of competing activities. Strategies typical for emotion-orientated coping style take the second place: seeking emotional support, religion, positive reevaluation and growth, acceptance and denial. Avoidance-orientated strategies are rarely used by medical rescue workers, i.e.: focus on and venting of emotions, mental disengagement, behavioral disengagement and use of alcohol or other psychoactive substances.

These results indicate that the majority of people in the medical rescue profession are problem-oriented and prefer active approach to coping with stress. They avoid performing actions that could jeopardize the completion of the task but instead, seek for constructive information that allow for dealing with the problem in a quick and efficient manner. Rescue workers characterized by type D personality constitute the minority, only 24.4% of the group; they are more susceptible to stress and perceive stressful situations in terms of threat. In the process of coping with stress, they more often apply maladaptive coping strategies focused on emotions and avoidance, which may lead to accumulation of experienced stress, overworking and contribute to the development of burn-out syndrome or other psychological dysfunctions.

Conclusions

Analysis of the results obtained in this study indicates that:

1) Medical rescue workers cope well with stress at their workplace (33.3% experience low stress levels, 42,2% - medium-intensity stress and 24% - high).

2) The great majority of medical rescue workers apply adaptive coping strategies.

3) The majority of studied rescue workers do not exhibit traits of stress-susceptible personality, only 24% of the studied group manifested features of type D personality.

4) Subjects with type D personality more often use avoidance-oriented style of coping with stress.

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Catastrophe Medicine

Rules for the use of collective protection measures against BST contamination in accordance with NATO normative documents

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Summary:

Personal protection against contamination is essential for soldiers, assuring their survival in the wake of the effect of weapons of mass destruction and their continuing ability to conduct combat operations. In order to meet the requirements of maintaining the capacity to act in the aftermath of contamination, OPBMR (Defense Against Weapons of Mass Destruction) measures must be continued, be flexible, mobile and characterized by systems enabling quick operational transition.
The following issues are presented in this report:
1) Elements of collective protective measures against contamination;
2) General standards for the construction and operation of collective means of protection against contamination;
3) Guidelines for work on improving systems of collective protection on the basis of NATO normative documents.

Key words: Key words: collective means of protection against contamination, contamination zone control, ST contamination, systems procedures of collective protection.

Introduction

The use of Poisonous Combat Substances (BST) during the First World War contributed to the development of individual means of protection against contamination (ISOPS), which included means and measures of protecting the respiratory tract and skin.

Personal protection measures against contamination are essential for the survival of personnel in the aftermath of the use of weapons of mass destruction and continued combat ability. Despite assuring basic protection, the application of ISOPS in combat conditions causes difficulties in performing tasks and weakens psychophysical abilities. Significant impact on the efficiency of continuing activities and time spent in such environments is the insulation / protection measures used for the skin in ambient temperature conditions and the type of activity that needs to occur.

Technical development has allowed for the replacement of hitherto used insulation protection measures for the skin by filtering techniques, but this does not eliminate all problems related to ISOPS requirements.

In order to maintain a high level of combat readiness, ISOPS is not the sole issue to be addressed. Therefore, all personnel, regardless of the tasks which must be done, must be able to benefit from the collective means of protection against contamination, to ensure the organization of rest periods, eating meals and addressing individual, physiological needs. In addition, Collective Means of Protection Against Contamination (ZSOPS) must assure the protection of the following work posts and facilities:

- Headquarters and operational centers;
- Hospitals, medical facilities and places of rest;
- Workshops and repair/maintenance facilities.

1. Classification of collective means of protection against contamination (ZSOPS)

Collective means of protection against contamination are divided into:
Permanent type – when once installed, without the possibility of displacement. These include installations of the hardened, semi-hardened and unhardened type. This breakdown is due to the degree of resistance of a given system as exposed to very serious factors of conventional weapons and weapons of mass destruction.

a) hardened or semi-hardened classification – military command positions, air bases and ports are included herein, requiring collective protection measures where ZSOPS can provide protection against conventional attack and attack with Weapons of Mass Destruction (WMD).

b) unhardened classification – buildings that do not have protection from the effects of conventional means of destruction, but protecting personnel against the obvious effects of weapons of mass destruction. Nonetheless, protection against conventional attack can be afforded by buildings and other structures (sheltered hangars), in which ZSOPS has been applied.

Existing buildings may be adapted in such a way to ensure collective protection, by the application of certain finished coatings or materials resistant to the penetration of poisonous materials (ST). Such coatings need to correspond to the sizes and shapes of any structures or premises, for which these shall be specified.

Collective protection measures possible for transport - the collective means of protection against contamination, which can be installed/applied and transported to any place depending on the need. These are mainly un-hardened (tent-type) collective protection measures and other satisfying these same criteria.

Mobile type - collective protection systems, which can be used in both armored and un- armored vehicles, having or not having the possibility of working at the time of driving. Most of the known systems do not have integral airlocks or contamination control zones.

The systems are mounted in tanks, transporters, radio/location stations, radar stations, command posts, guidance positions and missile stations, as well as special vehicles (ambulance type vehicles and fire trucks), driver's compartments (cabs) in transportation vehicles.

2. Elements of collective protective measures against contamination

All kinds of ZSOPS regardless of their size and type must have the following items:

Clean zone – in this zone personnel may be present without applying ISOPS. The zone can be divided into several areas, which must be sufficiently airtight to provide an overpressure (positive pressure) condition and protect the system from excessive "leaking" of air to the outside. In addition, the air flow must be directed in such a way, so as to prevent the formation of air stagnancy, especially in locations of connections to successive spaces.

Filtration unit - this unit should ensure a continuous process of air purification from all the particles and radioactive, chemical and biological vapors and their delivery, in order to:
- create a positive air pressure situation;
- deliver the required quantities of clean air exchange to the airlocks;
- ensure that the needs of the resident personnel are met.

In addition, so that people or equipment can leave or enter the clean zone assuring the collective protection system, the following items must be included:
Air lock - the air lock shall comply with the following features:

- be the only way through which the filtered air leaves the clean zone;

- be designed in such a manner as to be able to maintain a positive pressure situation when there is a sudden pressure drop due to any leaks in the airlock from the outside or to the contamination control zone;

- assuring the protection of the clean zone, through the exchange of air in the stipulated time and in such a manner, that will assure passage safety thereto without the likelihood of carrying in an amount of ST vapors that could cause a contamination threat. In addition, the use of the airlocks should protect against contamination originating from ST vapors, when the user has a guarantee, that the ZSOPS have not been penetrated by liquid-form ST. The threat of harm to the interior of the system of collective protection may result from the ability of de-sorption of transferred ST vapors on clothing, hair and skin. The level of risk from those sources is relatively small, when air flow is sufficient enough to allow for several air changes per hour. However, in situations where there has been an accumulation over a

longer period of time, ex. of ST vapors because of improper air flow, the level of risk may be considerable.

Contamination control zone - this area is located in front of the airlocks and clean zone in order to reduce the level of contamination from completely contaminated personnel to a safe level. The size of the contamination control zone depends on many factors, of which the most important are: the number of persons, type of activities they were involved in and the rate of entry and exit from the zone.

The contamination control zone contains:

- the area of contamination threat by liquid ST- located on the outside and allowing for the carrying out of disinfection and the storage of handling and processing equipment used within the contaminated zone. This area can be placed in front of the building, in a structure that is covered with an ST impermeable coating, where the supply of purified air is not required;
- changing area - in properly designed ZSOPS, the personnel can move directly from the zone with a danger of liquid ST contamination to the changing rooms. For the proper functioning of the changing rooms, conditions must be fulfilled for the safe removal or the dressing into protective clothing. To ensure such conditions, a large enough amount of airflow must occur, from the clean zone to the area of contamination control;
- area of ST vapor threat - located in front of the air locks, serving the area where gas masks are removed and kept along with other remaining component parts serving the needs of individual means of protection against contamination.

3. General ZSOPS protection and equipment requirements

The level of protection

The respiratory tract and eyes of personnel remaining in the clean zone for a period of 24 hours cannot be exposed to toxic contamination exceeding the following levels:

- 2 mg min/m^3 FOST;
- 25mg min./m^3 H, L;
- 1 000 mg/m^3 AC, CK.

The respiratory tract and eyes of personnel remaining in the clean zone for a period of one week cannot be exposed to toxic contamination exceeding the following levels:

- 2 mg min./m^3 FOST;
- 50 mg min./m^3 H,L;
- 2 000 mg min./m^3 AC, CK.

Where:
FOST-Vx, GB-Sarin
H - sulphur mustard, L-lewisite;
AC - hydrogen cyanide;
CK - cyanogen chloride.

All of the personnel remaining within the system of collective protection for a period of one week must be protected at such a level, so as not to be in contact with liquid ST up to the following levels:

- 2 mg Vx;
- 20 mg-GD;
- 0.001 mg/cm^2 (H), (L).

Where:
GD - Soman

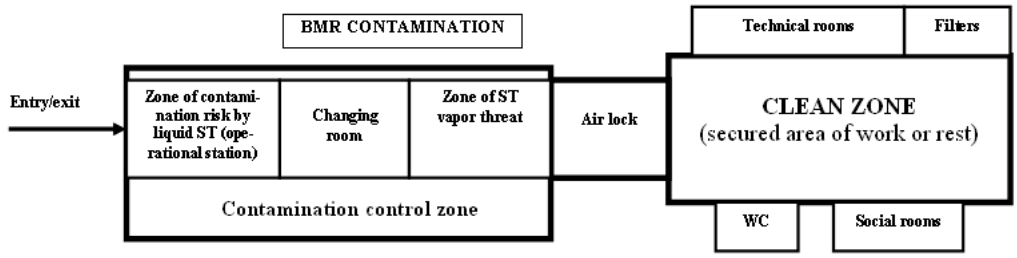


Figure 1: Components of a stationary area for collective means of protection against contamination

Note:
In simplified systems for collective protection, the changing room and the zone for contamination by ST vapors can be combined.

Operating parameters, air (filtering) purification

Filters must be designed and constructed so that they can clean the air from solid particles of toxic materials, and poisonous vapors. The filtration system must be adapted to the designed system

of collective protection so as to ensure appropriate technical characteristics and interchangeability within NATO standards. Any filter replacements should take place without having to wear gas masks by the personnel inside. So, therefore, in order to safeguard appropriate working conditions of all those benefitting from the means of collective protection, an additional (back-up) system of filtering and ventilating is required.

Air flow quantities must be calculated taking into account such factors as the volume of the space served, the number of personnel and most significantly, the number of air locks, and the implications of the number of exits and entrances to the building.

The required air flow is as follows:

- 8.5 m3/h - for each inactive person;
- 17 m3/h - for each working person.

In addition, the system should ensure an adequate exchange of air in the air locks and ensure the tightness of the entire system by maintaining the required positive pressurization. All filtering systems should be designed so as to use standard filters (specified below), or use a connection of a max. of 3 filters:

- -100 m^3/h;
- -400 m^3/h;
- -800 m^3/h.

Preference is given to the principle that any system of collective protection has a separate system of filter-ventilation. Work of the system's filters should be carried out with maximum +/-10% fluctuation from the adopted technical parameters. The system should have the instrumentation to measure the parameters of the air flow and an automatic alarm system to signal any disruption in the provision of sufficient quantities of air.

