

Kazan State University
A.M. Butlerov Institute for Chemistry

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**FUNDAMENTALS OF CHEMISTRY OF
BIOLOGICALLY ACTIVE SUBSTANCES**

Training manual for students of colleges and universities.

(Compendium of the lecture course)

*«Approved by the training department for classical higher education as a learning
aid for students of the major 020101.65 Chemistry»*

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Fundamentals of chemistry of biologically active substances: Training manual for students of colleges and universities..

The book is the compendium of the lecture course in chemistry of biologically active substances. It consists of four parts: medicines, drugs, pesticides and warfare agents. The information is delivered in form of lectures (17 lectures in total), every lecture course has a short introduction to the topic with historical background.

To ensure the thrill and better understanding the author has adapted both pure scientific articles and extracts from popular science articles about novel research in this interesting branch of chemistry.

The book is thought to be used by students and teachers in chemical, pharmaceutical, medical and biological colleges and universities.

The author hopes that this learning aid will help broaden students' outlook and improve academically in the chemistry of biologically active substances.

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FOREWORD

“Many have said of Alchemy, that it is for the making of gold and silver. For me such is not the aim, but to consider only what virtue and power may lie in medicines.”
Paracelsus, Alchemy.

The compendium of the lecture course **“Fundamentals of the chemistry of biologically active substances”** is thought to be useful first of all for the students of chemical departments, who are interested in the function of the nature and able to enthusiastically marvel and admire its complexity and simplicity, to peer into the fabulous infinite world of interacting electrons, atoms, molecules.

To the group of biologically active substances belong many compounds. The concept of **“biological activity”** reflects the interaction of a substance with an organism and its evoked response, for instance the sedative effect (of phenazepam), antipyretic effect (of aspirin), drug-induced euphoria (of cocaine), elimination of weeds (of herbicides), paralysis and suffocation (of warfare agent GD). Nowadays there is a great armory of biologically active substances serving for the need of humankind.

The main part of the information is delivered in form of lectures (17 in total) and consists of 4 parts: **“Medicines”, “Drugs”, “Pesticides in modern agriculture” and “Chemical warfare agents”**.

Every part starts with a short historical overview of the problem, since there is no way to learn something without considering our past. Due to lack of time, appointed for this course, "one can not embrace unembraceable"¹ and enlighten all aspects of unique branch of chemistry — chemistry of biologically active substances. Therefore we use the simplified protocols for synthesis of many compounds and sometimes only the final formulas or summary tables of compounds are given. They are provided as learning aids helping the big amount of information to sink in.

Every lecture is a self-consistent, complete teaching unit on the given topic and for the purpose of clarity has internal compound numbering.

The information about biologically active substances given in the manual covers the whole development of this branch from origins to 2004. It contains some subjective judgments and assessments, which could be disputable. This manual does not contain answers to all possible questions, but many recommendations, some of them, though, are quite difficult to follow. This lecture course interacts with many other subjects, in synthesis of every biological compound the achievements of many scientific branches, as organic, inorganic and pharmaceutical chemistry, bioorganic and biological chemistry, pharmacology, chemical technology, biotechnology and other branches.

However great the attainments of human development in all these branches may be, more thrilling discoveries are still awaiting us. This is probably the most interesting and productive part of scientific work. Nobody knows what this and next generation will discover and which new branches will spin off because of irrepressible human mind.

September, 27th

Irina Galkina.

¹ *“One can not embrace unembraceable”* – famous saying of Kozma Prutkov, a collective pen name of Aleksey Konstantinovich Tolstoy and three Zhemchuzhnikov brothers - Alexei, Vladimir and Alexander, which they used during the later part of Nicholas I of Russia's authoritarian reign (1850-1860) to publish aphorisms, fables, epigrams, satiric, humorous and nonsense verses, most notably in the literary magazine "Sovremennik" (The Contemporary). More: http://en.wikipedia.org/wiki/Kozma_Prutkov

A word from translator.

This book is a rare² example of an academic translation done from native into foreign language of the person in charge for translation. I hope this admission would serve as a little excuse for those who will be confronted with conjoining of Russian-English translation throughout the text. I would like to beg pardon for every mistake³, misspelling⁴, and mismatch⁵ of this work. I hope, that our work will not be misunderstood, misapprehended or misconceived. Taking into account the fact, that the books deals with some delicate topics as weapons of mass destruction and narcotics, I believe that you will not misdeem the author's intentions and not misapply the knowledge you can gather from reading this book. Do not misthink about the authors competency and finally, do not underestimate⁶ it.

Since we already began to talk about competency, I would like to emphasize that I am not a chemist, my educational background is medicine, theoretical biology, interpreting and general engineering. The first is the "first line" of my education, the primary higher education I received in Russia. Theoretical biology turned out to be the keynote of my doctoral thesis, another thesis deals with pharmacology and physiology. Additionally I studied for considerable amount of time German-Russian translation and interpreting (Berlin) and general engineering science (Hamburg). That is why the English version may seem a little bit biased towards medicine and biology, because I really love these topics and tried to check for every subtle detail mentioned or referenced in the manuscript. In the same time the authors have solid theoretical and practical background in chemistry and are responsible for veracity of the respective facts.

While translating the book I was constantly facing the problem known as "Marconi effect". This term was coined by the group of historians investigating the history of radio. They found that in almost every country there is a certain fellow-countryman claimed to be the inventor of radio (among the most known pretenders as Tesla and Popov there were dozens of less known personalities). Interestingly, this phenomenon can be found in many other branches of science and chemistry is no exception here⁷. That is why I beg you do not wonder if you find something that differs from what you were taught in school or in the university, these are the very "cultural differences" TV so obsessed with. From our side (both author's and translator's) we tried to check all facts mentioned in this work, including dates, spelling of personal names and places, historical facts etc and assure you that most of them are valid as of now.

This work could not be done without support on a solid encyclopedic work. For this purpose we used Wikipedia, the most complete and most rapidly expanding encyclopedia imaginable. Since the policy of Wikipedia does not encompass the mechanisms of verifications (or they are rudimentary at the moment), we tried to use other sources for double-sided blind control of all information we put into the book. In some cases the links below the articles on

² Though because of the ever growing power of English as an auxiliary language this phenomenon slowly becomes quite usual.

³ Despite the ever growing power of spell-checkers they are unable to eliminate all of them.

⁴ This applies in particular to the correct spelling of all chemicals, compounds, drugs, medicines, narcotics and pesticides, whose spelling is so weird in English that allows several variants to coexist in scientific literature.

⁵ Those of you who have the possibility to read the original manuscript (which is going to be published simultaneously with this English translation) will surely notice some mismatch between the "original" manuscript and the translation. Do not blame on me, translator, in many cases this mismatch aims improving of the original version, completing with additional information.

⁶ Every translated scientific book is a sort of an enemy intruding into the territory of other culture, the enemies should never be underestimated.

⁷ Here's an example: http://en.wikipedia.org/wiki/Oxygen#Scientific_history

Wikipedia pages helped us a lot to fulfil this task, in other cases profound googling was necessary. Nonetheless, every fact was thoroughly checked and confirmed.

This multistage inspection both of the original manuscript and translation was not possible without good and reliable dictionary with additional supplements for chemical, agricultural, slang and medical terms. Fortunately there was no need to thumb thick volumes, the “all-in-one” solution called Multitran⁸ took charge of all this.

At last, but according to the long-life tradition not least, I would like to thank my collaborators, who had the courage to read my raw translation and to criticize on it. These are first of all Rafis Kamaliev, a PhD student of department of pharmacology of Kazan State Medical University, who kindly read the whole translation and made a lot of valuable comments. I also thank to Dr. Evgeny Pryazhnikov and Oxana Burkina for their laudatory comments of my humble work, which encouraged me to continue the translation. Ultimately I would like to thank the boundless Internet-community which made efforts to digitalize and share the information we used as sources for this monograph.

After this not-so-short introduction I distance myself from the work and give you the full right to criticize it. Your feedback sent to alauddo@gmail.com will be very much appreciated. Off we go⁹!

Alexander Benke,
Hamburg, Germany,
28.11.2006

⁸ www.multitran.ru

⁹ Another famous phrase coined originally by a Russian.

MEDICINES

*Do not create medicine which is worse than your disease!
Hippocrates (allegedly).*

Lecture I. HISTORICAL OVERVIEW OF MEDICAL AND PHARMACEUTICAL PROFESSIONS.

Lecture II. DEVELOPMENT OF ORGANIC CHEMISTRY OF MEDICAL COMPOUNDS.

In the myths of ancient Greece one reads, that Prometheus disclosed the power of medicines to mortals. But how did it happen exactly? Prometheus — the most elevated and tragic figure of Greek mythology, the hero, who voluntarily accepted the torments for the sake of humankind (and therefore can be likened to Jesus Christ). His name stands for “forethought”(=“foreseeing”). He was a son of freedom-loving Titan Iapet and Clemene (Asia). When the War between gods and titans (*titanomachy*) brought out, Prometheus, following the advice of his grandmother Gaia – the goddess of Earth — switched the side and joined gods and the gods vanquished the enemy mostly thanking to the wisdom of Prometheus. Olympus became the residence of Zeus and Prometheus became his advisor.

Zeus commissioned Prometheus to create humans. Prometheus tempered clay and started to work. His brother Epimetheus assisted him (his name means “hind-thought”), which used up the whole clay for animals and forgot about humans. Prometheus had to create humans pinching small pieces of clay from different animals. The dream of Prometheus to create humans as perfect beings failed, the humans turned out to have obstinacy of a donkey, ruse of a fox and cowardice of a bunny... they did not duly esteem and venerated gods and wallowed in vice. The angered Zeus sent plague to humans, which he put into the *pithos*, the storage jar of sly and deceitful Pandora, the wife of Epimetheus. The mortals could not overcome this plague. (It is good time to remember the words of God: “*in the sweat of thy face shalt thou eat bread, till thou return unto the ground; for out of it wast thou taken: for dust thou art, and unto dust shalt thou return*” (Genesis, 3:19)). Prometheus, who felt sorry for humans, despite of Zeus’ will brought fire to humans from the hearth of gods, taught them to till the earth, cultivate crops, build houses, read and write, and, most important, to cure diseases.

Therefore diseases existed in all times. Cavemen had many types of diseases, but the most common diseases were those of extremities. The prove of this are the findings in the cave of Chappelle-aux-Saints (Corrèze) in France. The bones of every fourth Neanderthal skeleton found lived approximately 200 thousands years ago show the traces of arthritis (*inflammation and arthropathy*), often with complications. The most evident pathology is seen on the left thigh of Java man, who lived about 700 thousands years ago on the territory of the island Java. Severe changes as result of arthritis are found on the bones of brontosaurus, who dwelled our planet far before the emergence of bipedal arthropoids — Australopithecus.

Paleopathologists also noted the prevalence of cardiovascular diseases in cavemen. Atherosclerotic plaques are discovered in mummies of indigent inhabitants of North America, who are buried on the territory of Kentucky, USA. Ancient people died of tumors, TBC and even had caries. Using fossils scientists could estimate the lifetime in Stone Age with acceptable accuracy, it was below 30 years.

The war against diseases has been waged since ancient times. We often say, that the gift of fire helped humans to stand out from other living beings on Earth. They all, except for

humans, exist only in present time. No one of them is capable to foresee the inevitableness of his death. Therefore the “discovery” of death became a outstanding event and, without any doubt, war one of the propulsions of human evolution.

The struggle for existence progressed slowly, only technical achievements in different branches — including chemistry — could accelerate it. There are examples of traditional medicines of plant preparations, which were known many thousands years before they entered traditional medicine. The plant *ma huang* is described in the herbal of emperor Shen-Nun (approximately 3000 BC), but almost 5000 years must have been passed before the active substance (ephedrine) was extracted by Nagayoshi Nagai (1885).

The diverse of medical knowledge in ancient time are attested by “Ebers papyrus”, written in Ancient Egypt about 1500 BC. This is actually the first medical encyclopedia describing 877 remedies and magic formulas. As early as in 8 century BC the Indian surgeons possessed the techniques of Caesarian section, amputation, extraction of kidney- and gall-stones. In cooperation with ancient Indian median emerged the medicine of Ancient Tibet, which than broadly propagated in Buddhistic countries. The unique experience in using of biologically active substances has been collected. Nowadays this experience is the subject of pharmacology.

First medicines people become from natural drug-store: from plants (leaves, bark, fruits, roots, stalks), animals and minerals. During thousands years in India and China natural medicines, produced from natural sources are used. In ancient scripts more than 3000 medicinal herbs are described, they are in use since 2800 BC. In India there are more than 7500 medical plants, which are in use in folk medicine. One of these plants, *Rauwolfia serpentina*, is a source of alkaloid reserpine, whose annual volume of sales in the USA reaches 250 billions USD.

As far back as in ancient Russia first “**vertograds**” — *the hand-written herbals with descriptions of the ways to produce medicines from plants* were compiled. In medicine of many countries the medicines were prepared from bee propolis, amberat, *castoréum*, snake and scorpion gifts, mouse droppings, unossified antlers of dappled deer etc.

Scientific development in Arab caliphate was very much influenced by traditional Islamic ideology. Moslems segregated science into two parts: traditional “Arabic” (=related to Islam) and universal “foreign” (=secular or pagan). The former were predominantly human sciences which included the memorization of the entire text of Qu’ran (*hafiz*). “Foreign” sciences were considered secondary and were studied as and then necessary.

The knowledge of history was essential to understand the life of Mohammed, mathematics helped to compile the exact calendar, knowledge of geography helped to draw the borders of the subject territories. Medical science, approved by Allah, was considered useful and aimed at seeking of remedies created by the Lord. According to Islam Allah first created remedies and only them diseases emerged.

To begin of 10th century in Arab caliphate was formed a special education system. Secondary and higher educations were given in *madrasa*, its curricula covered the studying of The Revelation and natural sciences.

Thus medicine and apothecary started from religious dogmata, but gradually turned into secular philosophy and practical medical skills.

Baghdad is considered to be the origin of pharmacy. First drug-store, which dispensed medicines was opened in the central hospital of Baghdad as early as 754. Spanish cities Toledo and Cordova followed, to begin of 11th century pharmacies propagated through entire Europe. One can find mentioning about pharmacies in German language dated back in 13th century.

The term “pharmacy” comes from ancient times — time of Ancient Greece and adoration of Asclepieion, in whose sanctuaries ill people were cured; in every *healing temple* there was a store for medicines and drugs, in Greek *φάρμακον*, hence **Pharmacy**. Pharmacies

in Middle Ages were located in a single room, where the chemist dispensed simple potions, accepted visitors and even cultivated some herbs.

Development of the art of the apothecary led to increase of knowledge about dispensing medicines. In 14-15 centuries pharmacies were located in big buildings with many ample rooms. These became medical, trade and cultural centers of cities. In the most spacious room there was a store, where the chemist – the keeper of the pharmacy – accepted visitors, questioned them about their diseases and gave prescriptions. In his pharmacy, under his supervision juveniles learned the ABCs of pharmacy, photochemistry and medical chemistry. Potions and spices were sold here as well. Back premises were used as stores where the raw materials and grinding facilities were kept. Mixtures and powders were dispensed in the lab often equipped with a furnace and distiller. In that time the chemist was an outstanding person in the city, many young people were eager to become apprentices of the chemist. But pharmacies were very few in that time. They could be opened only with permission of magistrate, the right to keep a pharmacy were jealously protected and was passed on across generations. For example in Tallinn a famous pharmacy *Raeapteek* were in possession of Burhard family for 10 generations (from 1583 to 1853).