The resistance of the air flow must be at least 900 Pa (+/-) 5%. High-performance filtering systems, should have the associated hardware/instrumentation to allow for the carrying out of control functions of the resistance of air flow.

There are two types of high performance filtering systems:

- high-efficiency filters to clean the air of particles, which should stop their migration found in the air. However, the same filter should offer protection against any migration of solid particles of a diameter of 20 micrometers and larger;
- high-efficiency filters to clean the air from ST vapors should provide protection against all known ST vapors. In the case of carbon filters, the designer must ensure that the parameters of the filters will not change during their transport, storage and operation once installed.

General operating characteristics:

The system should provide for the proper functioning of personnel in different atmospheric conditions:

- external temperature from -25 ° C to + 30 ° C;
- outside humidity conditions to 100%;

The system must maintain the following internal conditions:

- -the internal temperature of + 10 ° C to + 30 ° C;
- -indoor humidity is below 80%.

Servicing, including the exchange of filters, should be so simple, so that it can be done by one person in individual protective garb in not more than 30 minutes.

The system should be powered by an autonomous source of electricity and have the ability of being hooked-up to other, reserve sources.

4. Design principles and equipment requirements for hardened/ semi-hardened systems of collective protection

For hardened/semi-hardened buildings/structures assuring collective protection, the following criteria for zone contamination control shall be applied:

- A two-door entry system and entry hall should be so constructed as to minimize the possibility of transmitting BST vapors from outside the building to its inside, in a situation when the entry/exit doors to the zone of contamination by liquids are open, especially during windy weather conditions. The order of the opening and closing of the doors will be required when entering or leaving the contamination control zone. The doors should be resistant to the wind and should be controlled so that only one door may be open at a time.

- The contamination control zone and entrance should be hardened to the same level as the clean zone, so that it can provide protection for the personnel, equipment, devices, filter-ventilation equipment, etc. from the effects of an explosion.
- The contamination control zone must be divided into two sections (the liquid BST contamination risk section and BST vapor contamination risk section), by a full height separation wall (from floor to ceiling), which will stop most of

the contaminants which may want to migrate from one zone to another. These two sections (the liquid BST contamination risk section - in which occurs liquid BST and the BST vapor risk contamination section) must be accessible – i.e., have a connection between each other only by a single door (preferably, jalousie type)

- The liquid BST contamination control zone adjacent to the entry hall, is an area where equipment and clothing contaminated by BST liquids can be removed and stored or held for further decontamination or subsequent use. Articles which may again be worn or carried back to a zone where there may be BST vapor contamination, must be de-contaminated by removing the BST liquid contaminants from their surfaces. In the contamination control zone, ground personnel must be assured the ability to change their ISOPS. Appropriate changing rooms can be added to the contamination by BST liquid risk zone in order to remove the overlay of their ISOPS. Changing rooms must have sufficiently large clean air flow, so as to reduce the concentration of burning (caustic) BST vapors to such an extent, so as not to endanger the skin during the removals and/or overlap. The liquid BST risk contamination zone must be so designed that the ground personnel removing their ISOPS, can safely and quickly move from the changing rooms to the BST vapor contamination risk zone, only by low concentration levels of BST vapors. In order to achieve the required concentration, make sure that there is no recycling of BST vapors from the storage area for the contaminated clothing and equipment found in the liquid BST risk contamination zone.

- The vapor BST contamination risk zone adjacent to the entry air locks before the clean zone must be designed to allow personnel to leave any equipment they might have and their ISOPS (which is free from contamination by liquid BST), before entering the air locks leading to the clean zone. The design should take into account the real needs of storage and handling equipment and have procedures which allow for the safe transport of gas masks to the clean zone area. In addition, and in accordance with national requirements, the vapor BST contamination risk zones can have showers installed or other equipment serving to wash-down radioactive fallout.

- Technological nodes should be equipped with handrails leading through the threshold of doors leading to controlled liquid BST contamination risk zones , and the vapor BST contamination risk zone. These access routes should be equipped with decontamination vessels, during which time personnel can decontaminate their protective footwear.

- In order to avoid excessive congestion in the BST vapor contamination risk zone, of extreme importance are the routes of exit and entry of personnel. In addition, due to the differences in the equipment used by the flying personnel and ground personnel, procedures of removal and dressing and storage may necessitate the designation of separate circulation routes for various personnel categories (for sub-units, consisting of both flying and ground personnel) in the zone of contamination control, where the process of removing and applying ISOPS occurs simultaneously for two categories of personnel.

- In collective protection buildings, special electrical outlets need to be installed meeting national requirements and codes.

- Electric lighting shall be so arranged within the contamination control zone to allow staff to perform all necessary operations. In situations where there is a possibility that the means of protection against contamination with the lighting in place may not function properly, emergency lighting at the appropriate level must be provided.

- Buildings/structures providing collective protection against contamination can be used in peacetime. Therefore, at the time of design the building should take into account the situation in which the non-contaminated personnel can pass through the contamination control zone to the clean zone.

- The design of the collective protection system must ensure safety conditions and permit for the implementation of in/out access procedures.

Air filtration system

1) All hardened and semi-hardened buildings offering collective protection must have an air filtration system that provides clean air, free of radioactive, chemical and biological agents. In addition, this system should be resistant to the impact of a war-induced shock wave and provide adequate ventilation and positive pressure conditions in the clean zone. Air patterns within the space should ensure a flow of filtered air from the clean zone area through to areas with increasing concentrations of contamination. For the contamination control zone the arrangement must ensure an adequate flow of air in order to achieve the following conditions:

   a) In the BST vapor contamination risk zone as well as in the BST liquid contamination risk zone, between the partition/separating wall and the changing room, the air flow should 'rinse out' the BST vapors, which could otherwise definitely

threaten uncovered/exposed parts of the skin, so that one can safely remain in that section and only wear a gas mask.

1b) In the doorways or passages through the walls between the zones, air flow must be sufficiently large to prevent excessive penetration of BST vapors, respectively from the liquid BST contamination risk zone to the BST vapor contamination risk zone.

2) The flow of air in the liquid BST risk contamination zone. In a situation where personnel is garbed in ISOPS (clothing and gas masks), the level of BST concentration is not a significant problem. However, when the personnel removes contaminated clothing and equipment, it turns out that the zone must have a certain large enough area, with adequate amounts of clean air delivered in such amounts as to ensure the safety of personnel once the protective clothing is removed. The dose absorbed by exposed parts of the skin should be several orders of magnitude smaller in relation to the dose accumulated in the process of movement through the contamination control zones.

3) The flow of air in the vapor BST risk contamination zone. The concentration of BST vapors in the zone must be kept at a sufficiently low level so as to ensure safe conditions for personnel stationed there, even if burning (caustic) substances have been found there. Despite the fact that some quantity of vapor will be emitted by the absorbers, even after disinfection, the risk to the skin is considered negligible in a room where the air is exchanged several times per hour. The main problem in this area is not to allow the penetration of the zone by BST vapors originating from the liquid BST risk contamination zone. Therefore, a very important issue is addressed by the partition/full-height separating wall between the zones. The flow of air through the door (transition) between zones must be adequately secured so as to prevent the undo backing up of air to the zone.

4) Environmental control. Temperature control in the contamination zone is very important due to the reduction of potential adverse effects which may result in its increase.

4a) the emission of BST vapors from contaminated clothing and equipment can be significantly reduced while maintaining proper temperature readings;

4b) low temperature can reduce heat stress and provide thermal comfort for the crew while in all parts of the contamination control zones .

Thermometers should be placed in both zones. System control parameters of supplied air to the collective protection zones should have the capacity for action in a wide range of temperature conditions. The system should ensure that the internal temperature remains in the range of 10-30 ° C and relative humidity below 80%.

5) Apparatus for measuring parameters of air flow and pressure

Apparatus for measuring parameters of air flow and pressure shall be used to monitor the positive pressure levels in the clean zone and the air flow in each air lock and contamination control zone. These systems should be equipped with alarms, which would signal any decrease below a safe level.

CHANGING ROOM

The changing rooms must have a reduction in the threat of contamination levels to the skin by BST vapors during the removal and dressing in contaminated protective clothing.

Protective clothing and equipment worn on the outside may be contaminated by liquid BST. In this situation, protective clothing should be removed in the BST liquid risk contamination zone area, where BST vapors coming from the same clothing as well as from the contaminated equipment of an individual may be present in concentrations of danger to exposed skin. To ensure appropriate conditions for the dressing and removal of protective clothing, the changing room may be the appropriate place, where clean air flows with a subsequent risk reduction to the body, which is otherwise not protected by the individual means of protection against contamination. Exposure of the body to BST vapors must be maintained at an appropriately low level, so that the personnel moving several times a day between control contamination zones remains not adversely effected. Protective clothing worn underneath the outer clothing layer, which has not been affected (contaminated) by liquid BST, may be applied and removed in the liquid BST contamination risk zone, where the concentration of vapor BST is low. In this situation, a changing room is not required.

It is advisable that the changing rooms be designed and built in as small a size possible, while not admitting or leaving liquid BST on its walls. Each changing room must have doors with mechanical ventilation provided at the end for supply air purposes.

AIR LOCK

The air locks are planned between the clean zone and the contamination control zone areas and serving as a barrier to the vapors. Each air lock should

have two doors which are connected with each other in such a way, so as to allow for the opening of any one door at a time. In the airspace, there must be achieved a proper reduction in the coefficient of concentration of BST.

Regardless of the size of the air lock or number of persons simultaneously passing through the air locks, the coefficient of reduction of concentration of BST levels needs to occur.

INTERNAL COMMUNICATION

Internal communication devices are required between different areas of the contamination control zone and the clean zone, in order to ensure the proper management of the collective protection areas.

WASH UP ROOM

As a necessary minimum required is the positioning of a stainless steel sink with cold water as a source of clean water for use in the BST vapor contamination risk zone for the cleaning of gas masks. Washing, as part of the procedure for individual decontamination in the liquid BST contamination risk zone or BST vapor zone can be determined separately in accordance with national requirements and the law. If the deactivation of falling radioactive contamination is required, these treatments should be carried out immediately before the personnel would enter the clean zone in accordance with national procedures. Decontamination must be carried out in the wash up room sinks or showers in the contamination control zone. In addition, one should secure the spent, contaminated water after the wash up occurs.

ROOMS FOR THE STORAGE OF CONTAMINATED ITEMS

Rooms for the collection of discarded contaminated clothing and equipment must be integrated in with the collective contamination protection building and should be adjacent to the contamination control zone.

FINISHES OF THE CONTAMINATION CONTROL ZONE

The interior walls must be finished with materials resistant to chemical agents. In addition, it is required to finish the floors in the contamination protection zone areas with non-slip, chemically resistant, non-absorptive paints.

The power supply. The collective contamination protection building should be fitted with an independent source of electricity-as an essential system, ensuring the proper functioning of the building.