Besides herbs European chemists also used ingredients of animal and mineral origin. One of the most popular remedies was ***theriak***, which considered being *panacea* until 20th century. The remedy consisted of about 13 ingredients and had to be infused for half a year.

Beginning from the 16th century medical professionals used established ***pharmacopeias***, which were *officially approved compilation containing directions for the identification of samples and the preparation of compound medicines*. The first pharmacopoeia was published about 1480 in Florence in Latin. Russian practitioners used their own pharmacopoeia since 1778 and which was translated into Russian only in 1886. The last, 11th edition of Russian pharmacopoeia appeared in 1987.

Development of the art of apothecary was owed to the development of medical branch in alchemy. “Curing” chemistry (iatrochemistry) was established as separate science in the beginning of 16th century. The most valuable contribution to its development was done by famous Swiss doctor Theophrastus Philippus Aureolus Bombastus von Hohenheim, known under the name Paracelsus (1493 – 1541). “Many have said of Alchemy, that it is for the making of gold and silver. For me such is not the aim, but to consider only what virtue and power may lie in medicines.” — wrote he in one of his books.

The fundamental of Paracelsus doctrine was the explanation of living processes from the viewpoint of chemical transformations. He thought that every living being is a combination of certain compounds, the imbalance (disease) should be coped with by addition of lacking chemical substances. With the purpose of medical application the compounds of different metals were studied: quicksilver (Mercury), lead (Saturn), iron, copper, arsenic and antimony.



Vain were the attempts to find the Elixir of Life, but these experiments laid the foundations of chemistry.

In these times pharmacies tested the therapeutic effects of chemical substances and plant extracts. For this purpose Paracelsus performed a set of improvements of lab equipment. Thus pharmacies in the time of iatrochemistry had the functions of scientific labs, which led to development of analytical chemistry. This considered to be the origination of pharmaceutical chemistry, which then influenced other branches of chemistry.

Not least are the achievements of famous polish astronomer Nicolaus Copernicus (1473-1543). Courageous reformer of medieval science he not only laid the fundamentals of contemporary perceptions of the structure of universe, he was an obedient servant of medical science all his life long.

In the middle of 16th century chemists were invited to Russia from Europe according to Tsar's directives. In 1567 British professionals doctor Reynolds and chemist Thomas Caver were invited to Moscow. They were the first medical professionals in Russia. But the first pharmacist was some Miamas, or simple "Lithuanian Matjushko-chemist" mentioned in Nikon chronicles in 1554. In that time there were already some small private chemists shops dispensing medicines. They were probably very popular, because in 1581 according to Ukaz of Ivan the Fourth (the Terrible) the first Russian pharmacy was opened on the territory of Moscow Kremlin.

The founder of the pharmacy was the British pharmacist and chemist James Franhem, who was sent to Ivan the Terrible by British queen Elisabeth. **Franhem, chemist and pharmacist, is the parent of chemistry in Russia**, the first pharmacy, opened by him in 1581 was the first place in Russia where chemical production followed the strict regulations of Western science and the purpose was to produce medicines.

"This year (1581) is year of foundation of chemical science in Russia." [These words belong to Pavel (Paul) Ivanovich Valden (1863-1957), an outstanding Russian chemist, specialist in organic chemistry, academician of Emperor Academy of Sciences. Valden was the author of fundamental works about history of chemistry "Essays about history of chemistry in Russia" (1914), "From the history of discoveries in chemistry" (1925) etc. He spent a lot of time on preparing his "Chronological tables in the history of chemistry..." (Berlin, 1952).]

The Kremlin pharmacy was managed by a British doctor Robert Jacob. During almost a century the dispensing of medicines was monopolized by Tsar's pharmacy. Because of permanent illness of Ivan the Terrible the work in the pharmacy didn't stop even at night. In 1634 a special factory producing vessels for alchemical experiments was put into service in the small village Duhovo, located in the surroundings of Moscow. According to Tsar Ukaz of 1671 pharmacies were opened in Kazan and Vologda.

Before 1701 besides the "higher" pharmacy in Kremlin there existed also field pharmacies, which were approved by Senate in 1730.

We would like to quote an extraction from the budget of Russian Empire in 1732, where the most interesting would be a comparison between the topmost and bottommost lines:

2 600 000 rubles	–	for court needs;
1 200 000 rubles	–	for the needs of Russian fleet;
1 000 000 rubles	–	for the needs of horse stables;
460 118 rubles	–	for salary of the state principals;
38 096 rubles	–	for pensions of military invalids;
16 000 rubles	–	for public health;
4 500 rubles	–	for public education.

The Ukaz of Peter the First from 22 November 1701 approved the foundation of first private pharmacies in Moscow. First pharmacists were predominantly Germans, but also a Russian named Merkulov, Polish Bishevski and Jew Ruth.

The first private pharmacy in Moscow belonged to the practitioner Daniil Gurchin, which he ultimately (1832) sold to Karl Ferrein due to terrible theft of "ill-natured workers".

In 1654 in addition to pharmaceutical administration (*Aptekarskij prikaz*) a first medical school was opened. Nonetheless, the systematic educational system was established only in 18th century. The second half of 17th century is characterized by a new direction in the development of pharmacy. The leading role is occupied by phlogiston theory (from Greek *phlogistos* flammable).

The representatives of this theory were J.J. Becher (1635-1682) and Georg Ernst Stahl (1660-1734), who used this theory to explain the processes of combustion and oxidation. They considered combustion to be a breakdown hence only compounds can burn. Stahl thought, that all bodies contain one universal “principle”, which he called *phlogiston*. During combustion *phlogiston* is released into environment, whereas the resting part of the body remained unchanged. Phlogiston theory was very popular among chemists of this time and promoted further development of chemistry. However, despite of its progressive significance, the theory had many wrong assumptions.

Famous Russian scientist Mikhail Vasilyevich Lomonosov (1711-1765) overturned the phlogiston theory and demonstrated, that essential role in the processes of combustion and oxidation is played by air. Lomonosov has established experimentally, that combustion is not a reaction of degradation upon the release of phlogiston, on the contrary, it is a reaction of binding of the compound being burnt to the oxygen of air. Some years later the same conclusion was drawn by prominent French chemist Antoine-Laurent de Lavoisier (1743-1794).

Among the scientist of that time one should mention several pharmacists-chemists, who made series of big discoveries in chemistry. Swedish pharmacist Carl Wilhelm Scheele (1742-1786), who extracted tartaric acid from tartar (wine stone), first discovered a series of organic acids: citric acid, malic (apple) acid, oxalic acid, lactic acid, gallic acid and uric acid. He also discovered glycerol, chlorine, manganese, prussic acid. Scheele was the first who obtained oxygen and nitrogen from air.

The 18th century is inaugurated by unusual growth and achievements of organic chemistry, that promoted the further development of chemistry. Pharmacists-chemists in this time made several outstanding discoveries. Louis Nicolas Vauquelin (1763-1829), the first director of the School of Pharmaceutics in Paris discovered chromium, beryllium, palladium and osmium. French pharmacist of a military hospital in Paris Bernard Courtois (1777-1838) discovered iodine while extracting mineral salts from ash of seaweed. German pharmacist Sertürner (1783-1841) isolated morphine in 1804, described its properties and ability to form salts if added to an acid. French pharmacists Pierre Joseph Pelletier (1788-1842) and Joseph Bienaimé Caventou (1795-1887) extracted from plant material alkaloids strychnine (1818), brucine (1819), quinine (1820) and others. Talented Russian pharmacist and later matchless chemist in inorganic chemistry Karl (Ernst) Klaus (1796-1864) became famous because of the only discovery of a chemical element, done in Russia, ruthenium. Eminent German chemist and pharmacist Karl Friedrich Mohr (1806-1879) developed volumetric analysis. He was the first who used burettes and dropping glass; he created special fixed weighers, which are named after him. Worth to mention also the so-called “Mohr’s salt”.

Thus, pharmacists played essential role in origination and development of chemistry as a science.

One should mention here, that many other outstanding European chemists of 16-17th centuries were working in pharmacies, which were *de facto* chemical research labs.

To the middle of the 18th century the chemical science in Russia was good developed. Its development was associated with the name of a famous Russian scientist Mikhail Vasilyevich Lomonosov, who contributed greatly to Russian and international science and who is deservedly called a “Russian all-round scholar”. His activity was linked with the development of Russian chemistry, physics, medicine and pharmacy.

It is worth to mention, that the first after Lomonosov Russian chemist Tovij Lowitz (Johan Tobias, 1757-1804) conducted the considerable amount of his research in the central pharmacy in Peterburg.

18th century was Renaissance in Russian science after 2 thousand years of ignorance, superstitions and religious fanaticism. Best scientists united into struggle for the development of Russian science, Russian education in newly established Universities in St. Petersburg and Moscow and later in the beginning of 19th century — in Kharkiv, Kazan, Tartu (Dorpat), Warsaw, Odessa and other Russian cities.

In 1845 there were 632 pharmacies in Russia, but still 165 cities did not have their own pharmacies.

In 1806 the first chemical lab was founded in Kazan State University. Later on Nikolai Zinin, talented alumnus (1833) of the faculty of physics and mathematics, ceding to the request of the rector Nikolai Lobachevski joined the teaching board of chemistry guided by very famous chemist and hereditary pharmacist Karl Klaus. In the first decade after constructing the new separate building for a new chemical lab (1834-1837) two worldwide discoveries were made: in 1842 Zinin synthesized aniline and in 1844 Klaus discovered ruthenium. They both were the founders of Kazan chemical school.

First pharmacies appeared in Kazan government in the beginning of 18th century. As of 1841 there were three pharmacies in Kazan: E.I. Helman pharmacy on Voskresenskaya street (today Kremlevskaya street), E.Ya. Bachman pharmacy on Poperechno-Voskresnaya street (today Astronomicheskaya street) and G.V. Nikolai pharmacy on Prolomnaya street (today Bauman street). In 1855 in the center of old Kazan, on the corner of Malaya Prolomnaya street (today Baumann street) and Poperechno-Voskresnaya street was opened the biggest pharmacy of Ferdinand Grache. The firm of F.G. Grache besides the pharmacy itself also possessed spacious stores, a lab, where medicines were dispensed. They also produces mineral and fruit waters and gelatin capsules. Mineral water produced in Kazan was one of the best mineral waters in the world. The pharmacy received orders for delivery of up to 1000 poods of magnesium sulfate, up to 100 poods of calcium chloride and for 400 other chemical and medical substances.

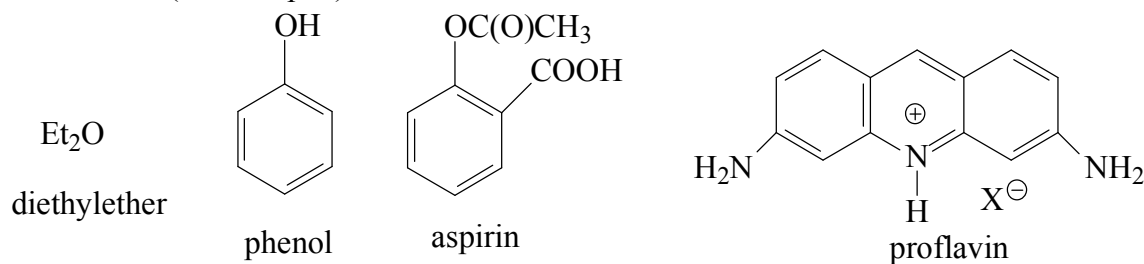
In the report of the Minister of Pharmacy L. Ya. Volpyan on the session of Pharmaceutical society in Petrograd in 1901 the activity of Kazan pharmacists was highly appraised. “Besides Klaus the Kazan lab prepared several talented chemists-pharmacists, like F.H. Grache – the close associate of A.M. Butlerov”. Butlerov helped Grache a lot in developing new medicines and production of mineral waters.

First individual natural compounds were isolated only in the 19th century. For example in 1804 Sertürner isolated morphine from opium. It was discovered then that tee, coffee, cacao and Kola nuts contain the same alkaloid — caffeine. An analogy can be seen in the history of antimalarial drugs, which were known since ancient time, for example the bark of cinchona tree, which was known to the aborigines of Peru. They sold it for centuries before the active component — quinine — was isolated in 1820 by Pelletier and Caventou.

Synthetic substances possessing pharmacological properties also first appeared in 19th century — in parallel with development of modern organic chemistry.

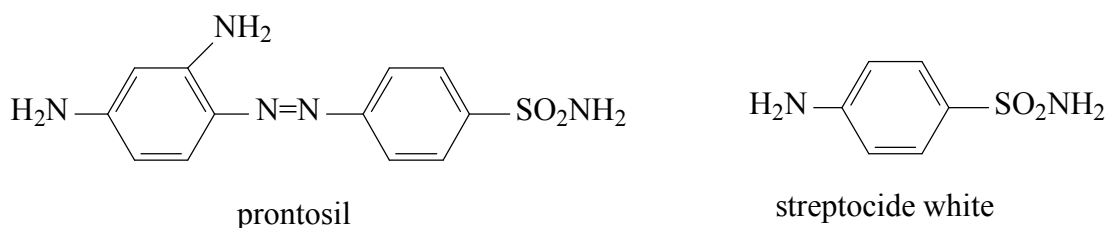
A general anesthetic sulfuric ether is in use since 1846, antiseptic phenol (carbolic acid) — since 1867. One of important periods in the development of this branch were two decades: from 1880 to 1900. During this time occurred the practical application of phenazone (antipyrinum, Knorr, 1884) and aspirin (Eichengrün, 1897). Besides in 1888 Sulfonal, today an obsolete hypnotic was discovered by accident. In 1902 Emil Fischer and Joseph von Mering synthesized barbital, which was marketed in 1904 by Bayer as veronal. In the same 1904 Friedrich Stolz synthesized epinephrine, it was the first hormone synthesized.

In the beginning of 20th century the antibacterial action of acid dyes used (like, for example, proflavin aminoacridinic salt) were successfully used during the first world war for wound disinfection (as antiseptic).



In 1908 first sulfanilamides were synthesized, but their therapeutic activity was proved only 24 years later.

The discovery of antibacterial properties of the synthetic dye prontosil (4-[(2,4-diaminophenyl)azo]benzolsulfonamide, its chloride is known as “streptocide red”) evoked the interest of scientific community to synthesized biologically active substances. So to the end of 30ies first sulfanilamides with expected antimicrobial activity (“streptocide album (white)”) were synthesized. This signaled the beginning of industrial pharmaceutical synthesis.



In 1939 the German scientist Herhard Dormagk (1895-1964) was awarded the Nobel prize in physiology and medicine for the discovery of antimicrobial activity of prontosil. By now there have been tens of thousands derivatives of streptocide synthesized, though only about 30 of them were introduced into clinical therapy.

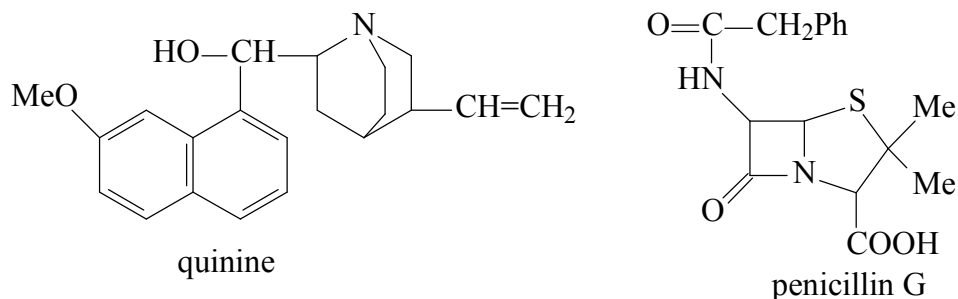
During the second world war the research was focused on the synthesis of chemical analogs of quinine, antimalarial agent extracted from the bark of cinchona tree.