PROCEDURES FOR THE USE OF COLLECTIVE PROTECTION SYSTEMS

The time during which hardened/semi-hardened collective protection systems will be used in combat situations, will be different for different units depending on the rules of operation and their deployment. Guidelines for use of these buildings for collective protection are as follows:

1) a threat level of zero or very low: check the availability of all hardened/semi-hardened buildings to serve as buildings of collective protection.
2) a low level of WMD threat. One should regularly check all elements of the systems of collective protection in terms of completeness and performance.
3) an average level of WMD threat. Enter the systems of collective protection to a state of readiness for inclusion.
4) a high level of WMD threat. Keep all of the buildings for collective protection in operation.

GENERAL EQUIPMENT - REQUIREMENTS

In this chapter were listed all the basic items concerning the equipment of contamination control zones needed to maintain an efficient operation for each zone where contamination control is required. Staff must have access to:

- decontaminants (in bulk) to decontaminate equipment.
- Non-breakable wall mounted mirrors to aid personnel in decontamination procedures, during the dressing and removing of their individual means of protection against contamination.
- Wall-mounted control list/checklists with essential steps identifying the sequential order for dressing and removing ISOPS, based on the requirements of ST ANAGU 2941. Individual countries should be aware of the differences in applicable equipment and procedures and, where necessary, obtain a clarification in their respective languages.

- Containers for contaminated items should be properly placed in the contamination control zones. All containers must be equipped with a cover.
- The number of bags for contaminated clothing (calculated as to the expected consumption per day) for the hauling away of contaminated clothing and individual equipment from the contamination control zones.
- Equipment for use in the liquid BST

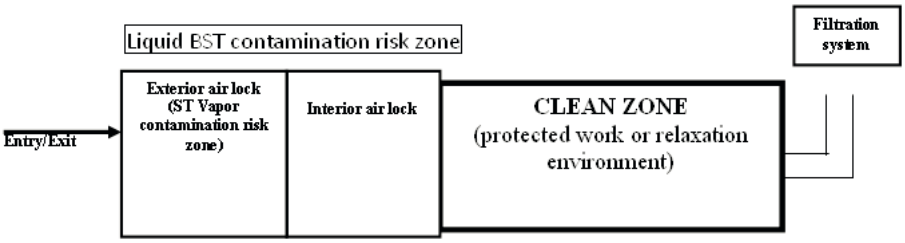
contamination risk zones and changing room to help personnel in the decontamination of gas masks and in the vapor BST contamination risk zone to help in the completion of the final disinfection of the masks in the "dirty" course before the final transfer of the mask racks and masks to the clean area.
- A workbench in each contamination control zone for the decontamination of individual equipment, which can be taken to the clean area.
- Measures to remove decontaminants from the contamination control zone.
- The master clock to synchronize watches, which once contaminated cannot be taken to the clean area.

ADDITIONAL EQUIPMENT

Additional equipment necessary for the proper implementation of procedures for the contamination control zones include:

- Stands for weapons and individual equipment (helmets, personal weapons, bags for gas masks, etc.), which again will be used, should be stored in the liquid BST contamination risk zone.
- A bench for the removal of protective shoes.
- Racks for protective clothing.
- Carrying (rolling) racks for gas masks and other specialized equipment, in accordance with national procedures.

Additional equipment is to ensure the safe completion of the procedures of operations prior to the entry/exit to the clean zone, regardless of the type of ISOPS, as well as other, individual equipment.



5. Non-hardened collective protection measures. Design criteria and hardware requirements. General requirements.

Non-hardened protection measures used against contamination will be necessary to maintain operations in a contaminated environment, where other collective protection systems are not available. They will be needed to provide rest periods and eating a meal in clean zones in two types of installations: fixed and mobile.

Permanent means of protection against contamination - requirements. Personnel in permanent means of collective protection must consistently remain at their work stations and also may be forced to act in the affected environment for a long time in their assigned ISOPS. Displacement of protection means against contamination into non-contaminated areas and may be unlikely, therefore, personnel will need access to a clean area close to their place of work, to be able to remove their ISOPS, relax, and meet their physiological needs.

Mobile means of protection against contamination - requirements. Personnel carrying out activities on the battlefield may have less risk than personnel in the permanent premises of the collective protection zone. It is unlikely that a moving, mobile object would be targeted for destruction, and in addition, there is the possibility of movement – to a non-contaminated area, however, a change of position or the avoidance of contaminated land is not always possible. In addition, a mobile role will indicate that is not in a position to prepare a sustainable, permanent means of protection against contamination to allow for rest, so one will need some form of mobile or transportable non-hardened protection system against contamination allowing personnel to rest without having to stay in their ISOPS.

GENERAL DESIGN CRITERIA

The constructions of non-hardened, collective means of protection against contamination may be done in many different shapes and sizes. A schematic plan for such a system is illustrated in Figure 1. The structure can be made from a fabric resistant to chemical substances. This structure does not provide protection against the effects of fire, however. To provide some protection from the effects of fire, the structure could be placed inside a building or other structure, which will provide some degree of protection.

6. Threats

In order to determine the real threats, testing has been carried out to determine the possible concentration of poisonous air in relation to the protective properties of the individual and collective means of protection against contamination. It was found that non-hardened collective protection measures deployed in defense as a plain target may be exposed to a concentration of

ST < 2000 mg min m^3. Hardened collective protection measures in the intense activity area of an enemy may be exposed to higher concentrations, but not exceeding 30000 mg min m^3. For example, a warship which is within range of multi-targeted rocket launchers or in the range of other measures of gunnery activity, can be exposed and "meet" contamination levels < 10000 mg min m^3. For comparison, vapors of hydrogen cyanide should not reach higher concentration levels than 25000 mg min m^3.

In addition, the frequency of attacks on targets was gauged. Depending on the arrangement on the battlefield theatre, during one campaign, one should expect from 10 to 20 chemical-based attacks.

Bearing in mind the possibility of long-term pursuit of wartime activities in a contaminated zone, works are being carried out on filtration systems to find regenerative recovery opportunities. The essential factors affecting performance parameters are weather conditions, the types of systems of destruction employed and experience gained from previous conflicts.

It is assumed that the possibility of new filtration systems, mounted in armored vehicles, can effectively protect the unit against chemical attacks. It is assumed that such an installation can withstand 60-120 chemical attacks, which is equivalent to 6 operations involving chemical weapons. However, the effectiveness of the protective system can be significantly impacted by atmospheric conditions, which may limit the defensive parameters by approximately 30%, which corresponds to 18-36 chemical attacks.

Table 1 shows the results of a study, conducted by specialists from the United Kingdom, with a view to identifying possible concentrations of ST vapors on the battlefield depending on the type of a poisonous substance used.

Table 1: Possible concentrations of toxic substances resulting from the use o chemical weapons

Concentration of contamination levels (mg min m3)	Type of ST	Comments
12750	Organophosphorus, generally toxic, penetrating ST	Average concentration levels
75000	Organophosphorus, generally toxic, penetrating ST	Very high concentration levels (extreme), though possible
6000	Concentrated ST	

The threat from liquid toxic substances.

An important risk that must be taken into account in the design and selection of suitable material for the construction of a collective protection building, comes from liquid toxic substances. Contamination with drops of ST is serious among other reasons, because of the density and viscosity of ST, allowing for its persistent lingering on different surfaces.

Currently, the permissible contamination density for combat vehicles is 10 g/m^2, however the aim is that new systems for collective protection ensure safety for the crew unit at a density of contamination - 50 g/m^2. For individual means of protection against contamination this value is respectively 10 g/m2 and in view is a level of 20 g/m^2. In relation to collective means of protection against contamination, tests are still being carried out.

Permissible ST contamination and the period of effective protection.

Currently, work is underway by a task group to determine the amount of allowable contamination. A group of experts from the United Kingdom has presented the results of its previous work in this area. Permissible ST contamination levels are as follows:

- GB (Sarin) – the LCt_{50} for working, active staff is 50 mg min m^3, whereas for sedentary personnel - 70 mg min m^3.
- (H) (sulfur mustard)-50 mg min m^3, can cause damage to the eyes;
- AC (hydrogen cyanide)-1000 mg min m^3 is the upper limit;
- CK (cyanogen chloride)-50 mg min m^3, causes irritation to the mucous membranes and eye watering.

To calculate protection factor (PF), the following conditions were assumed; exposure time-24 hours, during this period, there is an exposure to more than one chemical attack.

NATO normative documents do not indicate any concentration limits for toxic chemical combat. Based on extensive research concerning the effects of BST on organisms, guidelines have been developed, which contain values of concentrations, which have a negative health impact. Physically, these values reflect the NDS and NDSCh. The table shown below is a summary of risk concentrations, the value for which should not be exceeded in protected areas as well as the values for doses and inhalation.

Table 2: Summary of risk concentrations

Chemical substance	Deadly dose by injection LD50 [mg/kg]	Deadly dose by inhalation LCT50 [mg*min/m3]	NDS [mg/m3]	NDSCh [mg/m3]
Tabun	21.4	120	0.00003	0.0001
Sarin	24.3	60	0.00003	0.0001
Soman	5	60	0.00003	0.001
Cyclosarin	5	60	0.00003	0.001
VX	0.07	15	0.000001	0.00001
Sulfur mustard	20	1710	0.0004	0.003
Phosogene*	Lack of data	3 200	0.08	0.16
Lewisite	8-30	1 200-1 500	0.0004	0.003
Cyanogen chloride	Lack of data	11 000	0.6	0.77
Arsenic compounds	5	Lacko f data	0.01	0.5
Chlorine*	Lack of data	6000 – 19000	0.7	1.5
Ammonia*	Lack of data	7 500	14	28

***** Data as based on the Directive of the Polish Ministry of Labor and Social Policy in terms of maximum limits of concentration levels allowable

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Maximum concentration values listed in the table should be taken into account in determining the protective parameters at the design stage of the ZSOPS, assuring the possibility of long-term military action in contaminated circumstances.

In view of the remote probability of atmospheric contamination of chemical weapons occurring over large areas, with the newly proposed recovery systems for air-cleaning, it should be sufficient to maintain concentrations of toxin below the permitted time - NDSCh.

Presented and conducted research was made to identify realistic parameters, which should have future implications on collective protection systems. Currently, the PF factor for collective protection measures 30,000, but for filters based on ST respectively AC-2,000, CK-8,000 and GB-25,000.

Permissible contamination levels of SB and the period of effective protection.
For biological agents, characteristic indicators of risk of infections for the calculation of PF is the CFU (Colony Forming Unit). That coefficient for biological agents is essentially from 106 to 108.

For biological agents, specified doses causing infections ID50, ex. for anthrax, is generally 10,000 spores, while the expected dose is 100 spores, which is the same ID50 dose for smallpox. It was considered, that a 50% dosage leading to infections is a permissible concentration of biological agents in a clean zone. This means that in a 24 hour duration, there is the likelihood of escape to the clean zone - 50% of the dose of a biological substance, which an individual can absorb. The calculation assumes that one person's use of air is 30 dm/min.

It should be noted that recently work has intensified to solve a series of unresolved biological weapons' problems in the development of effective protection systems.

Permissible radioactive contamination levels and time effective protection.