Some years earlier in 1928 the Scottish microbiologist Alexander Flemming isolated small amount of antibacterial agent penicillin from mould *penicillium notatum*. He also carried out first experiments about treatment of contaminated wounds with fomentations from filtrate of the mould growth medium.

Moulds were used in the East even in ancient times. Remarks about therapeutic properties of the mould were done by medics from Ancient Greek and Rome. The French biologist Ernest Duchesne published his dissertation “Contribution to the study of vital competition in micro-organisms: antagonism between moulds and microbes”, where he describes the therapeutic properties of a *penicillium glaucum* mould, even curing infected guinea pigs from typhoid. Many researches then referenced back to his dissertation. Flemming could not estimate the importance of his discovery and was very skeptic about the medicine. One he said “it is not worth the work on it”, he also failed to get a pure extraction of the drug.

In 1940 Howard Walter Florey and Ernst Boris Chain with other researchers managed to isolate and purified sufficient amount of the first penicillin and named it *penicillin G*. In 1945 the Nobel Prize committee noted, that Flemming, Chain and Florey “did more for the victory against fascism than 25 divisions”.

The investigation and practical application of penicillin as antibiotic was done in Soviet Union by Z.V. Ermoljeva and T.I. Balezina (1942-1944). As early as in 1949 the unlimited amounts of penicillin were available for clinical application.



The early postwar years are characterized by active development of organic and pharmaceutical chemistry: steroid hormones, synthetic antibiotics, nerve and vascular agents were synthesized in chemical labs all around the world. In the time from 1950 to 1960 about 500 new drugs were created. During next 20 years further 750 medicines were developed, and finally between 1980 and 1991 about 500.

It requires from 7 to 10 years of work and from 100 to 500 billions of USD to develop every new medicine. To find out a new active component about 10 000 different derivatives must have been tested. Due to that a new branch of chemistry — combinatorial chemistry — appears in late 90ies. Its methods allow to synthesize a great amount of derivatives from the basic structure (to create so-called “libraries”) and to test them in specially designed biological conditions simultaneously.

1. Basic requirements for medicines.

Medicines are to meet many strict **requirements**. First of all, medicines **are to show high activity, selectivity, their action must last for reasonable time (duration)**. It should **not be toxic** and should not have unwanted side-effects. Moreover, it has to be chemically pure and be very stable during storage. The production costs should not be very high. And, finally, it should be accessible to the market and bring reasonable gain to pharmaceutical companies. All these factors define the life time of the medicine on the market of pharmaceutical products.

A considerable attention is paid to the study of potential toxic effects of medicines. This considerably increases the time of their development from lab to wide application (up to 7-10 years).

2. Preclinical development of new chemical entities (NCEs).

Today every promising *new chemical entity (NCE)* must be tested in three stages: pharmaceutically, pharmacokinetically and pharmacodynamically.

On the first stage the presence of desired therapeutic effect is proved. Then it undergoes a series of preclinical investigations. First of all a LD_{50} — *acute toxicity, e.g. lethal dose for 50% of experimental group* is determined. The units are mg of the medicine over kg of the target animal. Then the toxicity is tested by prolonged (during several months) administration of the medicine in therapeutic doses (usually 20-times less than LD_{50}). All discovered and potential side effects are deliberately noted.

After acute toxicity the *chronic toxicity* has to be determined. Therefore the tested medicine is administered daily during appointed time in three doses: 1) below the *therapeutic dose*; 2) suggested therapeutic dose; 3) maximal therapeutic dose. During the experiment the following parameters are registered: food and water consumption; body mass changes; changes of systemic conditions and behavior; hematologic and biochemical indicators etc.

On completion of the experiment for determining of acute and chronic toxicity the animals are dissected to allow pathomorphological and histological investigations of inner organs, brain, bones and eyes.

On the final stage the *specific toxicity* is determined: its allergic, immunotoxicity, carcinogenic and mutagenic effects, embriotoxicity, gonadotoxicity etc.

After all these tests are done the protocol containing all experimental conditions, results and a conclusion is compiled.

Only as soon as these experiments are done the entity can be accepted for clinical trials. They include the systematic investigation of the tested medicine on humans with the purpose of testing its therapeutic potential or revealing its side effects. During the same time the absorption, distribution in the human body, metabolism and excretion of the chemical, together with its effectiveness and safety are investigated.

The first phase of clinical trial is performed on a small group (30-50) of healthy volunteers. During the next phase (phase II) the trial is extended to 2-3 clinics with up to 400 patients (and some volunteers if needed).

Clinical trials are the most important stage of new drug testing. During this time the future of this potential drug is determined.

On the second (pharmacokinetical) stage – the distribution and metabolism of the chemical in human body is investigated, namely the routes of administration and absorption, distribution in the biological fluids in the body, ability to permeate through biological barriers, ability to reach the target organ, ways and velocity of biotransformation (breakdown of chemical into metabolites, which takes place predominantly in the liver), excretion ways (with urine, stool, sweat and during breathing).

Routes of administration can be:

1. **enteral (=enteric)** (from greek “*enteron*” – bowels) — through nose (intranasally), mouth (orally), or through colon (rectally).
2. **parenteral** (bypassing the bowels) — subcutaneously, intramuscularly, intravenously, through the skin surface.

During **the third (pharmacodynamical) stage** the problems of drug and its metabolites affinity to the target organs and their interaction is investigated.

Target organs can be inner organs, textures, cells, cell membranes, enzymes, nucleic acids, regulatory molecules (hormones, vitamins, neurotransmitters) and receptors.

The issues of structural and stereospecific complementarity are researched. The interaction between the agent and its receptor or acceptor, which leads to activation (stimulatory) or inactivation (inhibitory effect) of the target, followed by general response of the whole organism are usually achieved by weak bindings — hydrogen bridges, electrostatic, Van der Waals’ and hydrophobic forces.

A new branch of pharmacology — *pharmacogenetics* — appeared recently. It investigates the dependence of therapeutic and toxic effect not only upon patients’ sex and age, but upon their genetic characteristics, first of all their ethnicity.

Lecture III. DRUG DESIGN.
Lecture IV. CORRELATIONS BETWEEN STRUCTURE AND
BIOLOGICAL ACTIVITY.

The idea about correlation between the chemical structure of organic compounds and their biological activity was first suggested in the middle of 19th century. However, despite the 150 years of efforts only few certain correlations could have been established.

In this lecture I would like to enlighten the generalizations, which could be drawn about the effect of different groups of chemical elements on the biological activity of compounds, which they contain. These generalizations are just rough estimations of the effect to expect on introduction of new element, radical or groups into the target compound. The real effect is to be tested experimentally in every single case.

1. Effects of alkyl groups.

Very toxic compounds lose some of their toxicity if they bind alkyl groups. For example, if the hydrogen is substituted by an alkyl radical in HCN the resulting nitriles RCN and isonitriles RNC became toxic only then the alkyl radical is eliminated (Schmiedeberg, 1886). This suggestion by Schmiedeberg is doubted, since it excludes all possible diversity of nitrile effects. Similarly the cacodyl oxide (Schmiedeberg considers it as As_2O_3 , where two oxygens are substituted by four methyl groups) $(\text{CH}_3)_2\text{As-O-As}(\text{CH}_3)_2$ does not develop the effects specific for As_2O_3 until the compound is broken down in a human organism.

However there are many different effects, which require special attention. The convulsive effects of ammonia decrease if methyl groups are introduced: trimethylamine fails to develop the convulsive effect. In case of aniline, replacement of the hydrogen with amino group leads, similarly to ammonia, to the reduction of the convulsive effect, at the same time replacement of the hydrogen of the ring causes the increase of convulsive activity.

In many cases the replacement of hydrogen in hydroxyl group with a methyl one decreases the physiological activity. For example, pyrocatechol is more active than guaiacol, and o-methoxybenzoic and anisic acids are less active, than the salicylic acids (methylation in ortho- and para- position). On the other side, in some cases the meta-methylation of hydroxylic group promotes the increase of toxicity. So dimethyl-ether of resorcinol is dramatically more toxic, than resorcinol itself.

There is a considerable difference between the action of ethyl and methyl groups on the central nervous system, since the ethyl groups seem to have higher affinity to it. To this conclusion pushes the fact, that certain dyes containing diethylamino group $\text{N}(\text{C}_2\text{H}_5)_2$ can stain neurons, whereas the dyes containing dimethylamino group $\text{N}(\text{CH}_3)_2$ are devoid of this effect (Ehrlich and Michaelis).

Another example of differences between methyl and ethyl groups is the para-toxyphenylurea $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4\text{NHCONH}_2$. This compound is 200 times sweeter than sugar, whereas the corresponding methyl derivative $\text{CH}_3\text{OC}_6\text{H}_4\text{NHCONH}_2$ is tasteless.

The introduction of phenyl group often leads to dramatic changes in physiological activity, however this effect is not consistent and does not follow some general rules.

2. Effects of hydroxyl groups.

Introduction of hydroxyl group into aliphatic compounds usually leads to reduction of biological activity, whereas the degree of this reduction is proportional to the number of groups

introduced. For example the alcohols, bearing narcotic and toxic properties, are converted into inactive substances — glycerin, mannitol etc.

From somewhat active aldehydes — less active aldoses, like for example the compound $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{CHO}$. Further introduction of hydroxyl groups turns the compounds to completely inactive aldoses, like glucose $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CHO}$. Similar effects are seen in many other compounds: for example caffeine loses its biological activity being converted to oxycaffeine.

As an exception to this rule we can take ethylene glycol, which is more toxic than alcohol or glycerin, due to its partial conversion to oxalic acid in the human body.

Introduction of OH-groups into aromatic compounds usually leads to increase of physiological activity and toxicity. For example, hydroxylation of benzol increases its toxicity and simultaneously makes the well-known for phenol antiseptic effect to reveal. Introduction of OH group into the molecule of more non-reactive aromatic substance — benzoic acid — also leads to increase of its biological activity: o-oxybenzoic (salicylic) acid shows pronounced anti-inflammatory properties in case of rheumatism.

3. Effects of halogens in organic compounds.

The most important effect of chlorine introduction into a molecule of aliphatic compounds manifests in increase of their narcotic action, the inhibition of heartbeat and vasodilatation. The narcotic effect and lowering of blood pressure are the main effects of chlorine-containing compounds. A good illustration of the dependence of narcotic properties and toxicity of chlorine-containing compounds upon the number of chlorine atoms in the molecule are the chlorine derivatives of glycerin. The glycerin itself is inert, but its chlorhydrins possess narcotic and vasodilating effects. These effects are mostly pronounced in 1,2,3-trichloropropan $\text{CH}_2\text{ClCHClCH}_2\text{Cl}$ and less pronounced in monochlorhydrine $\text{CH}_2\text{ClCHOHCH}_2\text{OH}$.

The same can be seen in the series of chlorosubstituted methane (chloromethane CH_3Cl , dichloromethane CH_2Cl_2 , chloroform CHCl_3 and tetrachloromethane CCl_4), where the narcotic activity and toxicity are increased together with the degree of chlorination. Tetrachloroethane and many from other highly chlorinated derivatives of propane and butane are extremely toxic and lead to liver failure.

Introduction of halogen into the benzoic ring leads to the increase of general toxicity of the compound. Bromine and chlorine derivatives of both aliphatic and aromatic series show considerable similarity. Organic iodine-containing compounds differ from the compounds, containing other halogens by higher antiseptic activity and less pronounced narcotic properties (compare chloroform, bromoform and iodoform).

4. Effects of nitro- and nitroso groups.

Introduction of nitro (NO_2) or nitroso (NO) groups into a molecule leads, generally speaking, to the evident increase of toxicity no matter if these functional groups replace the hydrogen bound to carbon or oxygen.

Aliphatic nitrites cause vasodilatation and are therefore used for lowering of blood pressure. This effect is weakened on the decrease of carbon chain length from amylnitrite to methylnitrite. All nitrites share similar effects, whereas the secondary and tertiary nitrites are stronger, than the primary ones. This is probably due to the fact, that the former ones are more easily hydrolyzed and form alcohols and nitric acid. Esters of nitric acid have analogous effects: nitroglycerine, nitrosorbit, erynit and erythrittetranitrate.

A special group of NO releasing agents is introduced by derivatives of different heterocyclic compounds: 1,2-diazet-1,2-dioxides, which are broken down to alkenes and NO, furoxanes — the mechanism of NO release is thought to be linked with interaction with thiols.

Introduction of nitro group into aromatic compounds usually increases the toxicity: for example, nitrobenzol, nitro naphthol and nitro thiophen are more toxic than source compounds.

5. Effects of nitrogen-containing groups.

A lot of interest was paid to the experiments where amino group was introduced into benzol ring, the resulting compounds formed the basis of many antipyretic and analgesic medicines. Binding of second amino group to benzol ring leads to increase of toxicity. The compounds containing tertiary nitrogen are often low-toxic or free of any toxicity. In many cases highly active compounds may result when the tertiary nitrogen is converted into the secondary one. While converting from tertiary to quaternary ammonia bases the latter receives curare-like properties.

6. Effects of acid groups.

Introduction of acid groups into the molecule leads to significant decrease or total elimination of biological activity. Phenol C_6H_5OH is toxic, but phenylsernic acid $C_6H_5OSO_2OH$ is almost innocent. Morphine has high biological activity, morphinsernic acid is completely inactive. Aniline, which is more toxic than benzol, becomes almost innocent on binding of a carboxyl group, *p*-aminobenzoic acid is well tolerated by humans. The presence of carboxyl group decreases the toxicity. Derivatives of benzoic acid, for instance its sodium salt, are used in medicine.

7. Effect of saturation.

Unsaturated compounds are usually more toxic, than saturated analogues, that explained by higher reactivity. For example, the propyl alcohol ($CH_3CH_2CH_2OH$) has very weak narcotic effect and causes poisoning, but in moderate doses is innocuous. Whereas allyl alcohol ($CH_2=CHCH_2OH$) shows high toxicity without any narcotic effects. One has to mention, that unsaturated alcohols are very toxic.

On one side the many exceptions from the above given rules linking biological activity with rough chemical structures can be found. On the other side, vast generalizations are proved to be useful during synthesis of many remedies and, doubtlessly, will be useful in the future for approximate estimation of expected activity of newly synthesized chemicals.

8. Dependence of biological effects upon some physical and chemical properties.

Factors, which determine biological activity of potentially therapeutic compounds are so many and diverse, that attempt to consider them all in full measure is beyond our power. At the same time different approaches allowing construction of a model scheme for targeted drug discovery exist.

One has to consider the fact, that determining of the highest activity is insufficient for reaching this goal, i.e. at least important are the problems of low toxicity, optimal pharmacokinetic parameters of potential compounds, ways of biotransformation, possible side effects, such as influence on different biological systems, what often leads to unacceptable side effects.

Generally speaking the main task of a researcher is to find a possibility to build a structure, which would be able to interact selectively with those parts of biological system, which are responsible for certain physiological effects. From this viewpoint one should consider some properties of these systems, which can be defined as *receptor systems*. What are receptors? Definition, given by Paul Ehrlich, perfectly suits the modern state of science — *this is a small chemically specific part (on a big molecule of protoplasm), which normally regulates the process of cell nutrition and metabolism and capable to bind drug substances.*

A. Albert in his book “Selective toxicity” provides a more general definition: **“Receptor is an active group in the molecule of protoplasm, which binds an alien group”**. In other words, these receptors are material substratum of cell sensitivity and reactivity.

It is evident, that for substrate-receptor interaction some requirements are to be met, which derive from the “likeness” of their structures, presence of the groups, which can bind to each other, steric similarity etc.

As early as in 1937 German scientist A. Clark proved, that binding of substrate to receptor can be quantitatively described using the mass law and the drug-receptor interaction, as a rule, is not due to formation of strong covalent bond. Weaker interactions with formation of coordination bond, ion-ion and ion-dipole bonding, hydrogen bonds and Van der Waals forces based bonds, as well as formation of polar complexes are more often and of more significance in this case. The energy of this bonding is about 5 kcal/mole, whereas the covalent bonds have more than 50 kcal/mole (we would note, that non-enzymatic unlinking by 20-40 grades Celcium require more than 40 kcal/mole).

As regards the Van der Waals’ bonding, it should be mentioned, that they are formed when all molecules have enough energy for providing atomic oscillations and these oscillations give the possibility to form temporal dipoles — this accounts for attraction. Consider the fact, that the energy of interaction decreases dramatically if distance increases.

Notable is the fact that covalent bonding can also take place. For example, penicillins, acting on the membrane-bound transpeptidase of bacterial cytoplasmic membrane, irreversible inhibit it by acetylation leading to the opening of β -lactam ring. The irreversible effects due to formation of covalent bonds are seen also in the case of acetylcholinesterase inhibition by organophosphorus compounds.

Therefore we can conclude, that chemical structure of molecule is not the only factor, which influences the biological activity of drugs. Even if an optimal chemical structure is found, it is important to deliver the drug to its target in conditions, which allow it to interact with biological substrate. To fulfill this goal the substance must meet different physical and chemical criteria, which enable its correct distribution in human body.

Biological activity or, more precisely, biological response of organism depends upon many factors: permeability of the substance through the bilipid layer, its transport, processes of absorption, ionization, complexing, metabolism etc.

Biological response of organism to medicine depends first of all on its solubility, which determines its distribution in the organism and sets its pharmacokinetic properties. Solubility has an effect on medicine uptake from bowel lumen into blood, thus modulating the processes of absorption, filtration, diffusion etc.

To determine the impact of solubility some estimations during the synthesis of active compounds can be done. These are based upon general rule of effect of certain radicals (atomic groups) on *hydrophilic* or *hydrophobic* (=lipophilic) properties of the substance. It has been shown, that bond properties towards water decreases upon introduction of functional groups and radicals in the following order: carboxyl > hydroxyl > aldehyde > keto group > amino group > imino group > amido group > imido group (*hydrophilic groups*) and methyl > methylene > ethyl > propyl > higher alkyl > phenyl (*hydrophobic radicals*).

There is a further point to be made here, that the aquatic medium in human organism imposes some requirements to the structure of biologically active substances, whose molecules must have certain *hydrophilic-hydrophobic properties*. The latter defines the possibility of their distribution between water and lipids, and therefore their interaction with enzymes and receptors, permeation through cell membranes. The measure of hydrophoby is the decimal logarithm of distribution constants in the system “octanol — water” (lg P). This parameters is known for many drugs. The average values for hypnotics are 1.33, analgetics — 0.83, antibiotics — 0.27, sulfanilamides — 0.13 etc. Thereby all known pharmacotherapeutic groups

can be systemized. Their representers are distributed in a broad interval: from extremely hydrophobic to extremely hydrophilic compounds.

The absorption rate of the medicine depends on *pH of the medium*. Hydrogen and hydroxyl ions are practically impermeable for cell membrane. This is explained by their high reactivity, interaction with terminal chemical groups localized on the cell surface. Therefore changing of medium pH during oral administration can increase or decrease the drug permeation into cells.

Acids and bases have irritating and cauterizing effects due to formation of albuminates. These effects increase as the degree of acid dissociation increases.

Ampholites are widely used in clinical practice. These are chemical compounds whose molecules have both basic and acidic groups. The number of such drugs increases. Many acids and their derivatives (nicotinic, cinchoninic acids), amino acids (methionine, aminaloni), aliphatic and heterocyclic amides, derivatives of 4-oxypyridine, 4- and 8-oxyquinoline (chonosole, enteroseptol) etc belong to this group.

Molecular weight is one of the factors influencing the pharmacological activity. So, aliphatic carbohydrates and alcohols lose their activity and toxicity upon the increase of the molecular weight. Polymers depending on molecular weight often change their effects so much that they reverse compared to the effects of monomers.

The *surface tension* is also of great importance in the drug solutions, since their basic physical and chemical parameters also influence their biological activity. The correlation is established between surface tension and narcotic effects.

It should be noted, that no factor from those described determines the biological activity alone. All factors interact and mutually influence each other, depending on the chemical structure of medicines and other parameters. Diversity of the factors which determine the physiological effect makes drug discovery very complicated. Nonetheless, modern research methods allow us to get a general outline how to solve this problem.

9. Main directions for drug discovery and drug design.

From 300 to 400 thousands of new chemical entities are synthesized annually. Till begin of the third millennium more than 18 billions of individual substances were synthesized. 80% of them are carbon compounds with hydrogen, nitrogen, sulfur, phosphorus and halogens. Many of them pass through initial tests for certain biological activity. This stage is called **screening**.

The principle of screening was originally developed for antiluetic remedies — organic compounds with arsenic. Screening in biolabs is performed on living cells, microorganisms or textures specimens (*in vitro*), on healthy or purposely infected animals (*in vivo*): on mice, rats, guinea pigs, dogs and monkeys. On this stage from hundreds and thousands of substances just few most reactive ones are selected, which then proceed to more profound investigations. If the high efficacy of the substance is proved, it is thoroughly scrutinized to determine its toxicity and side effects, and only if those are acceptable human clinical trials begin. After clinical approbation the drug starts to be produced industrially and used in clinical practice.

10. Principles of automatic (computer-assisted) screening.

It is considered essential to perform initial tests of all newly synthesized chemical entities. However several billions chemicals are synthesized by now, moreover there are several thousands types of biological activity and diseases. It is evident, that the testing of all new chemicals remains to be utopian.

Computer assist chemical and biological professionals in testing. They allow to replace the experimental tests of synthesized chemicals by a computer-assisted screening. This

approach can be based on cluster analysis of great amount of already known drugs, grouped according to their structure and types of their bioactivity.

Another type of computer-assisted analysis can be computer modeling of drug-receptor or other empirical drug-target interactions. There is no more need for a chemist or biologist to have the substance in hands, it is enough just to feed its structure into computer. At the end of computer-assisted analysis operator becomes recommendations whether further trials are reasonable or not and what kind of bioactivity to expect. Such computer-assisted “screen” saves time, money and working hours during search for analogues. However, the eduction of principally new types of activity or new pharmacological groups will be still long be based upon experiment and researcher’s intuition.

11. Reproduction of known physiologically active substances.

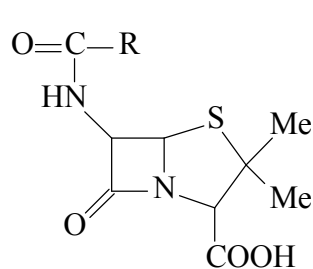
As an example of this widely used approach we would like to mention the development of full chemical synthesis of antibiotic Levomycetin. First of all Levomycetin (chloramphenicol) was isolated from culture medium of *Streptomyces venezuelae*. Today it is produced industrially in 10-step synthesis from styrene.

12. Modification of known structures.

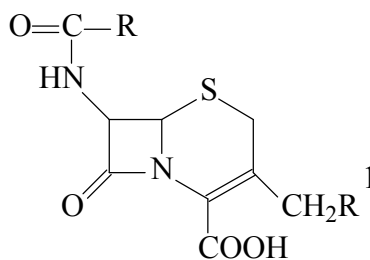
Structural modification of known synthetic and natural drugs is another approach to drug discovery. This is an intuitive and tentative approach, when from structural analogy the bioactivity of already known substance is “projected” to the new chemical. It is expected that the bioactivity of new substance will be higher.

First attempts to “construct” drugs were made at the end of 19th century (1886) by Nencki, who created the prodrug salol (phenyl salicylate), derived from the molecule of salicylic acid with attached phenyl radical (in reaction of phenol and salicylic acid).

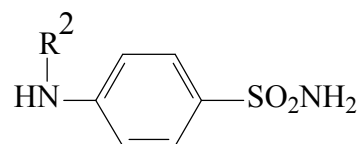
Another typical example is the structural modification of penicillins and cephalosporins through marked radicals R. This modification allowed to obtain many new drugs with improved antibiotic properties. Another vivid example is modification of sulfanilamides, which besides their antibacterial action initially showed a diuretic side-effect. As a result a new class of diuretics appeared.



penicillines
(oxacillin,
ampicillin,
ampiox)



cephalosporines
(cephazolin(kefzol),
cephotaxim,
cephalexin)



sulfanilamides
(furosemide, klopamide,
xipamide, bufenox)

The principle mentioned above is successfully used nowadays in the synthesis of many derivates of almost all classes of medicines.

13. Introduction of pharmacophore.

Pharmacophore is a structural element or molecular fragment, which accounts for pharmacological activity. Thus a new family of antineoplastic drugs was derived from nitrogen

mustard. It was done by introduction into different substances N,N-dichloroethylamine or aziridine fragment (for example, sarcolysin and other are described in details in Lecture 8).

14. Molecular modelling.

This approach together with X-ray structural analysis allow us to establish the chemical peculiarities of drug molecules and bioreceptors, the configuration of their chiral centers, to measure the distance between single atoms, atom groups and bioreceptive field of the receptor. These data allow synthesis of bioactive molecules with parameters defined on the molecular level. This method was successfully used in synthesis of highly effective analgetics, morphine analogues, as well as for obtaining a series of chemical substances which act on the central nervous system like natural neuromediator GABA.

15. Composite medicines.

Joint effects of several components in one medicine — for example, bactrim is a combination of trimethoprim and sulfamethoxazole, characterized by synergism (activity amplification). This allows to use lower doses of medicines and thus decrease toxicity. Joint application of these medical compounds provides high bacteriocidal activity as regards gram-positive and gram-negatives microorganisms, including bacteria resistant to sulfanilamides. The drug is used for therapy of dysentery, bronchitis, infections of urinary tract.

Another example is the medical compound sulfaton including sulfamonomethoxine and trimethoprim. It shows even higher antibacterial activity than Bactrim due to higher efficacy of sulfamonomethoxine compared to sulfamethoxazole.

One more example is the combination of sulfazine and Chloridin. Sulfazine, as well as other sulfanilamides described here, blocks the attachment of *para*-aminobenzoic acid to the molecule of dihydrofolic acid; Chloridin inhibits the next step — the reduction to tetrahydrofolic acid, which serves as basis for synthesis of pyrimidine and purine compounds (*the most important components of nucleic acids*).

16. Methodology of combinatorial chemistry.

This principle to combine chemistry and biology started to develop frantically in 90ies as a part of general strategy to discover new medical compounds. Strategy of combinatorial chemistry is based upon recent development of several novel chemical and biological methods of parallel synthesis and testing of many compounds. A new technique to miniaturize synthesis and biotests allowing the synthesis in solution (*liquid-phase synthesis*) or on a solid support (*solid-phase synthesis*) hundreds to thousands of new (*congenerical*) compounds daily (in amount from 5 to 1000 mg) and their subsequent quick testing in mixtures or isolated was developed.

17. Search of antimetabolites (antagonists of natural metabolites) based upon metabolism investigation.

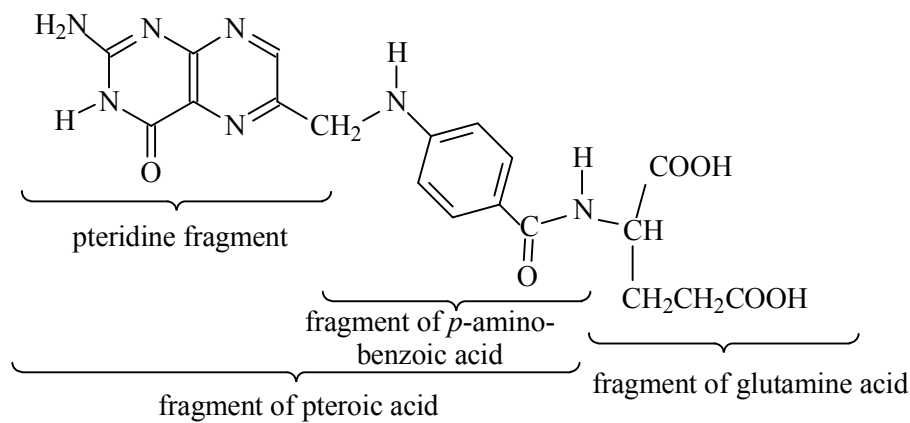
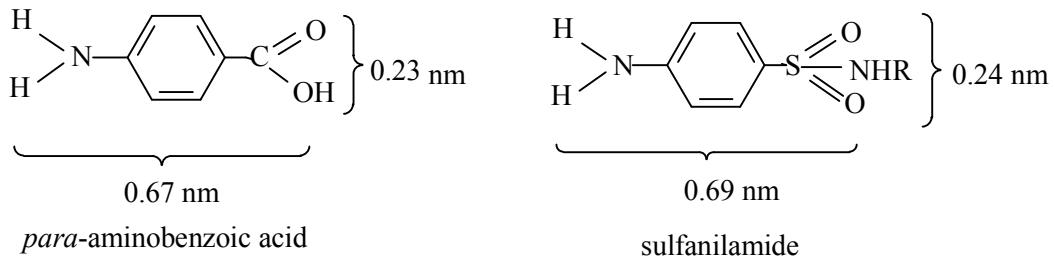
Some medical compounds are metabolized in human body with production of more active substances. Well-known analgesic codeine and half-synthetic narcotic heroine are metabolized into morphine, a natural analogue of opium.

An interesting fact was discovered during investigation of red streptocide (or prontosil) metabolism, which shows high activity against hemolytic streptococcus. It turned out, that in human body it is converted to the active compounds – sulfanilamide, e.g. streptocide.

Further investigations showed, that sulfanilamides are structural geometrical analogues of *para*-aminobenzoic acid and deteriorate the synthesis of folic acid: the enzyme responsible for its synthesis used sulfanilamine instead of aminobenzoic acid. Folic acid is needed for

purine synthesis and subsequent synthesis of nucleic acids. Presence of sulfanilic acid in medium leads to growth cessation of bacteria.