In considering the impact factors of nuclear weapons on the objects of collective protection, it was determined that the main threat will come from radioactive fallout. The research on the development of a system of collective protection uses a scenario involving radioactive contamination as a result of a land-based nuclear explosion. It was estimated that a nuclear strike would result in radioactive particles with a diameter of 20 to 200 micrometers. The average density of radioactive precipitation at ground level, in such terms, 64 g/m2 and the radioactive dosage is 50 mSv/h.

The conclusions of these studies have huge importance when designing filtering systems, as well as in the selection of appropriate materials to cover objects/buildings of collective protection. At present, the results of the work are being reviewed by nuclear weapons' experts and it should be expected that there will be changes made to existing documents, together with the part concerning protection from biological agents, because they are smaller particles in size (2-3 micrometers). In addition, it is planned to introduce an appropriate test to control filter parameters.

7. Development directions on the improvement of systems of collective protection

Having in mind the requirements of NATO and the broad development of appropriate hardware providing comprehensive protection against

contamination, intensive work is being carried out, among other aspects, on the improvement of parameters of individual means of protection against contamination as well as on the development of the non-hardened (light) systems for collective protection. An excellent example of the work being done on measures for collective protection was a recently implemented project by the British company DERA.

In ongoing work, the aim is to achieve interchangeability of components (filters) at a high level, and thus to achieve full compatibility to connect individual panel system, regardless of their place of origin. These tasks are carried out by the introduction of new construction requirements, including the increasing of resistance requirements of materials to the impact of chemical, biological and radioactive doses.

For the main areas of interest, which today are the themes of work of the working groups of NATO, the following might be adopted for application:

- introduction of tests for determining the effectiveness of measures of protection against biological agents, and:
- determination of the essential factors of protection;
- defining the requirements for complete systems and systems input-output after taking into account all aspects of the battlefield using weapons of mass destruction (in an atmosphere of chemical and biological vapors and radioactive substances);
- improvement/modernization of tests to check collective protection measures in a toxic vapor atmosphere;
- introduction of tests to check the auto-regeneration qualities of filtering systems.

8. Summary

Collective protection against contamination is a defense element, whose goal is maintaining the required capacity to act in terms of contamination by WMD and thus is an integral part of the overall means of protection for troops. In order to meet the requirements of maintaining the capacity to act in terms of toxic pollution, OPBMR agents must meet the following conditions of: durability, flexibility, mobility, and a short time period of implementation. The objective of collective protection is to ensure the continuity and functioning under the threat of WMD, the organization of rest periods for personnel and treatment of affected personnel. Collective protection devices contribute to easing psychological and physiological effects of prolonged use of ISOPS. This objective can be achieved through selective application of the various types of collective means of protection against contamination.

In order to ensure interoperability in NATO, the ATP-70 document is a general standard for the construction and operation of collective means of protection against contamination. Application of similar constructions and operations of the procedures to create the conditions for the efficient and effective use of ZSOPS, aim at eliminating long-term training of personnel, also of other nationalities. The rules contained in this standardization document can be used also in collective protection to protect civilians. The ensuring of air, free from contamination inside a building/structure can be attained after the completion of the necessary requirements for the design, which includes a ZSOPS room with its functional purpose, measures to eliminate contamination and contamination detection. An essential condition for security in the ZSOPS is the setting up and consistent observance of procedures of entry/exit to the building/structure and the rules for contamination control. In the case of ZSOPS intended for a large number of people, the key to success is following appropriate guidelines and the development of detailed procedures and tasks for each functional person. In this way, an adequate level of protection from contamination and physical protection can be achieved.

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Hematology

Plasma-derived products – manufacturing conditions; product release

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Summary:

Proteins acquired through the process of industrial plasma fractionation are invaluable, essential medicinal products that find application in treatment of many diseases. In this article, we presented problems associated with manufacturing of plasma-derived products.

Plasma-derived products made according to the current regulations are the lowest-risk biological therapeutics presently in use.

Key words: plasma, plasma-derived products, plasma fractionation

Plasma – the liquid component of whole blood devoid of its morphotic elements. It is used as a therapeutic product (therapeutic plasma) but it may be also a source material for other invaluable therapeutics.

The works of E. Cohen and his coworkers published in 1946 constituted a crucial landmark that allowed for the development of industrial-scale fractionation of plasma proteins. Techniques they proposed for precipitation and purification of particular proteins have undergone further modifications and improvements in the subsequent years related to changing from laboratory yield to industrial-scale production. The main physo-chemical factors utilized in this process remain: ethanol concentration, pH, ionic strength of used reagents and temperature (1,2).

Plasma used for production of plasma-derived therapeutics may come from the whole blood following the separation of its morphotic components or it may be acquired directly from the donors in a process of plasmapheresis.

This biological complex contains hundreds of proteins that serve important functions in physiological processes. However, some of the roles they play in those processes remain unknown.

Basic proteins used in fractionation are the following: albumins and immunoglobulins are present in the plasma in concentrations 35 g/l and 10 g/l, respectively. They comprise about 80% of all plasma proteins. Other proteins important for industrial processing of plasma are: clotting factor VIII – few ng/l, antithrombin III – 300 mg/l, and α-antitrypsin – 1.5 g/l.

One may state that plasma-derived products manufactured around the world in 35% come from the plasma acquired through centrifugation of the whole blood and in 65% from the plasma obtained via plasmapheresis.

Generally, there are 20 different products, protein preparations essential in treatment of many diseases produced through plasma processing.

Over the past several years plasma fractionation business transformed from small centers manufacturing blood products to cover the needs of local communities into a large, world-wide industry.

Currently 23-28 million liters of plasma are handled in the course of its processing, commonly known as fractionating, in 70 facilities of various sizes around the world.

The modern process of plasma fractionating is conducted with meticulous care and standardized according to international regulations, recommendations and guidelines.

Validated, strictly abided procedures regarding removal and destruction of pathogens, especially viruses, are integral to the process of making plasma-derived products.

All these actions are aimed at releasing high-quality therapeutics with guaranteed virological safety in light of current state of knowledge in this area.

The substrate – plasma – plays an extremely important role in the production process in terms of ensuring their highest quality and safety.

Because of that, a great deal of attention is focused on establishing quality management systems at every site of blood/plasma collection that supplies the fractioning facility.

Activities and procedures applied at the blood/plasma collection facilities exert great influence on the quality and safety of acquired material and, as a result, on the finished therapeutic product. Therefore, it is understandable that plasma "production" is an integral part of the fractionation industry (3, 4, 5).

Every collection center must possess a documented quality management system. Its main goals are presented below:

- to possess implemented operational procedures,
- to have a system for registering and tracking donations,
- to have an implemented management system for printing labels, storage and transportation of donations,
- clearly defined quality specifications for blood and plasma,
- to ensure constant internal quality control,
- appropriate accommodation for blood and plasma collection.

Simultaneously, such collection centers must be subjected to regular formal inspections by appropriate authorities tasked with supervising manufacturing conditions of medicinal products according to the Good Medical Practice (GMP) requirements.

Plasma fractionation plants are also obliged to audit their partners (plasma suppliers) regularly.

Conduction of audits is aimed at constant, mutual monitoring in order to avoid deviations from the quality parameters of plasma agreed on contracts [6]. Areas of particular interest are the following:

- principles of donor qualification and examination,
- system of labeling and documenting donations,
- storage of acquired material.

Donors must be selected according to the recommendations of the European Council and fulfill health criteria specified by appropriate regulations.

Every donation must be examined using specific, validated diagnostic tests for detection of virological markers such as HBs, HIV 1 and 2, HCV and syphilis.

Individual donations must be negative for anti-HIV and anti-HCV antibodies as well as for HBs antigen. Examination for the presence of non-encapsulated viruses such as HAV and B19 using NAT (nucleic acid-based test) assays is also obligatory. (7)

A system should be created that would allow for constant collection of data regarding:

- fulfillment of donor selection criteria,
- information on potential positive results of virological tests in a donor,
- verification of performed tests,
- information on infections caused by the use of plasma-derived products,
- occurrence of the symptoms of Creutzfeldt-Jakob disease,
- appearance of post-transfusion infections caused by the treatment with blood or its products.

Plasma collection bags constitute an important safety factor. Therefore, their manufacturer, serial number and the type of used anticoagulant as well as sterilization methods applied during their production should always be noted.

Temperature is a crucial element influencing protein content in collected plasma, especially of clotting factor VII.

Obtained fresh frozen plasma (FFP) must be frozen at a temperature of -20^0C, -25^0C or -30^0C for 6-8 hours after it was collected depending on local requirements.

There is one exception to this rule: plasma intended for production of albumin or immunoglobulins

may be frozen at a temperature of -20oC within 72 hours from its collection.

Frozen plasma may be stored at a temperature of -20^0C or lower for several months (maximally over a dozen). Plasma storage and transportation temperature should be kept constant.

Information on all of these actions as well as storage conditions and local epidemiological data are contained in the Plasma Master File (PMF), which is also an annex to the registration dossier of every plasma-derived therapeutic [14].

It contains a set of data and information required by law regarding collection and further processing of plasma. Despite it being a part of the registration dossier, it is an independent document. The scope and type of data contained in this document is determined by appropriate regulations.

The content of Plasma Master File must be updated by the responsible entity every year, regardless of the validity period for the authorization for marketing (registration).

According to the requirements, plasma is pooled before the beginning of plasma processing/fractionation. Every donation included in the pool must be registered. Typical plasma pool contains 2000 – 4000 liters.

All documents together with plasma samples must be stored for at least one year after the end of the validity period for the therapeutics that were produced from it.

Simultaneously, each plasma pool must undergo retesting by the fractionator in order to ascertain that it is free of viruses mentioned previously.

Slowly unfreezing the plasma pool constituting a particular batch begins a technological process of isolating consecutive fractions (intermediate points) that may be stored, mixed and even sent to other plants for the manufacture of the ultimate plasma-derived drugs. Care must be taken to validate all actions ensuring the virological safety of the end product. Also, stability testing of particular fractions stored at given conditions should be performed.

After isolating specific fractions in the initial stage of production, obtained proteins undergo further processing in order to attain the greatest possible chemical purity while sustaining their biological activity.

The following methods are used at this stage of production:

1) physical methods: e.g. centrifugation; acquiring cryoprecipitate – the source material used for production of Clotting Factor VIII, purified and formed into an end medicinal product through a series of steps including precipitation, absorption and use of chromatographic techniques.
2) physico-chemical methods: concern mainly fractionating with the use of ethyl alcohol. This technique is used in isolation and purification of albumins and immunoglobulins. Further purification of proteins is done in the next steps of this process with the use of chromatographic techniques, i.e. molecular filtration chromatography, ion exchange, affinity, immunoaffinity, ultrafiltration and microfiltration [12, 13].

One may say that main goals of above mentioned chromatographic techniques are:
1) obtaining products of the highest purity,
2) acquisition of proteins that occur in small (trace) concentrations,
3) limiting the losses of valuable proteins – increase in efficiency,
4) removing reagents from the end product that have been previously used for virus inactivation.

Currently produced plasma-derived therapeutics must be virologically safe. Therefore, various techniques and procedures for virus inactivation are used according to the pharmacopeial requirements [8, 9, 10, 11].