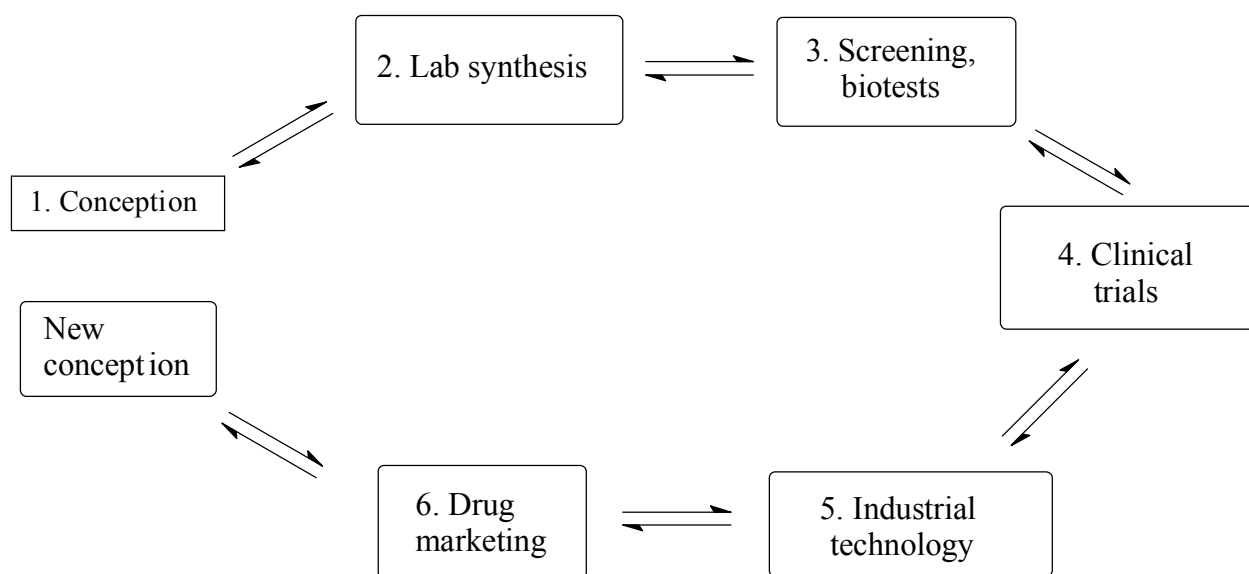
In formulas showed below one can see that sulfanilamides are antimetabolites of *para*-aminobenzoic acid:



folic acid

18. Scheme of new drug development.

The way of a medical compound from conception to marketing is very complicated, laborious and long. The cumulative expenses can reach several billions USD. The development scheme consist of the following stages:



The **first stages** is the theoretical or computer-assisted screening of chemical structures and selection of a potentially active base structure. On this stage the conception is created, what to synthesize and what for. Development of target structures is performed together with specialists in organoelemental, inorganic, pharmaceutical and bioorganic chemistry, chemistry of natural and biologically active substances.

They also contribute to the **second stage** for development of the methods to synthesize the target compounds or its close structural analogues. The methods are screened by their stability, simplicity, yield, solubility and production costs.

Biotesting on the **third stage** is the main screening step, where the main set of inactive or low-active substances is rejected. Only the most promising substances with high physiological activity and having no toxic or other side effects are taken for next more profound tests.

The most important is the **fourth stage** — clinical trials on humans. On this stage the high therapeutic efficacy is to be proved. The substance is also tested for possible minor negative side-effects, the presence or absence of those is noted. The third and the fourth states are most long ones and require collaboration of pharmacologists, biologists, toxicologists and medical doctors.

If the clinical trials are positive the substance receives an official status and is forwarded to the development of industrial synthesis — **the fifth stage**, which is the most costly, laborious and time-consuming. This task is performed by technologists, engineers, chemists and economists.

After industrial production the medical compound comes into the market (**sixth stage**).

19. Correlations between structure and biological activity.

Chemical spatial structure of the compounds defines its bioactivity. However, its level (efficacy) can depend greatly on various factors.

The majority of medical compounds must be well soluble, since they are transmitted in human organism chiefly by blood flow, that accounts for effective concentration of the drug in target place.

Many medical compounds must be highly lipophilic (*soluble in lipids*) and be able to permeate through cellular semi-permeable membranes, therefore affecting the biochemistry of metabolism. Remedies, which act on the central nervous system, must easily pass through the

blood-brain barrier, defending the brain from penetration of alien substances circulating in the blood.

Another barrier preventing the permeation of medical compounds from blood to the tissues of target organs is the capillary wall. For majority of medical substances this barrier is permeable, that is explained by their low molecular weight.

One more barrier is the placental barrier, which separates the host (mother) organism from foetus. It is normally easily permeable for drugs, which could be dangerous. Generally a molecule of medical compound, besides the main pharmacophore, must contain hydrophilic and (or) lipophilic fragments (in balanced proportion). This is a prerequisite of optimal delivery of the substance to the target.

During “construction” of medical substance one tries to consider all facts given above, introducing the respective chemical groups into the molecule of potential medicine.

Water solubility increases, basicity or acidity changes, therefore increasing the activity of the compounds, if phenol, carboxyl or sulfo-groups, basic or ammoniac nitrogen (quaternary salt) are introduced into the molecule.

Presence of *n*-alkyl chains, their prolongation and introduction of halogens, on the contrary, increases the lipophilicity of medical compounds (solubility in lipid tissues, which could serve as storages) and facilitates the permeability through membranes. Arborized alkyl radicals and presence of halogen atoms hinders the metabolism (in particular the biooxydation) of medical compounds. Cycloalkyl groups improves the affinity to receptor due to Van der Waals' forces.

Active alcohol or carboxyl group in the form of their esters or ethers change the polarity of drug molecule, improve pharmacological activity and inhibits decarboxylation of the substance.

Biological systems often do not distinguish synthetic medical compounds where benzol ring is replaced by pyridine, furan ring – by pyrrole or thiophen, e.g. the replacement of one flat ring with another does not affect the desired bioactivity. Therefore such substitutions can be a part of drug design strategy and be used for changing molecule polarity, introduction of different substituting group into aromatic ring (this task is facilitated if benzol ring is substituted with a π -superfluous heterocycle) aiming at the increase of substance-receptor interaction and increase of pharmacological activity. However changes in stability and activity should be considered.

Different pharmacophores which “inculcate” desired activity to the molecule of potential medical compound are found. For instance, presence of phenol groups can add antiseptic properties to the compound. Introduction of carbamide fragment promotes narcotic effect. Diaryl(aminoalkyl)methane group is responsible for antihistamine activity. It should be noted, that these means for “implementing” of desired medical activity are not absolute and often can lead to undesired effects.

During development of new medical compounds with chiral centers one should consider that different enantiomers can have different, sometimes even opposite effects.

We would also like to describe some modern ways to prolong activity of medicines. Usually medicines contain the medical compound itself and components of pharmaceutical form, used to provide the optimal route of administration (adjuvants: pills, powders, capsules, ointments and solutions).

The majority of medical compounds are quickly metabolized and only about a tenth reaches the target. Therefore researchers work steadily on development of administration routes, which enable long-lasting and even introduction of medical compounds to the human blood flow. One of novel and effective direction is to use biologically acceptable polymers with attached medical compound. Introduction of this medicine increases pharmacokinetic and

pharmacodynamic properties, dramatically prolonging its effect and allowing to control its concentration in blood due to delayed diffusion from injection place.

Thus some prolonged forms of antibiotics were synthesized using the attaching of poly-N-vinylpyrrolidone.

So-called cutaneous therapeutic systems use the delayed diffusion of the medical compound from solution, which is applied between the outer non-permeable membrane and inner low-permeable membrane with micropores, produced from esters of cellulose or polypropylene. Using solutions of trinitro glycerin in co-polymer of 2-hydroxyethan and 2-hydroxypropan acids a new drug against angina pectoris called Trinitrolong was synthesized. It is administered in the form of plaster, which is glued to patient's gum; the effect lasts for 4 hours.

Targeted synthesis of medical compounds with preset properties is the main priority direction of modern theoretical and synthetic organic chemistries.

Lecture V. CLASSIFICATION OF DRUGS.

MAIN HUMAN DISEASES AND BASIC CLASSES OF HUMAN DRUGS.

What is a medicine (remedy)? There are many definitions of "medicine"(remedy), they all reflect to some extent the peculiarities of application of chemical compounds, individually or in mixtures, with the purpose of healing. **Medicines are compounds of natural or synthetic origin, used for prevention, diagnosing or functional modification of certain organs, biological structures in human or animal body.**

Another definition is linked to so-called "selective toxicity" – in this case **medicines are chemical compounds, synthesized or natural, which influence certain cells without affecting other adjacent cells.**

The problem of drug classification is very important, because bringing order to the diversity of currently known drugs is essential for investigation of rational approaches to the use of known drugs and to the synthesis of new medical compounds.

There are three main classifications of drugs:

1) according to activity; 2) according to origin; 3) according to chemical structure.

According to activity medical compounds are subdivided into 3 groups – chemotherapeutic, neuropharmacological and regulatory agents.

Chemotherapeutics are anti-infectious agents: antiprotozoal, antiviral, antibacterial (antibiotics, antiseptics), anti-tuberculosic, anti-malarial, fungicidal (antimycotic), anti-neoplastic and anti-helminthic remedies.

Neuropharmacological agents are medical compounds affecting central nervous system (narcotics, anesthetics, dormitive and other psychotropic agents), and substances, affecting peripheral nervous systems (for example, local anesthetics).

Regulatory agents are vitamins, hormones, metabolites and anti-metabolites (substances, which regulate activity of enzymatic, hormonal, immune or genomic systems).

According to origin compounds are divided into **synthetic** (about 70% of all medicines), **half-synthetic** (*acquired from natural compounds but undergo chemical modification*, for example antibiotics of cephalosporin and penicillin groups) and **natural** (for example alkaloids, vitamins, hormones etc).

According to chemical structure medical compounds are divided into **inorganic** (salts, oxides, complexes), **organic synthetic** derivatives of aliphatic, acyclic, aromatic and heterocyclic series (within every group the substances are subdivided into subgroups, according to presence of certain functional groups and radicals), **organic natural** compounds (alkaloids, antibiotics, hormones, vitamins, glycosides etc).

However one should notice that there is a much more comprehensive classification – “International classification of medical compounds” by World Health Organization (WHO).

Traditionally the **classification according to Mashkovsky** is widely used in Russia¹⁰. It includes following groups of medicines:

1. Drugs affecting predominantly central nervous system.
2. Drugs affecting predominantly neuromediator processes in peripheral nervous system.
3. Remedies affecting predominantly sensitive nervous endings.
4. Remedies affecting cardiovascular system.
5. Remedies increasing renal excretion.
6. Remedies stimulating or relaxing womb musculature.
7. Remedies affecting metabolic processes.
8. Antihypoxic remedies and antioxidants.
9. Immunomodulators and immunocorrectors.
10. Antibacterial, antiviral and anti-protozoa remedies.
11. Antineoplastic agents.
12. X-ray contrast agents and other diagnostic tools.

There are the most important groups of chemical compound often used in medicine.

1. Main human diseases and basic classes of human drugs.

More than 200 years ago doctors considered cavemen absolutely healthy and diseases were regarded as god punishment for human sins; later on diseases were thought to be consequences of civilization. Despite all these statements as written above diseases existed in all times. Probably Lenin was right, writing “there was no Golden Age before us, prehistoric man was completely crashed by difficulties of existence and difficulties of the struggle against nature”.

The most ancient people were ape-men, appeared about 2 billions years ago. Unlike Australopithecus they were able to move completely on feet, had free hand with opposing thumb and better developed brain. It was in this time then humans acquired articulate speech, primitive thinking and consciousness. Gathering crops for nutrition these ancient people learned about their healing properties, step by step elaborating the bases of phytotherapy.

In spite of high level of medical development and efforts of medical professionals, diseases of unknown origin still kill billions people. Modern medicine classifies more than 10 000 human diseases (theoretically several tens of thousands are possible). It is thought, that from known diseases about 3 000 are hereditary, e.g. having genetic (“molecular”) origin. Pressing problems of modern society are cardiovascular and neoplastic diseases, ulcerous diseases of gastro-intestinal tract, infectious diseases and diseases of nervous system.

One of global problems of passed century was the complex of cardiovascular diseases. Myocardial infarction is being investigated since the end of 19th century. First attempts to systematize the observations on heart work were done by K. Knoff in 1878 and U. Osler in 1892.

Russian therapist Vladimir Mikhailovich Kernig, the head physician of Obukhov hospital in Saint-Petersburg described pericardial inflammation after severe heart strokes and explained the mechanism of the disease, thereby laying the fundamentals of cardiology. Active

¹⁰ *Mikhail Davidovich Mashkovsky* (russian: Михаил Давыдович Машковский) (March 1st, 1908 - June,5th 2002) was famous Russian pharmacologist, academician of Russian Academy of Science, the author of the famous Soviet and later on Russian pharmacopoeia "Medical compounds", which had 15 successful editions (the last 15th edition was published after his death in 2005 in Russia). More: http://en.wikipedia.org/wiki/Mikhail_Davidovich_Mashkovsky

investigation of this disease started by V.P. Obrazcov and N.S. Strazhesko. The main symptom of myocardial infarction is an increasing, sharp pain in chest, not alleviated by cessation of physical activity and administration of nitroglycerin. Risk factors are nerve overstrain, negative emotions, fatty diet, hypokinesia.

In the majority of cases the cause of infarction is a long-lasting ischemia (*oxygen insufficiency due to severe shortage of blood perfusion*) of myocardial wall.

The clinical picture of the ischemic heart disease was first described by William Heberden in 1768. If during relatively “peaceful” 18th century this disease was rare, today its prevalence can be classified as pandemic. At risk are overweighted people, people with sedentary professions, smokers and alcoholics, people suffering from hypertension and those amenable to hysteria.

To a great disaster turned neoplastic diseases. It is proved, that cancer more often affects elders. According to the rising statistic of cancer incidence, the latter is connected to population ageing and worsening of ecology. About six billions die annually of malignant tumor. In 1996 about 225 thousands died in Moscow.

Neoplastic diseases were known already in ancient time. In ancient manuscripts descriptions of this dramatic disease, accompanied with severe pain and suffer, were found. The word “cancer” (from latin “carcinoma”, greek “karkinos” – “crab, crayfish”) was “popularized” by Galen, who wrote “this disease has the veins stretched on all sides as the animal the crab has its feet, whence it derives its name “. Still, it is generally considered that Galen just adopted the terms used by Hippocrates in his works. It is believed, that the original term comes from the appearance of the cut surface of a solid malignant tumour, with a roundish hard center surrounded by pointy projections vaguely resembles the shape of a crab. Later on his suggestion was proved by Pavel Eginiski, who added, that the disease like a real crab, is persistently attached to the affected body part. In Europe this disease “appeared” in 1692 in the annual British Almanac “Bill of mortality”.

Famous German-Jewish pathologist Julius Friedrich Cohnheim suggested the theory of embryonal rests, e.g. the cancer is preceded by irreversible deformation of tissues, like polypes in stomach or birthmarks. Nonetheless more serious causes like changes in cellular genetic are needed for a tumor. Risk factors are hyperproduction of hormones, ionizing or UV rays, mutations due to viruses or chemicals. Normally functioning immune system can partially or even completely eliminate tumor. Immune system gets compromised in old age and elders become susceptible to this disease.

Type and level of tumor prevalence depends to the great extend upon residence. Citizens of Japan or Russia are susceptible to stomach cancer. In developed counties of America and Europe, as well as in big cities of Russia dominates lung cancer. This is due to high level of smoking, air pollution with production byproducts and exhaust gases. Liver cancer due to deficit of proteins in food became national catastrophe of African countries. Population of Mongolia, Kazakhstan, Buriatia and Altai, used to consume hot and fatty food, often suffer from gullet cancer.

In the latest time in the USA (and now also in Russia) fast food became very popular – for example, the network of McDonalds. Inclination to the easily digestible food without ballast components led to increase of rectum cancer. Some physicians believe, that a vague hope for rescue could give the change of residence place. Thereby the danger of cancer in „traditional“ form is diminished, in some cases leading even to the complete recuperation of „incurable“ patient.

In the end of 70ies AIDS (Acquired Immunodeficiency Syndrome) appeared, which propagated through all continents like conflagration. According to medical sources, AIDS is a collection of symptoms and infections in humans resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV).

First symptoms of the disease, like fever, dyspepsia, manifestations on skin, inflammation of lymphatic nodes appear after 3-60 days after contamination (sexual contacts, homosexuality, blood transfusion, injections of narcotics). Secondary symptoms (tumors, kahexia, purulent and septic processes, pneumonia) can be noticed 8-10 years after, then the disease reaches its maximum. Due to drastically compromised immunity appear foci of opportunistic infections, caused by viruses, bacteria or fungi. In 1-5 years the patient dies.

Within a short period of time HIV-infection became the problem number one for physicians in the whole world, supplanted cancer and cardiovascular diseases. The number of infected population in developing countries (according to WHO) in the beginning of 90ies was about 2 billions, at the end of 1994 already 17 billions (about 11 billions live in Africa).

According to one of numerous versions, the Fatherland of this disease was Africa, from where it invaded America and Europe through infected seamen from trade ships. In the book of the famous American journalist Randy Shilts "And the Band Played On: Politics, People, and the AIDS" there are interesting facts about emergence of this disease in America. According to the author, the citizens of the USA "got" this mortal African disease on the July, 4th 1976, during the celebration of 200th anniversary of American independence. "Tall sails scraped the deep purple night as rockets burst, flared, and flourished red, white, and blue over the stoic Statue of Liberty. The whole world was watching, it seemed; the whole world was there. Ships from fifty-five nations had poured sailors into Manhattan to join the throngs, counted in the millions, who watched the greatest pyrotechnic extravaganza ever mounted, all for America's 200th birthday party. Deep into the morning, bars all over the city were crammed with sailors. New York City had hosted the greatest party ever known, everybody agreed later. The guests had come from all over the world. This was the part the epidemiologists would later note, when they stayed up late at night and the conversation drifted toward where it had started and when. They would remember that glorious night in New York Harbor, all those sailors, and recall: From all over the world they came to New York". Today the number of HIV-infected people steadily increases. Every 5 minutes somebody gets infected. More than 200 thousands are already dead.

Here is statistics on other infectious diseases, as published by "Science". Incidence of malaria in developing counties reached 300-500 billion cases annually, about 2.7 billions die. Tuberculosis affects up to 3.4 billions. Annual mortality of the most dangerous dysentery, caused by Rotavirus gastroenteritis reached 4 billions (from them about 1 billion children). Industrially developed countries are characterized by infectious diseases of respiratory tract, pneumonia and influenza (about 4 billions annually, mortality is about 1%).

According to the number of medicines produced industrially the first place is taken by medicines against cardiovascular diseases. The second place belongs to antibacterial compounds. Then come anesthetics and antineoplastic agents.

The total net sales of medical compounds around the world in 1990 is 155 billions USD, in 1995 already 160 (shared by USA (38%), Japan (19%) and Germany (12%)). The mostly sold medicines in 1995 in the USA were remedies against diseases of CNS (17% of country net sales), in Japan – remedies against diseases of gastro-intestinal tract (15%), in Britain and Spain – cardiovascular medicines (12%), in France – antibiotics (15%), in Germany – medicines against respiratory diseases (11%). In total the mostly sold medicines around the world were medicines against respiratory diseases (10%), cardiovascular diseases (8%), anti-rheumatic agents (4%) and analgetics (2%). As a single medicine the first place was taken by anti-ulcerous agent omeprazole, which was sold totally for 6 billions USD.

Lecture VI. SYNTHESIS OF CHEMICAL COMPOUNDS OF ALIPHATIC SERIES

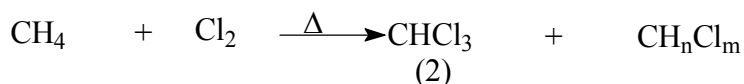
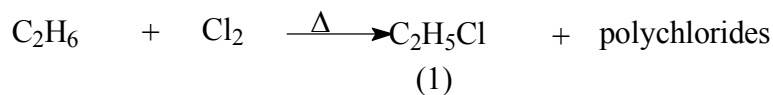
1. Halogen-containing derivatives of acyclic hydrocarbons.

Hydrocarbons with one or several hydrogen atoms replaced by halogen are widely used in medicine. In their molecules all four halogens (fluorine, chlorine, bromine or iodine) can be present. Sometimes they all are present simultaneously and each of them attenuates chemical, physical and pharmacological properties of these compounds.

Physiologic activity of halogen derivatives comes from the fact that they are soluble in lipids therefore lead to physical and colloid changes of lipids of nerve tissue and have anesthetic activity.

The degree of their activity and toxicity depends upon the degree of halogenization of hydrocarbons.

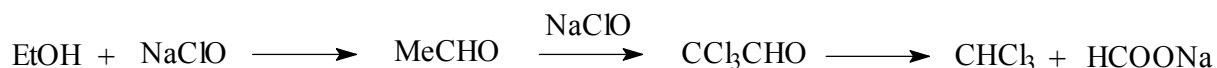
Alkylhalogenides, as **ethyl-chloride (1)**, **chloroform (2)** (trichloromethane) and **Ftorotan (3)** (1,1,1-trifluoro-2-chloro-bromethane) are used for inhalator narcosis (general anesthetics). It has been found, that the increase of halogenization, as well as change from iodide to bromide and further on to chloride, leads to increase of narcotic properties of alkylhalogenides. Ethyl-chloride and chloroform are produced industrially by high-temperature chlorization (at 400 degrees Celcium) of ethane and methane:



Methylchloride as well, as **ethyl-chloride** are used in medical practice for local anesthesia. These remedies, being applied to skin quickly volatilize thus cooling the traumatic surface, making it insensible to pain (in case of bruises, strains, dislocations and fractures).

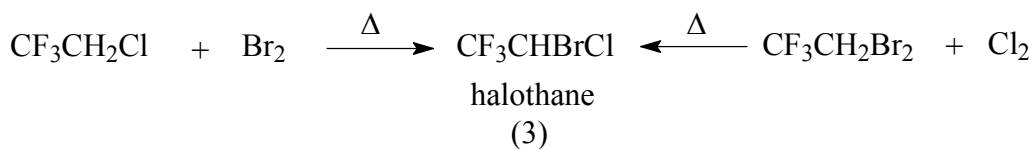
Methylchloride can be produced for medical purposes from the draff of molasses, which contains a lot of betaine glycine. The draff is decomposed by dry distillation at 300 degrees, the resulted trimethylamine is converted by heating with muriatic acid into methylchloride or ammonium chloride.

Chloroform (first used for narcosis in 1846) is synthesized by adding hypochlorites to ethanol, ethanal or propanone (in presence of hypiodite iodoform is synthesized, it is used in medicine only as antiseptic agent).



In 1950ies a new group of fluids for inhalator narcosis was discovered: these are fluorized hydrocarbons (**Ftorotan**, **methoxyflurane** and **enflurane**). They were synthesized for technical purposes (screening for new freons), but high narcotic effect was revealed during investigations. It turned out that they are non-flammable (compared to diethylether), these substances provide higher deepness of narcosis, better control during operations requiring roentgen- and electro-equipment, and most importantly, have less side effects. They were rapidly introduced into clinical practice and are widely used until now.

Industrial production of Ftorotan is based on radical (at high temperature) bromizing or chlorizing of respective freons:



There are no more doubts, that one of the most essential properties required for narcotics, used in inhalator narcosis, is lipophilicity, which is determined as the ratio of concentration in lipid phase (octanol) to the concentration in aqueous phase (on distribution between these phases). It is generally considered today, that general anesthetics are just easily absorbed by sensitive areas and block openings of ionic channels, increase the excitability threshold and block propagation of action potential, without depolarizing nerve fibers.

As external antiseptic **iodoform** CH_3I (triiodomethane) is often used in medicine. It acts due to loose connection between iodine and carbon in its molecule, the iodine is easily hydrolysed and acts as antiseptic.

2. Alcohols and their derivatives.

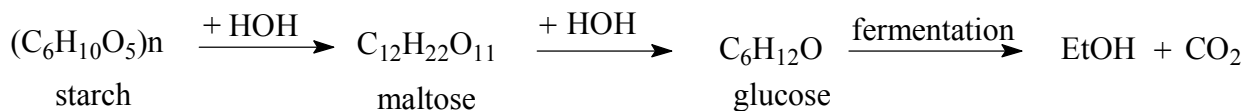
Alcohols are hydrocarbon derivatives, where one or several hydrogen atoms are replaced with hydroxyl groups.

Depending on the number of hydroxyl groups in the molecule of alcohol, molecular weight, type of carbon whose hydrogen atom is replaced, the type of hydrocarbon alcohols can have some differences in physical and chemical properties.

From aliphatic alcohols widely used in medicine one should mention **ethanol**, which can be used as antiseptic and irritating agent for cold sponge-bad or compresses. It is also often used for preparation of extractions and other medicines. Industrially it is produced by vapor phase (direct) or liquid phase (via intermediate ethylsulfate) hydration of ethylene.



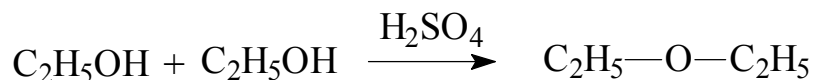
Besides it is enzymatically produced from saccharides. So, from starch using the enzyme malt amylase (*malt is pulverized germinated barley*) disaccharide maltose is produced on the first stage, it is then converted in presence of yeast maltose into glucose. The subsequent fermentation of glucose by yeast zymase leads to formation of ethanol.



The resulting "hooch" containing from 14 to 18% of alcohol is rectified and purified using activated coal.

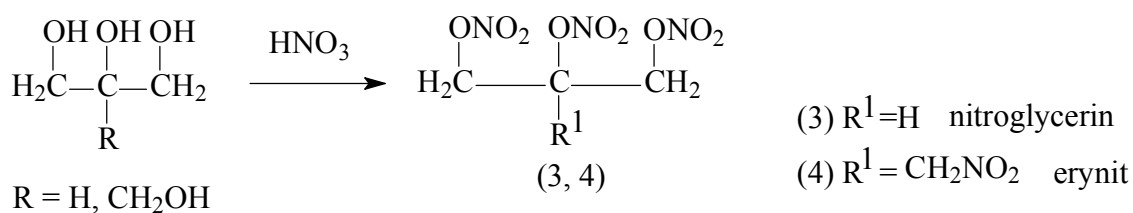
Diethyl ether has been used for more than 160 years as systemic anesthetic, it revolutionized the surgical practice of its time. Long-lasting inhalation of ether leads to the loss of consciousness, this fact was used by an American dentist William T. Morton (following an advice of his friend and scientist Charles T. Jackson) on 30th of September 1846 during tooth extraction. The first application of ether in clinical practice dates back to 1842, when Crawford W. Long from Georgia used it for the first time, regrettably his experiment was published only in 1949, more than a century later).

Diethyl ether is produced by heating ethanol together with catalytic amount of sulfuric acid:

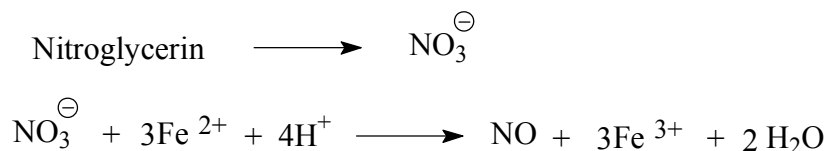


Esters of nitric and nitrous acids with one or polyatomic alcohols are widely known as good and quick antispasmodic agent.

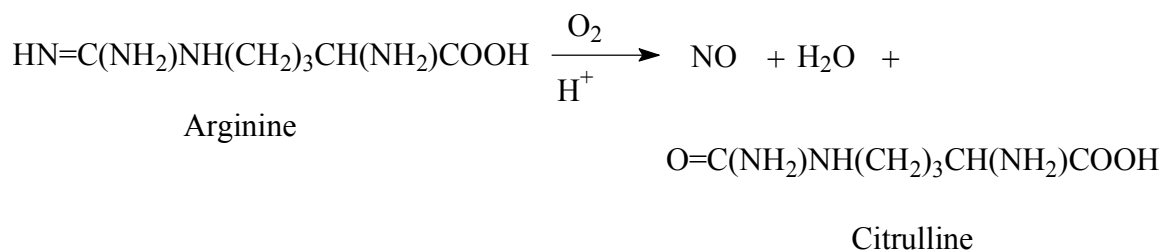
Polynitrates of glycerin (**nitroglycerin**, 3) and tetrahydroxymethylmethane (**erinit**, 4) are produced by etherification of polyols with a mixture of nitric and sulfuric acids during cooling.



It has been found recently, that nitro esters act as prodrugs, which are easily converted in nature into nitrate-ions, further reduced by blood hemoglobin and iron-containing enzymes into **nitric monoxide (NO)**.



NO exerts its medical activity by dilating vessel smooth muscles, decreasing the blood pressure and arresting ischemia-induced heart pains. During last 10 years the conception about NO being an endogenous molecule for intercellular signaling was established. This signal molecule is produced in organism from arginine by NO synthase.



Nitric monoxide acts as neuromediator, evokes immune response and takes part in long-term memory processes. For its discovery American scientists Robert F. Furchgott, Louis J. Ignarro, Ferid Murad were awarded Nobel Prize in medicine and physiology in 1998. Nowadays novel drugs which would promote NO-generation in organism are being intensively investigated.

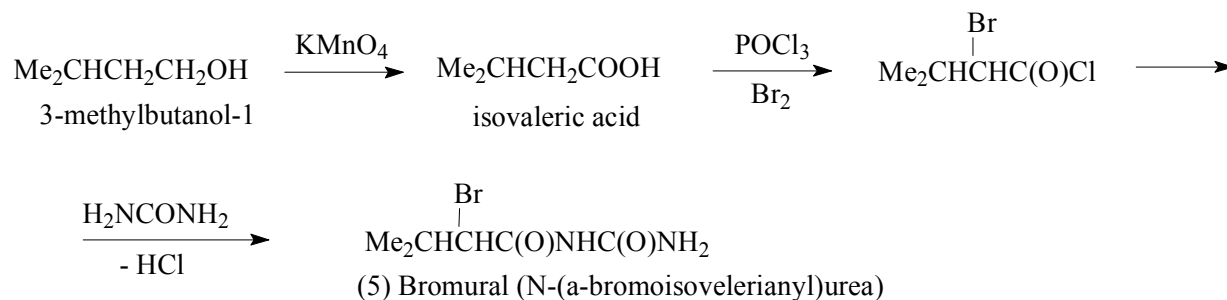
3. Aldehydes and acids. Vitamins F and B₁₅

The simplest aldehyde – methanal – is used externally as antiseptic agent in the form of weak water solutions for hand, skin and tools disinfection. It is produced industrially by

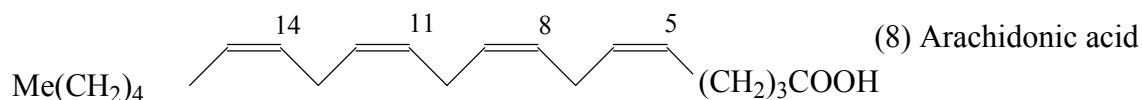
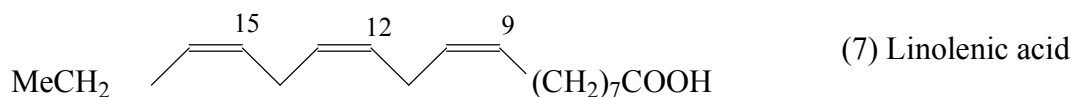
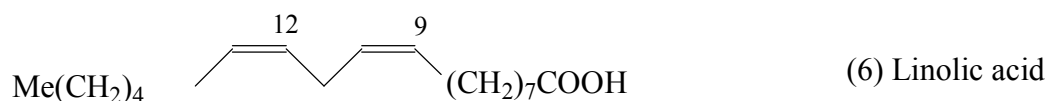
oxidizing methanol (350 °C, catalysts –Fe/Mo oxides), or methane (600 °C, catalyst – nitric dioxide).



Urea derivative of α -bromisovaleric acid (5) is used under the name **Bromural** as sedative and moderate hypnotic agent. It is produced from 3-methylbutanol-1 by oxidation with potassium permanganate to isovaleric acid, which is then turned by adding phosphorus chloroxide into chloranhydride. The latter is brominated in alpha-position and then by acting with urea Bromural results.