The following are some of the recognized and required methods of viral inactivation:
- heating of water solutions – mainly used in production of albumins,
- heating of lyophilized end products – mainly used in the process of production of clotting factors,
- inactivation of viruses with detergents – this technique is used for destroying encapsulated viruses in production of the intermediate product,
- using nanofiltration for removal of viruses,
- conditioning of the intermediate product in low pH (about 4).

All these techniques require validation in production conditions of every fractionating plant and may be also treated as successive steps of the technological process.

In the production process, a lot of attention is focused on interoperative monitoring. The fractionator is required to provide precise descriptions of the used equipment and instruments as well as sampling techniques and storage of collected and examined material.

Actions such as: plasma pooling, testing of the source material and virological markers must be fully validated.

Monitoring of parameters important for the technological process such as: pH, temperature, ethanol concentration and sterility control including testing for bacterial endotoxins must be thoroughly documented.

Quality control of the end products must fulfill pharmacopeial requirements. If the manufacturer is using his own testing and monitoring methods, he is required to conduct the validation process in such way that would prove their full compatibility with the methods described by the European Pharmacopoeia.

Individual stages of production must be validated and documented. An assessment of technological "efficacy" and productivity of the applied process as well as biological activity of the product must be conducted.

It is especially important to give proof of effective removal of undesirable components such as: chemical reagents used in the process and natural biological factors dangerous for the well-being of the patient, e.g. compounds determining blood types or active forms of clotting factors.

Use of chromatographic techniques, especially in case of affinity chromatography, requires proof that undesirable substances are not released from the columns.

Washing and disinfection effectiveness is also an incredibly important factor for validation of the production process.

Effectiveness of the steps of the technological process as well as methods of inactivation and removal of viruses must be assessed based on strictly specified model virus strains, both encapsulated and non-encapsulated. However, the fundamental condition is that the following viruses must be used in conducted tests: HIV 1 and 2, HCV, B 19.

For the greater certainty with regard to the quality and safety of plasma-derived products introduced into the market, according to separate regulations, each batch of the finished product is required to undergo a formal preliminary release. The manufacturer covers the costs.

According to those requirements each batch of the product together with a batch report and testing samples must be delivered to an official laboratory designated by a competent body.

According to the requirements of the Polish Act on Pharmaceutical Law, all blood-derived products, i.e. clotting factors, clotting inhibitors, fibrin glue, human albumin, human immunoglobulin, or inactivated plasma must undergo serial preliminary control which, within the European Union, is abbreviated to OCABR (Official Control Authority Batch Release).

Only after obtaining a certificate confirming that the quality of the product conforms with its registered specification may the manufacturer introduce the plasma-derived therapeutic into the market.

Summarizing the briefly discussed problems associated with plasma fractionation, one may state that plasma-derived products, despite their high price, are indispensable and irreplaceable therapeutics used in treatment of many diseases.

At the same time, constant development of methods and techniques for the safety of produced preparations as well as continuation of clinical studies that would allow for further extension of indications for their therapeutic use pose an endless challenge for the plasma fractionation industry

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Hematology

Acute radiation syndrome

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Summary:

Ionizing radiation has a mutagenic effect. Depending on the absorbed dose, age and general health condition, it may cause specific organismal changes and disturbances of varying degree. This paper describes different forms and symptoms of radiation sickness and its impact on respective systems of the human body.

Key words: radiation sickness, haematological syndrome, clinical symptoms.

As the effect of short-term high-dose ionizing radiation exposure to the whole body, symptoms of tissue and other internal organ damage occur. In consequence, it leads to a gradual development of complex, systemic pathological syndrome, called radiation sickness. Besides, ionizing radiation also induces mutagenesis, i.e. it causes mutations. Specific changes and disturbances of varying severity may occur in human body, depending on the age, general state of health and, in particular, the absorbed dose. Depending on the radiation amount absorbed by the human body, different forms of radiation syndrome can be distinguished. Main classification includes chronic and acute radiation syndrome. There are also other methods of classification. Some authors identify severity grades of acute radiation syndrome, distinguishing mild, moderate or severe form.Other authors classify acute radiation syndrome considering the received dose and time of exposure, identifying three types of manifestation: haematological (haematopoietic), gastrointestinal and neurovascular syndrome, also referred to as fulminant. Haematological syndrome occurs at the absorbed radiation dose of 0.8 Gy to 8 Gy. Gastrointestinal manifestation develops due to radiation dose ranging from 8 to 20 Gy, and the neurovascular form appears as a result of doses exceeding 20 Gy.

Haematological (haematopoietic) syndrome

The hematopoietic manifestation of acute radiation syndrome (ARS) is a combination of symptoms resulting from hematopoietic and immune system damage, and dominates the clinical picture after whole body irradiation with doses from 0.8 to 8 Gy of gamma radiation, or equivalent doses of X-ray or neutron radiation. Damage to these systems is of much greater intensity after irradiation with higher doses. In such case, however, symptoms of damage to other systems (gastrointestinal, nervous, cardiovascular) may appear, which leads to death of an irradiated individual before symptoms of hematopoietic system damage develop. In some cases, the above mentioned forms of ARS may occur simultaneously.

Medical intervention is particularly important in haematological manifestation of acute radiation syndrome, as the treatment may be crucial for patient's prognosis. Clinical picture of this form of manifestation includes four stages:

1) First stage characterized by initial (prodromal) symptoms (also called primary reaction symptoms).
2) Latent stage.
3) Stage of fully developed clinical symptoms.
4) Recovery or death

Based on the intensity (severity) of clinical symptoms, the following clinical forms (grades) of radiation syndrome are identified:

- mild, when the absorbed dose of radiation ranges from 0.8 to 2 Gy;
- moderate, when the radiation absorbed dose ranges from 2 to 4 Gy;
- severe, when the radiation absorbed dose is from 4 to 6 Gy;
- very severe, when the absorbed dose of radiation reaches a value from 6 to 8 Gy.

The above mentioned clinical stages of the radiation syndrome may vary in time of duration and the severity, depending on the clinical manifestation form. Data regarding the duration of particular clinical stages, as well as time to primary reaction and its severity constitute an important factor for further prognosis. Accordingly, initial period symptoms of mild radiation syndrome occur in 2-3 hours after irradiation, mainly as nausea, single vomiting, short-lasting headaches, anxiety and a lack of generalized skin reaction. These symptoms last from a few to over a dozen hours. Latency period is three to four weeks. In some cases, the third stage develops subsequently, however, without severe clinical symptoms. Coexisting diseases or injuries (mechanical, thermal) may result in a long and severe course. Death occurs only in case of complications.

Moderate form of radiation syndrome is characterized by the onset of initial period symptoms within 1 to 2 hours after irradiation and lasts 1 to 2 days. The main symptoms are: constant headaches, vomiting, insomnia, mild irritation of the skin. The duration of the latent stage ranges from 16 to 25 days (3 weeks on average). The period of full manifestation of clinical symptoms is from 3 to 4 weeks, the period of recovery – from 1 to 2 months. Fatal outcome is estimated at 20-50%. Deaths occur with a full development of clinical symptoms and complications.

In case of severe manifestation of radiation sickness, the symptoms of the initial period appear within 30 to 60 minutes following irradiation and last for 1 to 3 days. Primary symptoms are: agitation, persistent vomiting, loss of appetite, severe headache, elevated body temperature, evident skin irritation, possible diarrhea. Latency period lasts from 8 to 17 days (approximately 2 weeks), the period of full manifestation of clinical symptoms lasts up to 4 weeks, period of recovery is from 3 to 6 months. Estimated fatal prognosis is more than 50%.

A very severe form of acute radiation syndrome is characterized by extremely intense symptoms of initial period beginning within 30 minutes after irradiation. These symptoms include persistent vomiting, loss of appetite, severe permanent headache, high temperature, severe skin irritation and diarrhea.

Latency period ranges from 6 to 8 hours. Full development of radiation sickness symptoms follows after a short latency period. Patients die within 5 to 12 days. Mortality is up to 100%.

Clinical symptoms.

The initial period of hematological manifestation of acute radiation syndrome, as already mentioned, can last from several hours to 2-3 days. During this period, agitation is observed, usually followed by apathy and general weakness, as well as headaches and dizziness. Severe forms may lead to impaired consciousness. In very severe cases, meningismus with nuchal rigidity and positive Kernig's and Brudziński's sign is observed. Mucous membranes are hyperemic, small hemorrhages occur occasionally, as well as transient skin hyperemia and elevated body temperature or fever. Apart from nausea and vomiting, other gastrointestinal symptoms may appear, such as abdominal pain and diarrhea. Polyuria occurs, and abnormal components are found in urine test, such as protein, glucose and acetone. Women suffer from menstrual disorders and uterine bleeding. The initial period gradually gives way to the latent stage. Patient starts improving, appetite returns, as well as the ability to sleep. Nervous system symptoms diminish. Despite a general improvement, the hematopoietic system shows the aggravation of lymphopenia, leukopenia and thrombocytopenia.

Alterations of haematopoiesis are characteristic for the third stage of acute radiation syndrome. They appear even with low doses of radiation, which cause no symptoms of damage to other systems or organs. In the first period of radiation sickness, as a result of haematopoietic stimulation, there is an increase in all morphological blood components, except for lymphocytes. Leukocytosis measured within the first 36 hours correlates with the severity of radiation sickness. Lymphopenia is the most sensitive indicator of irradiation and can be noticed on the first day at radiation absorbed dose of 0.25 Gy. Peripheral blood lymphocyte level decreases immediately after irradiation, and the decline reaches a maximum after a few days and, to some extent, is proportional to the absorbed dose. After sub-lethal doses, lymphocytes may completely disappear from the blood. According to M.R. Dambro, decrease in lymphocyte count may be proportional to the absorbed dose, and the total count of lymphocytes measured 48 hours after exposure determines the severity of radiation syndrome:

- over 1500 - trivial exposure (mild form of radiation syndrome),
- over 1000 - survival without treatment (mild form of radiation syndrome and some cases moderate forms of radiation syndrome)
- from 500 to 1000 - survival, if treatment is implemented (moderate and severe forms of radiation syndrome),
- from 100 to 400 – lethal, if bone marrow cannot be transplanted (severe and very severe form of radiation syndrome),
- below 100 - certain death (gastrointestinal or cerebral manifestation).

Normalization of lymphocyte count is a slow process, lasting up to several months. After initial leukocytosis in the first 36 hours after irradiation, at the end of the second period (latent stage), and especially in the third period of radiation syndrome evolution, an increasing leukopenia is observed, positively correlating with the absorbed dose and reaching its maximum within 40 days after exposure. It reverses slowly, and values below normal range often persist for several months. Blood smear test reveals the presence of immature cells with segmented multilobular nuclei, reflecting the pathological cell division. Toxic granulations and vacuolation of granulocytes are frequently observed.

In the third period of radiation syndrome, but not earlier than 3-4 weeks from onset of the disease, the red blood cell count decreases gradually. This is an effect of reduced production or medullar aplasia, as well as increased hemolysis or bleeding. The absence of reticulocytes within 48 hours following exposure is an evidence of high-dose irradiation. The reason for this is a significant radiosensitivity of erythroblasts. In severe forms of radiation sickness, erythrocytopenia can be as low as 1 million of red blood cells with hyperchromic type of anemia (embryonic type of blood cell formation and megalocytosis are observed). Osmotic resistance of blood cells decreases. Signs of regeneration are observed during the recovery period, mostly regarding red blood cells. Increasing reticulocytosis corresponds with returning efficiency of bone marrow. Serious reticulocyte crisis, up to 70%, is observed, correlating with the severity of anemia. Megaloblastic reaction also occurs with megalocytes and megaloblasts appearing in the peripheral blood. Red blood cells count increases gradually - the average cell value is increasing, while the osmotic resistance remains decreased.

Gastrointestinal system

Immediately after irradiation, all dyspeptic symptoms occur: nausea, vomiting, heartburn, xerostomia, loss of appetite – all resulting from increase of gastric juice acidity. Abdominal pain and diarrhea may appear. In the third period, after asymptomatic latent stage, a prolonged reduction of gastric juice secretion is observed with decreased acidity and reduced fraction of free HCl. Tongue becomes dry and coated. Along the gastrointestinal tract (mouth, esophagus, bowels) ulcerations occur, which can create a route of entry for infection or cause perforation.

Due to reduced tension of intestine muscular layer, bowels may become partially enlarged, which can lead to invagination and symptoms of adynamic bowel obstruction. Intestinal epithelium becomes atrophic and exfoliates, food absorption is significantly impaired. Diarrhea appears, often with blood traces. Degenerative changes can be found in the liver.

Mucous membranes and skin

During the first period of radiation syndrome, irritation of conjunctiva is noticeable. Oral, gingival and palatal mucosa is red and swollen, hypersensitive to cold and heat, prone to mechanical damage. In severe cases ulcerations, abscesses and necrosis occur. Erosive inflammation with atrophy expands in mucosa of the upper respiratory tract. Initially, the skin becomes remarkably pale. Later on, it gets dry due to the atrophy of sweat glands and even with high temperature it does not perspire. In case of radiation absorbed dose of 3.5 Gy, it comes to a hair loss. In moderate manifestation, epilation begins in third week of disease and it is limited to the most exposed areas. Hair regeneration starts in 1-2 months after epilation. Due to hair follicle atrophy, the hair growth occurs only in less exposed areas of the skin. New hair is thin, dry and turns grey occasionally. Irradiated parts of the skin remain hyperpigmented for a long time.

Respiratory system

The initial stage is characterized by a mild dyspnea and tachypnoe. Second phase is asymptomatic. During the third period, all symptoms of acute inflammation in the upper and lower respiratory tract occur. In addition, impaired bronchial tone and expectoration difficulties often lead to bronchopneumonia. Severe cases are prone to radiation pneumonitis with pleural reaction.

Cardiovascular system

Initially, tachycardia and hypotension is seen. Second stage is asymptomatic. Third period includes cardiac enlargement and quiet heart sounds. Occasionally, systolic murmur can be heard. Electrocardiography reveals decreased voltage in all leads, S-T segment depression and intraventricular conduction defects.

Urinary system

During the initial period, polyuria is observed with pathological components (proteins, glucose, acetone) appearing in urine samples. These symptoms are a consequence of renal damage manifested by increased tubular permeability. During the third stage, the amount of urine is reducing. Urine specific gravity decreases and proteins appear. A significant number of erythrocytes and lymphocytes is found. Glomerular changes embracing capillary endothelium and some focal thickening of basement membrane occur.

Reproductive system

Sensitivity to radiation of the human gonads is as follows:

- abnormal gametogenesis in females at a dose of 2-3 Gy,
- abnormal gametogenesis in males, 3-6 Gy,
- permanent infertility in women, 5-6 Gy,
- permanent infertility in men, 9-12 Gy.

Moreover, menstrual dysfunction and intrauterine bleedings occur. Miscarriages occur in pregnant women in 1-2 week of pregnancy. In 2-7 week of pregnancy, it comes to major anomalies of embryonic development.

Additional laboratory tests reveal increased urea and creatinine levels in blood serum, resulting from intense protein disintegration. This process is also responsible for increased urinal concentration of free amino acids which are normally absent: proline, tryptophan, phenylalanine, alanine, aspartic acid. Composition of plasma proteins, particularly in the third stage, is subject to significant alterations. Albumin proportion decreases considerably, whereas globulin percentage elevates. Electrophoresis showed an increase in α- and β- globulins (with an evident reduction of gamma globulins).

Based on studies, it was found that tissue content of nucleic acids is reduced. RNA/DNA ratio also becomes imbalanced, with a significant reduction of the latter. Due to DNA disintegration, urine elimination of beta-aminoisobutyric acid (BAIBA) is increased. Within a few hours after irradiation, elevated levels of glycemia are found, and the glucose concentration curve resembles the one in diabetes. As a result of glycogen depletion, lipid metabolism is disturbed. Oxidative processes are reduced causing lipid metabolism limitations with increased production of ketones. This may lead to ketonuria. Mineral metabolism is also disturbed. Chloride and sodium levels are significantly reduced.

Gastrointestinal syndrome

Gastrointestinal manifestation develops at radiation absorbed doses of 8-20 Gy. The radiation absorbed dose of 12 Gy immediately provokes gastrointestinal symptoms of acute radiation syndrome. The symptoms of the initial period include strong nausea and persistent vomiting, watery diarrhea and abdominal pain. The clinical presentation of intestinal mucose damage occurs 5-7 days following latency period. Hemorrhagic diarrhea, fever and adynamic intestinal obstruction appear – so called post-injury shock. Small intestine loses its structure; heavy gastrointestinal bleeding, diarrhea and abdominal pain occur within three days. Haematopoietic manifestation develops subsequently. Death occurs as a result of blood loss or sepsis, usually caused by Gram-negative bacteria. Patients who survive this phase die at later stages due to bone marrow suppression. Death occurs within several days, mortality is up to 100%. Damaged intestines become a route of entry for infections, and immune system collapse enables bacteremia and toxemia. According to many authors, water-electrolyte imbalance is the most important factor of gastrointestinal syndrome and mortality.

Cerebral syndrome (fulminant).

Cerebral manifestation occurs with doses exceeding 20 Gy. According to the recent data from the literature, this form of radiation syndrome should be rather referred to as neurovascular syndrome. Primary changes include the damage of blood vessels, mainly epithelium of capillary, leading to irreversible shock. Cerebral hypoxemic changes are only the final effect of these processes. Death occurs within several hours to a few days after exposure.

Tremor, ataxia, vomiting, arterial hypotension and seizures occur after 15-30 minutes of asymptomatic period, resulting in death. Mortality is 100%.

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Emergency Medicine

Treatment of status asthmaticus in Emergency Medical Systems practice

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Summary:

Status asthmaticus may develop within minutes or hours and could jeopardize life and health of the patient. It constitutes one of the challenges of the modern Emergency Medical System. The aim of this study was to evaluate the relationship between age and sex of patients, a time of the day, season and the incidence of status asthmaticus.

Material and Methods: The research was conducted on the group of 84 patients (41 women and 43 men) aged from 20 to 101 years (average age 64.92 years) in status asthmaticus. We analyzed exit cards of Medical Rescue Teams from the administrative district of Piaseczno and Otwock.

Results: The prevalence of status asthmaticus was comparable in male and female. The average age of women was slightly lower than the average age of men (63.37 years vs. 66.4 years). Most interventions took place for patients aged from 60 to 69 years.

Discussion: Status asthmaticus is a life-threatening condition. Salbutamol administered intravenously or via inhalations is a first-choice drug for patients with status asthmaticus. Most medical interventions due to the status asthmaticus take place in the afternoon and in the autumn.

Key words: emergency medicine, status asthmaticus, risk factor

Introduction

Being one of the most difficult to define image of asthma, status asthmaticus is considered to be a life-threatening condition. It is described as severe, extensive narrowing of bronchial tubes which lasts over an hour despite the use of the standard treatment.

There are many factors that cause status asthmaticus including exposure to allergens and infectious agents, inadequate treatment, a significant physical exertion or the use of NSAIDs and beta-blocker drugs.

In most cases status asthmaticus develops in a few days or weeks and is caused by the above-mentioned factors. In such cases patients require immediate medical aid. Medical Emergency Teams arriving to the site should possess full knowledge of symptomatology and the principles of proceeding with a patient with status asthmaticus

One of the most crucial element of proceeding in every case is to collect appropriate medical history from the patient himself or from the people from his environment. Medical history should include information about previous incidents of

asthma exacerbations, comorbidities, number of interventions of Medical Emergency Teams and hospitalisations in the last period and currently taken medications.

Patients with status asthmaticus usually complain of dyspnoea persisting despite administration of higher dosages of medicines, irritability and anxiety, escalation of dyspnoea on exertion and nocturnal dyspnoea. Symptoms observed in the physical examination depend on the level of the severity of asthma exacerbation. These levels are described in Table 1.

In patient with status asthmaticus several symptoms may be observed including increased respiratory rate (>25/min), tachycardia (>120/min), declined arterial oxygen saturation, hypertonia of additional respiratory muscles. During auscultation additional murmurs can be heard in the form of numerous wheezes and crackles above the lung fields. Lack of respiratory murmurs indicates substantial bronchial obstruction and thus a significant reduction of the airflow through the bronchial tubes.

Recent guidelines concerning diagnosis and treatment of asthma were published by Global Initiative for Asthma in 2010 (GINA 2010).

First stage of proceeding with a patient with status asthmaticus is the administration of the oxygen through nasal catheter or oxygen mask by medical personnel. It is the best method improving arterial oxygenation what results in the increased SaO_2 above 90%. The next stage is establishment of intravenous route and administration of β_2-adrenergic agonists via inhalation with use of nebulisation (2.5-5 mg of Salbutamol), subcutaneously in a dose of 0.5-1mg or intravenously (2.5-5 mg diluted in 500 ml 0,9 % NaCl). Sabutamol is a first-choice drug in treatment of asthma exacerbations or status asthmaticus in the conditions of pre-hospital care performed by emergency medical services.

Another group of applicable drugs include corticosteroids, which representative generally used in health care is hydrocortisone. It is administered in a dose of 200-300 mg in the form of intravenous injection. The other drugs are methylprednisolone administered IV in the dose of 62.5-125 mg or prednisolone administered IV in the dose of 25-50mg.

Second-line drug is Atrovent, a type of anticholinergic drug, which dilates bronchi. It should be used in nebulisation in the dose of 0.25-0.5mg.

During the period of hospitalization magnesium sulphate may be also administered in the dose of 2.0 g IV bolus over 20 minutes.

In cases when the patient's condition deteriorates despite the treatment implemented by the medical personnel, tracheal intubation may be considered.