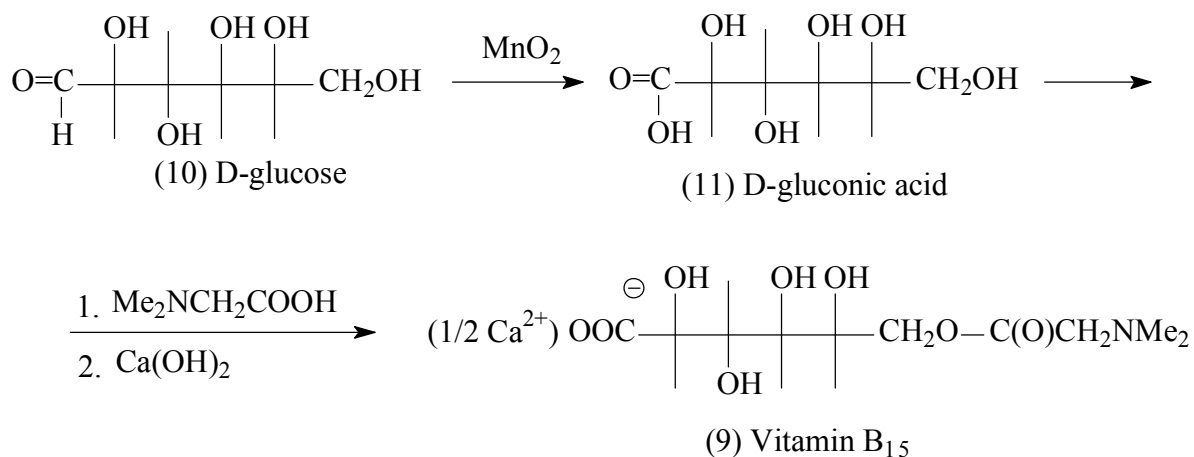
To the class of derivatives of aliphatic acids belong **two vitamins – F и B₁₅**. Generally speaking vitamins are organic compounds, which are present in small quantities in every cell and take part in cell's normal functioning. They act as catalysts, or, more precisely, catalyze various chemical transformations of food compounds, what is called "metabolism". Vitamin F is a mixture of three non-saturated aliphatic monocarboxylic acids, where all olefinic links have *cis*-substitution.



Linolic (6) and **linolenic** (7) acids have both 18 carbon atoms. They can be found in plants and in animal fats. The linolic acid (9,12-octadecadienic acid) contains two non-conjugated olefinic links, and the linolenic acid (9,12,15-octadecatrienic acid) – three ones. The third component of vitamin F is **arachidonic acid** (8), which is contained in some animal fats. It contains 20 carbon atoms and four non-conjugated olefinic links in the positions 5,8,11 and 14 (eicosatetraenoic acid).

Vitamin B₁₅ (*calcium pangamate*) (9) is the most demanded vitamin on the market today. Its action on human organism is not yet well-studied. Having relatively simple structure it has unique properties. This vitamin is used in clinical practice as calcium salt for complex therapy and prophylaxis of atherosclerosis, hepatitis, hepatosis, liver cirrhosis, psychiatric disorders, alcoholic intoxication etc.

Vitamin B₁₅ is a pentahydro-substituted hexane acid, where the OH-group in C-6 is etherized by N,N-dimethylaminoуксусная acid. This vitamin is obtained by oxidizing D-glucose (10) by manganese dioxide to D-gluconic acid (11), where the primary OH-group is then etherized by N,N-dimethylglycine, the resulted ether is turned into calcium salt (9) by adding calcium hydroxide.

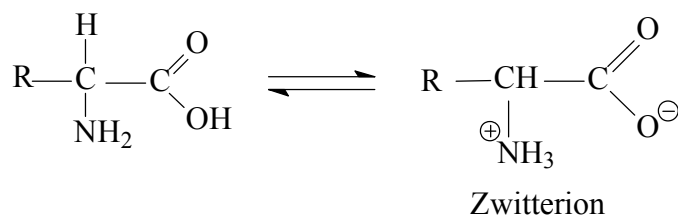


4. Amino acids

Amino acids are bifunctional compounds, containing both carboxyl and amino groups in the same molecule. Depending upon the location of amino group relatively to carboxyl group α -, β -, γ - and further amino acids are known.

α -amino acids, where carboxyl and amino groups are attached to the same carbon atom play important role in the process of functioning of every living being, since they are compounds for every protein synthesized.

α -carbon atom in all α -amino acids, except for glycine is asymmetric (e.g. it has 4 different substitutes). Hence all α -amino acids have a property of chirality (from greek "hand") and therefore can have optic isomers. All amino acids which form proteins are L-isomers. Being amphoteric electrolytes, amino acids exist as bipolaric ions (internal salts) in both aqueous solutions and solid states:



Amino acids are widely propagated in nature and are main "bricks" of tissue-specific proteins, enzymes, peptidic hormones and other physiologically active compounds. Some amino acids (alanine, asparagine, glycine, glutamine, proline, serine, tyrosine, cysteine, aspartic and glutamine acids) are synthesized in human body – these are non-essential amino acids. Synthesis of non-essential amino acids requires a great amount of enzymes. Other, so-called essential amino acids (arginine, valine, histidine, leucine, isoleucine, lysine, methionine, threonine, tryptophan, phenylalanine) come with food.

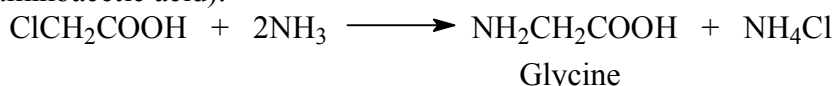
Some amino acids (glutamine, GABA, metionine, glycine and others) are used as drugs.

Of special importance are amino acid mixtures for parenteral nutrition (bypassing gastrointestinal tract) – vamin, infusamine, aminosteril, aminocrovine and many others.

Natural amino acids can be obtained by hydrolysis of animal and plant proteins. All α -amino acids, often found in living organisms, have traditional generic names.

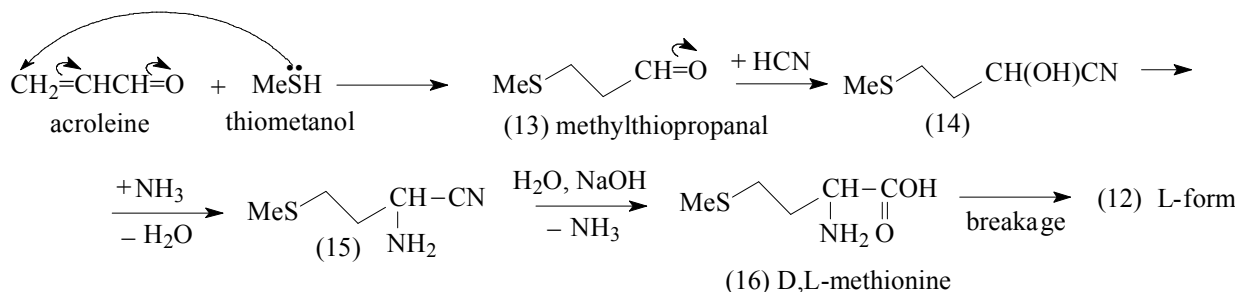
Nowadays the total production of α -amino acids is about half a million tons a year. About practical significance of individual amino acids one can judge by the amounts of their synthesis: tryptophan – 0.3 thousand tons, glycine – 10 thousands tons, lysine – about 50 thousands tons, methionine – 150-200 thousand tons and glutamine acid – more than 200 thousands tons a year.

Similarly as amines are produced by adding ammonia to halogenic derivatives of hydrocarbons, amino acids can be produced by adding ammonia to α -halogen acids, for example **glycine** (aminoacetic acid).

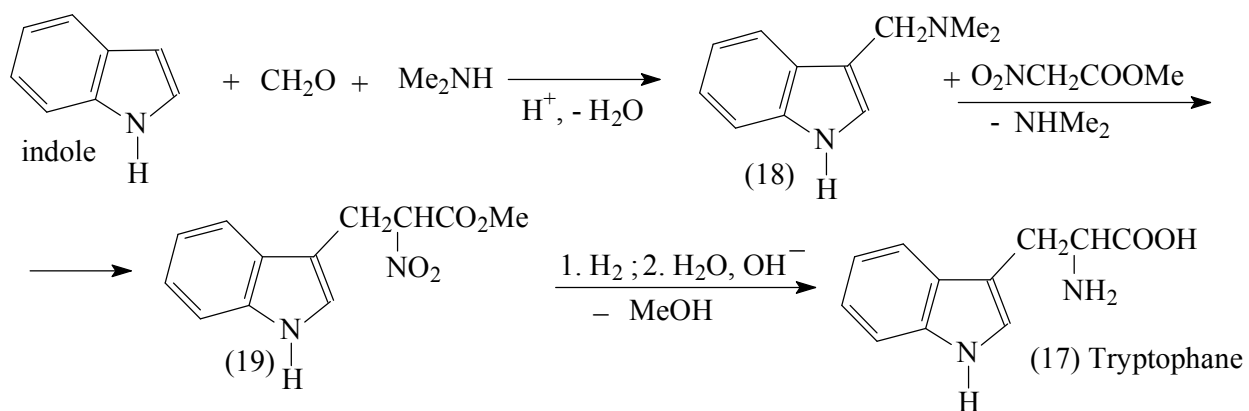


Today this is the main production method of α -amino acids synthesis.

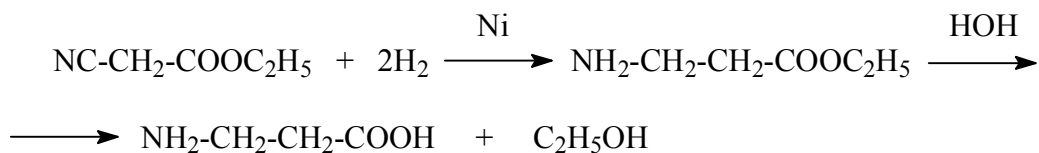
Methionine (122) (2-amino-4-methylbutane acid) is used in medicine for treatment and prophylaxis of toxic affection of liver and diabetes. It is produced synthetically from acrolein and thiomethanole. Reaction of thiomethanole binding to C=C-link results methylpropanal (13). The latter is then in the Strecker-reaction is cyanided in carbonyl group with production of cyanhydrine (14), where ammonium nucleophilic replaces the OH-group. On the next stage the obtained germinal aminonitril (15) is hydrolyzed in acidic medium to racemic methionine (16). Its active L-form is isolated enzymatically or via distinct crystallization with optically active compounds.



Tryptophane (17) (amino acid with heteroaromatic – indole – substitution) is used for therapeutic nutrition. The first step of its synthesis is the aminomethylation of indole with Mannich-method. The obtained 3-aminomethylindol (18) is condensed with ester of nitroacetic acid. During reaction the methylene group of this ester releases a proton (as CH-acid), and the resulted carbanion easily replaces dimethylamino group in indole (18), that leads to methylate-3-indolynitropropionic acid (19). The nitro group is then reduced to amino group and after acidic hydrolysis tryptophane (17) or its sodium salt is obtained:



Whenever amino acids with other location of amino group are needed, the following ways are used: ammonium is attached to unsaturated acids, aldehydes are condensed with malonic acid in the presence of alcoholic solution of ammine, reduction of cyanosubstituted acids, oximes or hydrazones of respective aldehyde- and keto-acids. Reducing cyanoacetic ester it is easy to synthesize **β -aminopropionic acid**:



Lecture VII. MEDICAL COMPOUNDS OF ACYCLIC AND AROMATIC SERIES.

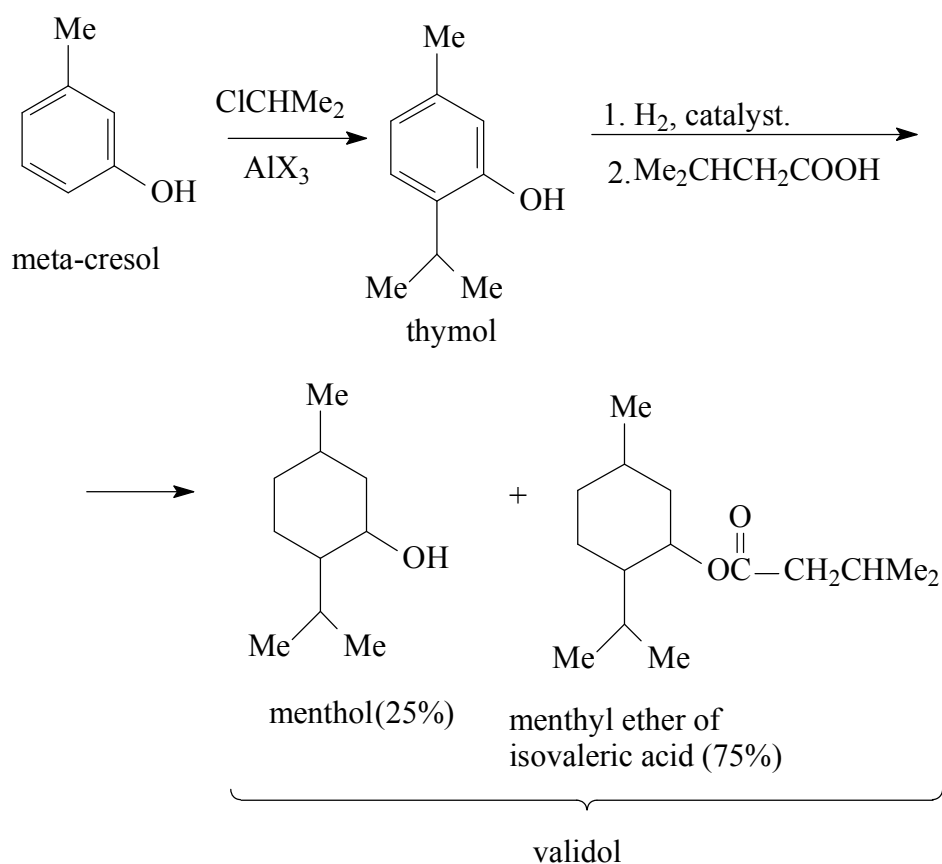
From derivatives with small cycle only **non-substituted cyclopropane** is used in medicine. It is a low-toxic narcotic, which is used for inhalator narcosis (as general anesthetic mixed up with oxygen). Industrially it is produced (according to Haas, 1936) from allylchloride by attaching bromide-hydride and subsequent dehalogenization of 1-bromo-3-chloropropane in presence of zinc:



1. Substituted cyclohexanes.

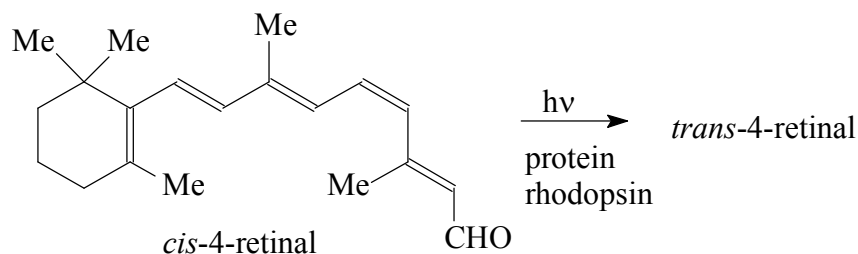
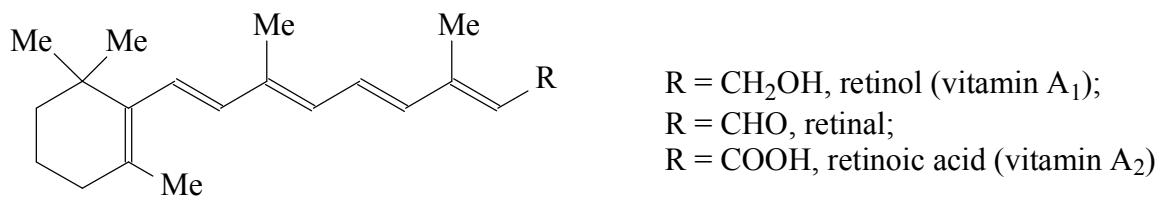
Menthol (2-hydroxy-1-isopropyl-4-methylhexane, where all radicals are in equatorial position) is used as external analgesic and antiseptic agent in therapy of inflammations of higher respiratory tract. Moreover, it is used as antispasmodic for treatment of angina pectoris (under the name **validol**, which contains 25% of menthol and 75% of methyl ester of *isovalerianic acid*). Menthol has natural-like peppermint flavour, “freezing” taste and is widely used for flavoring of food and toothpaste. It can be found in natural ester oils (peppermint and geranium oils).