The indications which appeal for this method of mechanical restoration of respiratory tract is respiratory muscle exhaustion manifested by paradoxical movements of the diaphragm, disturbances of

Table 3: Table 1 – Levels of severity of asthma exacerbations

Level	Signs	Symptoms
I	Wheezes Heart rate 100/min Respiratory rate <15/min	Limitation of full physical activity by shorter breath Patient may assume recumbent position
II	Wheezes Heart rate 111/min Respiratory rate 18/min	Shortness of breath while climbing stairs Limitation of full physical activity through shorter breath Discomfort in the recumbent position Night awakenings due to dyspnoea
III	Wheezes Heart rate 120/min Respiratory rate 19-20/min	Breathlessness preventing a patient from assuming recumbent position The use of additional respiratory muscles Exacerbation of exertional dyspnoea
IV	Less intensified wheezes Heart rate >125/min Respiratory rate 20-25/min SpO_2 91-92%	Sitting position with bent (the use of additional respiratory muscles) Single word speech Exacerbation of exertional dyspnoea Patient is agitated (conscious)
V	Rapid, shallow breathing Heart rate >130/min Respiratory rate >25/min SpO_2 <90%	Dyspnoea Disturbances of consciousness/Agitation No wheezes

consciousness occurring in the form of confusion or coma, cardiac and hemodynamic disturbances.

Every patient with status asthmaticus or whose condition improved thanks to the appropriate treatment in a hospital setting require ultimately an observation and further treatment in a hospital setting.

The aim of the study

The aim of this study was to analyze the frequency of ambulance trips paying special attention to the patients presenting status asthmaticus symptoms.

Materials and methods

The study was conducted on the basis of the exit cards of Medical Rescue Teams from the administrative district of Piaseczno and Otwock. The analysis of exit cards allowed for distinguishing 84 cases of interventions due to status asthmaticus on the basis of International Classification of Diseases (ICD-10)

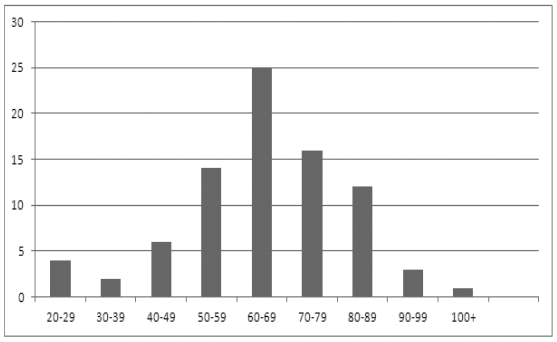

Figure 2: The relationship between prevalence of status asthmaticus and age.

Method of analysis of medical documentation (trip commission cards of medical emergency services) was incorporated in the study. The following factors were subjected to the analysis: age and sex of patients, a time of the day, season, time from symptoms onsets to calling emergency medical services and symptoms associated with the cerebral stroke.

The analysis covered 2009 and was based on the medical documentation. It was conducted in accordance with the provisions of the Law on Personal Data Protection exercising due diligence.

T-student test, chi-square test, Wilcoxon signed-rank test, Cramer's V were used for the analyses. All tests were performed at significance level $\alpha = 0.05$.

Results

The study showed no significant difference in occurrence of status asthmaticus in relation to sex. Men constituted 51.19% of all medical interventions due to the status asthmaticus in the period considered (43 cases). Status asthmaticus was reported in 41 women ($p = 0.3336$).

The age of the group researched was from 20 to 101 years. The average age amounted 64.92 years and was slightly higher for men than for women (66.40 years vs. 63.37 years). Status asthmaticus occurred most frequently in patients within the age group of 60-69 years constituting 25 cases (29.76%), followed by the age group of 70-79 years making up for 16 cases (19.05%). The least cases (not counting a single case of status asthmaticus in a person at age 101) were observed in patients aged from 30 to 39 years accounting for 2 cases. (2.38%) (Fig. 1) ($p = 0.2554$).

The analysis was also conducted on the basis of the type of called medical rescue team. Basic rescue teams were far more often dispatched to the patients with status asthmaticus constituting 65 cases (77.38%), while special teams were dispatched in 19 cases (22.62%).

In order to analyze the prevalence of status asthmaticus in the daily cycle, the test group was divided into 24 hourly intervals. Status asthmaticus occurred most frequently at 3 p.m. accounting for 9 cases (10.71%). In addition, the allocation into four six hour cycles was incorporated. According to this division of the day, cases of status asthmaticus was most common in the afternoon - 35 cases, while from 12 p.m. to 6 a.m. there were only 5 cases (Fig. 2).

Analysis of the seasonal occurrence of status asthmaticus showed the greatest escalation of incidence in September - 20 cases (23.81%), followed by February - 10 cases. (11.9%).

An analysis regarding seasons revealed that asthmatic conditions occur most frequently in the autumn - 31 cases., and the least frequently in summer - 12 cases (fig.3). The analysis showed a statistically significant relationship between the occurrence of status asthmaticus and seasonality ($p = 0.0041$) (Fig. 4).

Among the study group the most common symptoms reported by patients during status asthmaticus were increased demand for corticosteroids reported by the majority i.e. 53 people (63.10%), 20 people indicated physical effort intolerance as the symptom signifying exacerbation of asthma and 11 presented themselves with nocturnal dyspnoea

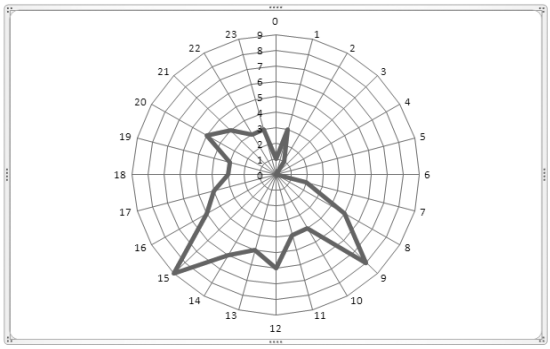

Figure 3: The relationship between frequency of status asthmaticus occurrence and hour.

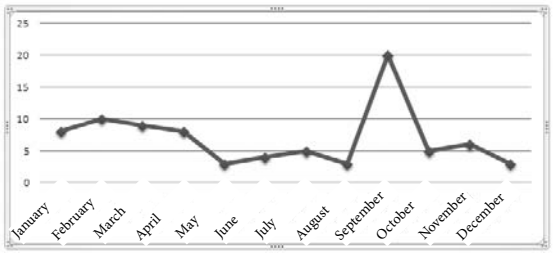

Figure 4: The relationship between the incidence of status asthmaticus and month.

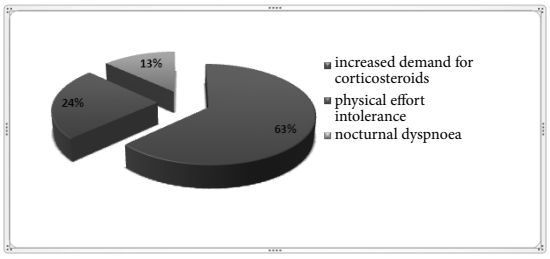

Figure 5: The most common symptoms reported by patients in asthma.

making sleep impossible.Fig. 4 - The relationship between the incidence of status asthmaticus and season.

Discussion

Status asthmaticus due to respiratory disorders may constitute a threat for the health and life of patients. Treatment is based on the restoration of proper ventilation of the lungs, resolution of clinical signs and restoring and maintaining the efficiency of the respiratory and circulatory systems, and transport to a medical facility.

Our analysis indicated the relationship between occurrence of status asthmaticus and season. Similar results were reported in other studies.

The analysis showing the relationship between the occurrence of status asthmaticus and time of day has not been published yet. This analysis shows that the peak incidence occurs around 3 p.m.

Global studies indicate that the most common symptoms of exacerbation include physical effort intolerance, an increased demand for corticosteroids, nocturnal dyspnoea. These results are consistent with the results of the analysis presented herein.

Conclusions

1) Status asthmaticus is a life-threatening condition.
2) Salbutamol administered intravenously or via inhalation is a first choice-drug.
3) Most medical interventions due to status asthmaticus take place in the afternoon and in the autumn.
4) With the average age being 66.4 years, men requesting medical rescue teams due to status asthmaticus are older in comparison with women, the average age being 63.37 years.

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Catastrophe Medicine

Healthcare during crisis situations

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Summary:

Medical protection of population in case of natural disasters or other mass threats needs coordination of the medical rescue system and many other subjects which can support its effort. Decentralized rescue system determined by the Polish law significantly depends on engagement and adjustment to local public administration structures on the province level.

The following text describes basic functions of provincial authorities and attempt to systematize them on the example of Łódź.

Key words: medical rescue, mass threats, crisis situations.

Introduction

In the most recent version of the Crisis Management Act, the point defining a crisis situation was revoked. However, when reading this Act, it can be assumed that a crisis situation is directly related to the national safety, and in particular to:

- threat to public administration functioning;
- threat to functioning and ability to restore critical infrastructure;
- continuous monitoring of threats;
- perturbations in rational management of forces and measures connected with normal functioning of the community;
- aid given to population at risk, ensuring conditions necessary to survive.

The last two points may be especially related to the constituents of healthcare safety.

Pursuant to the Ministry of Health guidelines on the plan for crisis preparations, a crisis situation 'is defined as any situation in which a hospital admits new patients for such a large scale that its resources are depleted. A crisis situation can be well described by the rule of balance between demand and supply (i.e. providing medical services). Such a situation takes place, when a hospital admits a large number of new patients in a relatively short period of time; a deluge of patients results in hospital inability to provide adequate services if special actions have not been taken.'

Planning

The basis of health safety in this mening are actions intended to prepare the public administration, combined administration and other units to work in emergency circumstances, i.e. increased threat to human life and health, or increased percentage of population at risk. The most important element of this phase of crisis management is planning. The fundamental rule that should be observed when planning, is to maintain the basic organizational healthcare structure characteristic for the time of peace, also during a crisis situation, state of emergency or during war. Such a structure should be completed with elements that enable to increase its therapeutic capabilities and take quick actions by healthcare organizational units, aimed at providing first aid to increased number of injured and ill people, and public administration units, first of

all local government administration, to perform coordinative and organizational activities supporting the actions taken by healthcare units. The plans should allow the local authorities to implement tasks ensuing from general regulations and imposed by authorized organs of public administration. The rule of compliance should not mean any limitations for organs drawing up such documents to include in the plans their own needs and solutions. Special attention should be paid to considering the issue of cooperation during the implementation of tasks included in the plans. The public administration organs supervising task accomplishment are obliged to agree the procedures of cooperation between organs participating in the process of implementation.

Planning population health safety (as part of the general civil planning) includes preparing:

- operating plans for healthcare units in case of catastrophes and natural disasters;
- operating plans for the state Emergency Medical Services (prepared at the regional level of public administration);
- operating plans in case of epidemics (prepared by the National Sanitary Inspector);
- plans of distribution of potassium iodide tablets in case of radiation events (prepared by district, regional and national administration);
- operating plans for the veterinary surgeon in case of crisis events (prepared by the Chief Veterinary Surgeon);
- plans concerning the adjustment of public and nonpublic healthcare to the defensive needs of the country (including plans for organization and functioning substitute hospital sites);
- abstracts of plans for material and personal services, in aid of functioning of substitute hospital sites.

Tasks concerning public health safety

Daily functioning of public and nonpublic healthcare as well as public administration, regardless of permanent statute activity within the scope of public health safety, is based on the accomplishment of the following tasks:

preparation and updating plans of adjustment of public and non public healthcare institutions to the defensive needs of the country;

- flow of information between the organizational units in order to update plans concerning the adjustment of public and non-public healthcare institutions to the defensive needs of the country;
- frequent analysis of the plans by healthcare institutions obliged to implement defensive tasks;
- correction of the prepared plans, concerning the use of maintained medical sets intended for broadening the hospital base and creating substitute hospital sets;
- updating the operating plans for healthcare institutions in case of catastrophes and natural disasters;
- preparation of plans for providing medical help in case of catastrophes, natural disasters and other events;
- continuation of actions aimed at protecting the population against epidemic, contamination and infections;
- continuation of preparing healthcare organizational units for implementation of tasks for the needs of the Polish Armed Forces and allied military forces;
- functioning of emergency departments, based on personal and material benefits;
- updating information concerning possessing by healthcare organizational units sources of energy, water intake and heat source;
- efficiency of substitute sources of energy (power generators);
- frequent updating documentation concerning the national healthcare security stocks;
- providing and control of rational management of medicinal product and medical device reserves;
- supervision of subordinate healthcare units by the public administration, within the scope of defence preparations and readiness to act in crisis and emergency situations;
- preparation and updating plans of evacuation from healthcare institutions in case of threat;
- control (by the public administration) of the organizational statutes of healthcare institutions taking defensive actions, regarding documentation of task accomplishment.

In the plan concerning increased number of hospital beds (within the 'total number'), not only the number of 'surgical' and 'nonsurgical' beds should be defined but also the number of 'contagious' and 'observational-contagious' beds. With regard to informative needs, it is necessary to attach an appendix including a list of selected specialist medical equipment, containing the number of devices declared by general hospitals in their 'MZ-29' reports and additionally: respirators, cardiomonitors, infusion pumps and electric suckers.

The public administrative authorities should control (in the administered area) whether statutes and regulations of the healthcare organizational units implementing defensive tasks contain records on task accomplishment for the defensive needs of the country. In the case of lack of such recordings, actions should be taken to include such records into the above mentioned documents.

In the operating plans of healthcare units for catastrophes and natural disasters, special attention should be paid to:

- timeliness of plans of evacuation and functioning of evacuated healthcare units in substitute buildings - establish the principles of cooperation between rescue, emergency and civil defence services,
- ensuring adequate manning of the positions for defence in the healthcare organizational units,
- logistic protection of hospital needs at the level assuring proper functioning of the institution.

Substitute hospital sites

For the plans drawn up by public and non-public healthcare organizational units obliged to provide hospital beds for uniformed services, a set of documents should be developed in cooperation with representatives of Departments for which these services are intended (Ministry of National Defence, Ministry of Internal Affairs and Administration, Internal Security Agency). This documentation should contain the binding procedures following a disposition of assigning beds for uniformed services and be based on 'Instruction for drawing up plans concerning assignment of beds for uniformed services', prepared by the Ministry of Health in cooperation with Inspectorate of the Military Health Service.

Taking into account other possible assignments of substitute hospital complexes, and abilities to provide medical services in buildings intended for ZMSz (Organisation of Substitute Hospital Sites), it should be considered that these complexes, depending on the situation, may work as:

1) evacuation sites for people who are:
   a) injured or directly endangered after a dangerous event (e.g. fire, explosion or another local threat) in buildings or in the area (first degree evacuation),
   b) preventively evacuated from the area and buildings, in case of imminent threat, e.g. connected with spreading of dangerous events (flood, chemical catastrophe, etc.) or threat of military actions in case of war perils (second degree evacuation),
2) quarantine and isolation sites, which are defined in the Act of 5 December 2008 on prevention and control of infections and contagious diseases in humans.

Increasing number of possible use of substitute hospital sites and fact that assigning medical staff with tasks related to, e.g. protection of ZMSz functioning, is based on the assignment to Civil Defence formations; in this process it is necessary to use guidelines presented in Section IV of the Act of 21 November 1967 on General Defence Obligation of the Republic of Poland, and, issued on this basis, ordinance of the Council of Ministers of 25 June 2002 on detailed scope of responsibilities of the Chief of National Civil Defense, chiefs of regional, district and local civil defence.

Economic Reserves

When planning implementation of tasks by healthcare organizational units, special attention should be paid to the possibility of independent actions related to administrative, economic and technical aspects (kitchens, laundries, steriles, etc.). In case of logistic protection of organizational healthcare units based on external services and companies, it would be reasonable to consider the possible continuation of services provided to the units during crisis situations, national risk and war, by entering into agreement with relevant service providers, also using the administrative procedures based on the Act of 23 August 2001 on organizing tasks related to national defence implemented by entrepreneurs.

When planning the use of national reserves, one should bear in mind that each medical set should have its own recipient and specific intended use, and ready plans concerning increased number of hospital beds and creating substitute hospital sites in the district should be consistent with the register of medical sets of the national reserves intended for districts.

On 29 October 2010 the Polish Sejm passed the law on strategic reserves. The Act entered into force on 5 February 2011, replacing the Act of 30 May 1996 on the national reserves. The new regulation introduced only one type of reserves, i.e. strategic reserves. Pursuant to the provisions of the new Act, the currently existing economic reserves created by the minister in charge of economic affairs, will become strategic reserves on the date the Act comes into force. As for mobilization reserves, within 12 months from the date the act becomes effective, the minister in charge of economic affairs will hold an inspection, whose results will decide what assortment and amount will be recommended to be included into strategic reserves. Within 24 months from the date the act comes into force, for the matters related to the management of mobilization reserves (within the meaning of the Act), the hitherto regulations are binding. Therefore, in 2011 all decisions concerning mobilization reserves (medical sets) will be made by the Minister of Health.

One should bear in mind that in case of making decision on a dislocation of reserves within the district area, the local autorities should always notify the regional authorities, who will make relevant arrangements with the Material Reserves Agency

and Department of Defence, Crisis Management and Medical Rescue of the Ministry of Health.

Planning the distribution of stable iodine preparations (potassium iodide tablets) within interventional actions in case of radiation emergency event

The administrator of stable iodine preparations is the Minister of Health, who secures the demand at the regional level (governors). The number of stable iodine preparations, the place of their storage and distribution within districts and communities, is defined by district and village heads in cooperation with provincial governors in charge of the territory, and based on the number of inhabitants belonging to risk groups that should be first protected against radioactive iodine absorption.

Risk groups and iodine preparation dosage in individual groups (one tablet is equivalent to 25 mg of iodine) are presented below:

Table 4:

No.	Risk Group	Iodine dose (single)
1.	Neonates and infants younger than 3 months	12.5 mg (1/2 tablet)
2.	Infants older than 3 months and children younger than 2 years	25 mg
3.	Children from 2 to 6 years of age	50 mg
4.	Children older than 6 years and adolescents younger than 16 years	100 mg
5.	Pregnant women	100 mg
6.	Breastfeeding women, who by reason of the age group (mothers under 16 years of age) are qualified to thyroid protection (instructed to stop breastfeeding for 48 hours and use an infant formula).	100 mg
7.	Adolescents from 16 to 18 years and adults who, from medical recommendations, should be given prophylactic iodine preparations in case of radioactive contamination	100 mg

Pursuant to the Act of 29 November 2000 - Atomic Law, a detailed plan of preparing and distribution of stable iodine preparations in case of radiation events should be included in the plan of iodine preparation distribution for individual levels of governmental or local administration; the basic sites of iodine preparation distribution should be healthcare units, pharmacies, sanitary and epidemiological stations, schools and kindergartens. In special situations, a mobile distribution point should be considered.

Direct distribution of iodine preparations (interventional actions) should be supervised by a medical professional (e.g. physician, pharmacist, nurse, or medical rescuer). The number and location of points distributing iodine preparations will be determined by a local authority: no more than 5,000 inhabitants for one point of iodine preparation distribution. The methods transport of iodine tablets to distribution points within districts and communes are defined, in cooperation with the provincial governor, by district and village heads; the collected iodine tablets belong to national reserves of medicinal products.

In case of radiation hazard involving a district or commune, a decision to release the national economic reserves of stable iodine preparations is made by the provincial governor at the request of district or village head.

Other aspects of health safety management by government administration authorities in crisis situations

Regardless of tasks included in planning health safety, public administration authorities are obliged to ensure coordination of subordinate services (guard and inspection) as well as formation of armed forces, in at least three phases of crisis management (the other aspects of management during crisis situations).

Prevention Phase: it also includes health prophylaxis.
Preparation Phase: apart from the above aspects, it also includes tasks related to safety assurance

during (previously planned) actions, concerning other forms of community functioning, infrastructure and nature. It is assured by the crisis management plans and other, regarding civil planning, and actions related to equipment and training. It particularly concerns the needs connected with the process of evacuation of population at risk of other actions of humans or nature forces, not requiring immediate healthcare service. This population needs common, regular healthcare protection.

Reaction Phase includes task accomplishment, sometimes by means of a 'manual' control of individual elements, due to the specificity of a particular situation. Normal functioning of unthreatened population should be protected in the aspect of its social needs.

Reaching these targets is based on general tasks implemented mostly by public administration authorities, or imposed by these authorities in the form of local regulations and agreements.

Conclusion

Proper healthcare protection during mass events requires a cooperation between many specialist entities, as well as systematic and effective accomplishment of planned and scheduled tasks which often considerably exceed routine (or less frequent) procedures for governmental officials.

Thus, the process of continuous improvement is necessary with respect to both planning and accomplishment of tasks in specific circumstances. The most important aspect is, as usual, awareness of decision-makers and their ability to react quickly and firmly, also during improvised situations.

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14. Rozporządzenie Rady Ministrów z dnia 18 maja 2004 r. w sprawie warunków
15. i sposobu przygotowania oraz wykorzystywania publicznej i niepublicznej służby zdrowia na potrzeby obronne państwa oraz właściwości organów w tych sprawach – Dz. U. Nr 143, poz. 1515, z późn. zm.
16. Zarządzenie Nr 85 / 2010 Wojewody Łódzkiego z dnia 25 marca 2010 r. w sprawie opracowania planów przygotowań służby zdrowia na potrzeby obronne państwa.
17. Wytyczne Wojewody Łódzkiego z dnia 29 stycznia 2010 roku dotyczące zasad przygotowań ochrony zdrowia do działań w przypadku wystąpienia zdarzeń nadzwyczajnych, sytuacji kryzysowych, zagrożenia bezpieczeństwa państwa i w czasie wojny na 2010 rok.
18. Wojewoda Łódzki - Zasady planowania, organizacji i funkcjonowania zespołów zastępczych miejsc szpitalnych (ZMSz) na terenie województwa łódzkiego.
19. Wojewoda Łódzki - Instrukcja dotyczącą planowania, organizacji i funkcjonowania zastępczych miejsc szpitalnych (ZMSz).
20. Prezydent Miasta Łodzi - Plan zarządzania kryzysowego miasta Łodzi.
21. Zarządzenia (decyzje) organów (podmiotów) nadzorujących działalność ZOZ-ów lub nakładających na nie zadania obronne.