Industrially it is produced as racemate in the reaction of electrophilic alkylation of *m*-cresol by 2-chloropropane in presence of Lewis acids. The isopropyl group mostly substitute hydrogen in sterically least problematic *ortho*-position to phenolic hydroxyl. This isomer is then hydrogenized under pressure and heat on nickel that leads to menthol.

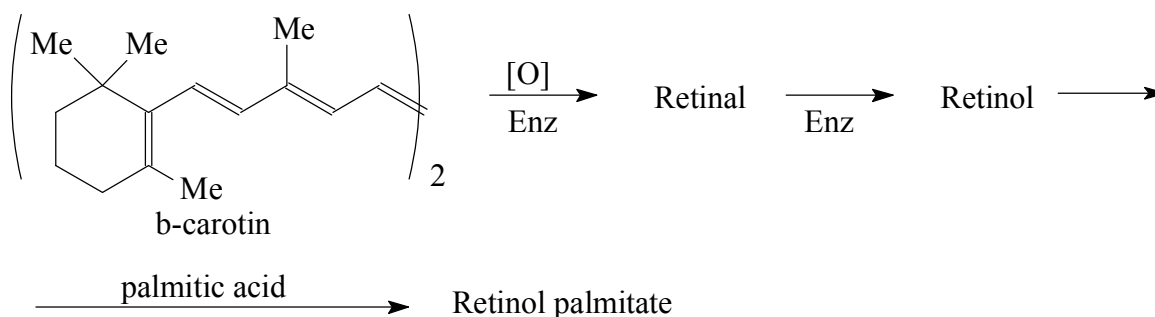


Vitamin A was discovered by Stepp in 1909. During 20 years Drammond and Heilbron were working on the methods of its extraction and quantitative analysis. In 1931 Carrier, Morf and Shopi determined its structure. This formula was accepted and many useless attempts were made to synthesize this vitamin, until Baxter with collaborators managed to receive the crystallized vitamin in 1942 (with melting temperature 64 centigrades).

Vitamin A belongs to tetraenoic derivatives of cyclohexene and consists of four isoprenic fragments. Several vitamers of vitamin A are known: **retinol**, **retinal**, **retinoic acid** etc. Retinol has a terminate hydroxymethyl group (it is important for growing and normal functioning of skin and bone tissues). Retinal has an aldehyde group (important for sense of vision), and retinoic acid has carboxyl group (same as retinol).



Every exocyclic double bond is in *trans*-configuration, except for retinal, where the pre-last connection is in *cis*-configuration (*cis*-retinal), which easily transforms into *trans*-configuration on absorption of one light quantum. This isomerisation is the fundamental of light absorption by visual pigment rhodopsin in the rods of retina, which contains retinal. This isomerisation enables the conversion of light into nervous signals, which are propagated then upstream to the brain. The fat from fish liver contains a lot of vitamin A. Plants are rich with provitamins, the most important of those is β -carotene (carrot, salad, lettuce). Carotene is enzymatically oxidized in human body and is converted to retinal, which is then reduced to retinol, the latter as ester of high lipid acids is stored in liver.

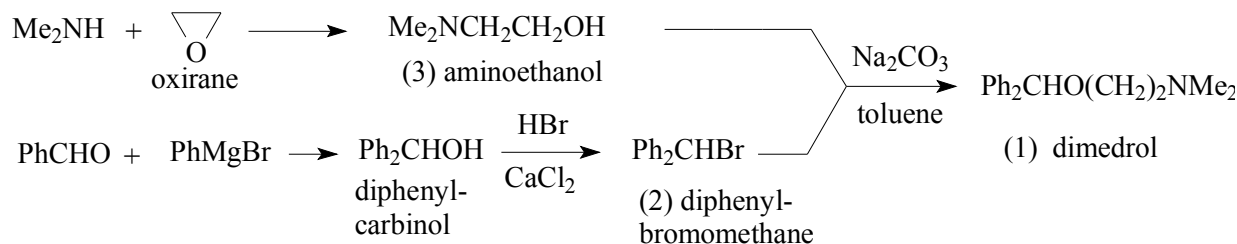


Vitamin A is used for therapy of eye and skin disorders, as well in case of some catarrhal and infectious diseases.

2. Synthesis of aromatic derivatives.

A good example of remedies of aromatic series is well-known antihistaminic agent **Dimedrol**. In 1939 Berdget and Perx wrote a perfect review on Dimedrol and its synthetic analogues.

Dimedrol (diphenhydramine) (1) is a powerful antihistaminic agent, which is used in therapy of urticaria, hay fever, allergic rhinitis and other allergic disorders. It is produced by nucleophilic replacement of bromine in diphenylbromomethane (2) by aminoethanol (3) when both are heated in presence of sodium carbonate. The compound (2) is synthesized from benzaldehyde and phenylmagnesiumbromide via diphenylcarbinol, where the hydroxyl group is substituted by bromine.



In 1823 Leer managed to isolate crystalline glycoside salicyne from the bark of willow (*Salix alba*), which had antipyretic activity. The nature of salicyne (its being glycoside of salicylic alcohol) was confirmed by Pairia in 1839. It was also him, who first synthesized the salicylic acid by heating of salicylic aldehyde with potash. Due to high toxicity the salicylic acid was hardly suitable for therapy. Although Hilm first synthesized the acetylsalicylic acid (4) already in 1859, only 40 years later Dreser managed to notice it as a way to decrease toxicity of salicylic acid preserving its antipyretic and analgesic activity.

Salicylic acid (5) (o-hydroxybenzoic acid) is a natural compound, which is found as ester of acetic acid (4) – o-acetylsalicylic acid in the flowers of *Spirea ulmaria*. This ester (4) was already introduced into clinical practice for therapy of acute joint rheumatism in 1874, but the industrial production started only in 1899 by “Bayer and Co” under the name **aspirin** (the prefix “a” was used to indicate that the substance is chemically synthesized and not extracted from spirea).

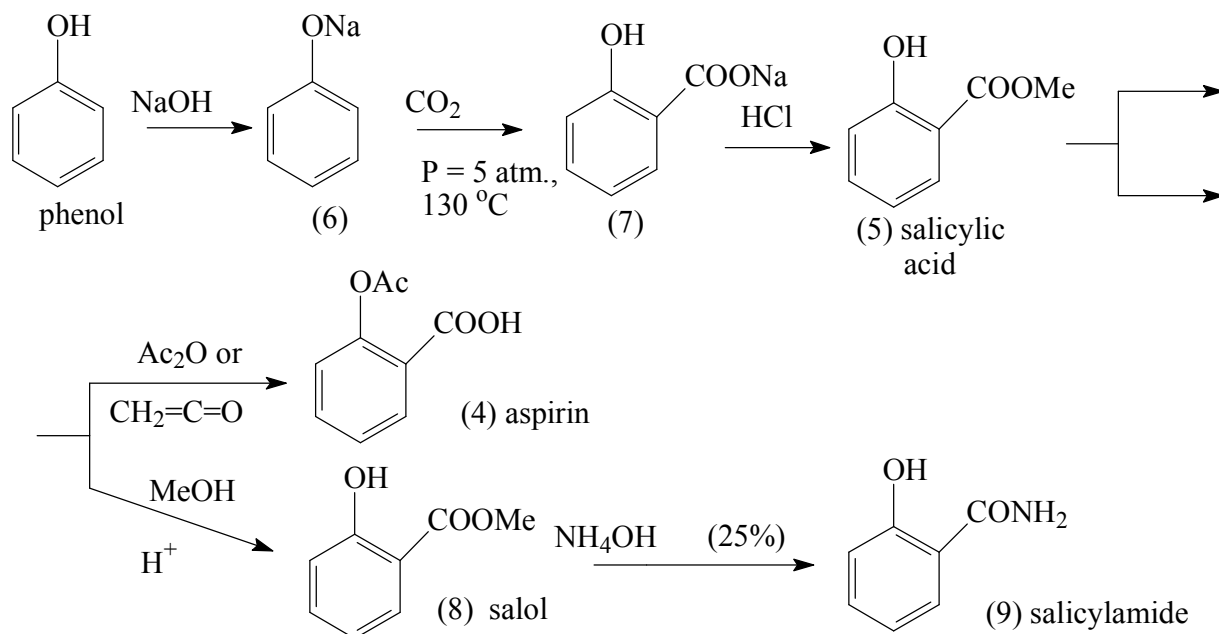
Aspirin is called the medicine of 20th century, nowadays it is produced world-wide in quantities exceeding 100 thousands tones a year. Its anti-inflammatory, antipyretic and analgesic effects are well-known.

Before the World War II Germany held monopoly for pharmaceutical production almost for all countries. The outbreak of the war was marked with boycott of other Germany in providing drugs for other countries (including Russia), this applied also to aspirin. With frantic energy scientists of Britain, France, Japan and Russia started to build pharmaceutical industries.

As many other scientists, active part in the setting-up of chemical production of **aspirin** in Russia was taken by Alexander Erminingeldovich Arbuzov. In 1915 he presented during an exhibition in Moscow some samples of aspirin, which were synthesized in the lab of organic chemistry of Kazan University. Today these first samples are on display in the Museum of Kazan Chemistry School in the Butlerov institute (chemical faculty) of Kazan State University.

The first Russian aspirin passed through all tests and received a high approbation of medical and pharmaceutical professionals around the world, because aspirin from Kazan judging by its therapeutic properties and purity was better than world-known aspirin from “Bayer” and less known aspirins from American and Swiss companies.

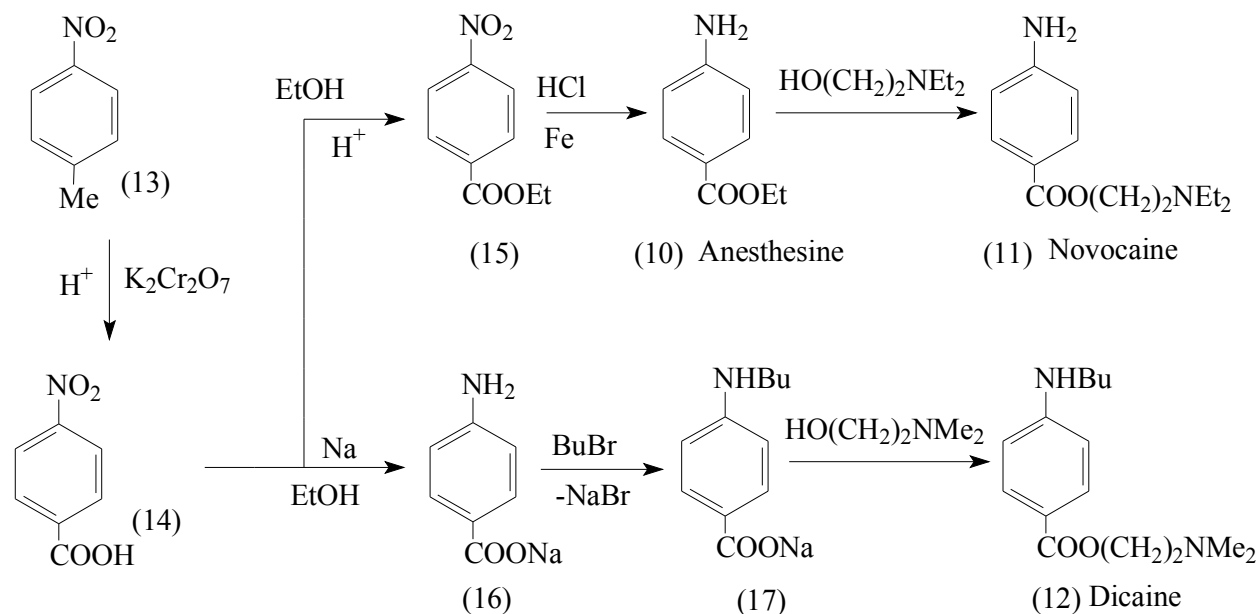
The modern way to synthesize aspirin includes carboxylation of dry sodium phenolate (6) during heating under pressure. After isolating of sodium *o*-salicylate it is converted by HCl into free salicylic acid (5), which is then acetylated by acetic anhydride or ketene that results in aspirin (4). By methylation of the acid (5) with methanol methylsalicylate (**salol**, 8) is produced, which was used previously as external agent for rheumatism, arthritis and radiculitis treatment. Acting by ammonium on salol (8) **salicylamide** (9) is received that is one more aspirin-like agent.



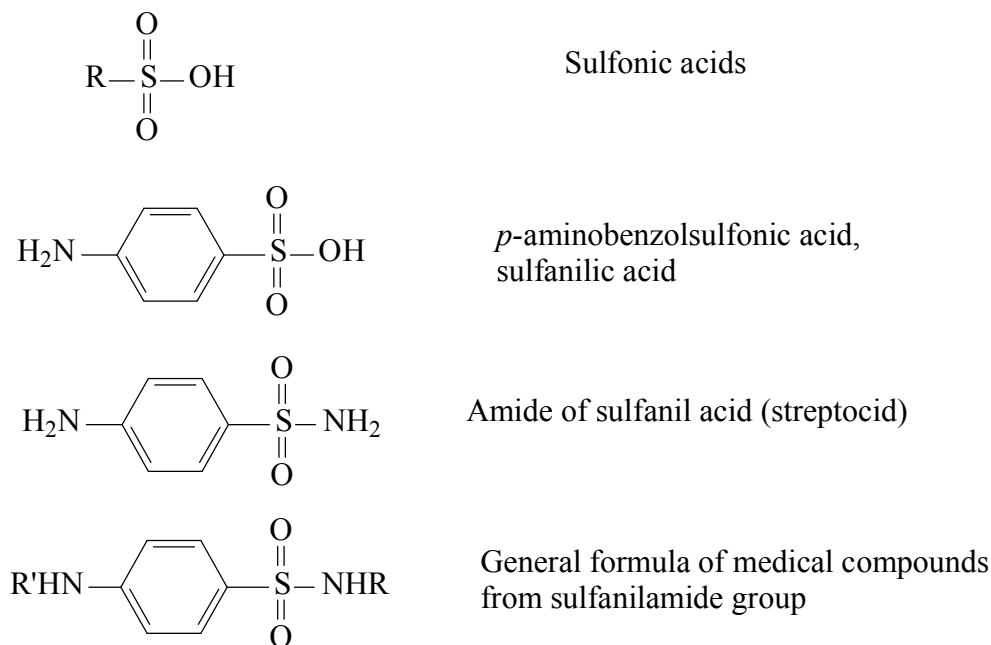
Some research is being conducted on synthesis of other derivatives with salicylic fragments.

From many thousands derivatives of *n*-aminobenzoic acid a series of very effective local anesthetics – remedies which inhibit the sensitivity of nerve endings — was found. Its ethers like **Anesthesine** (10), **Novocaine** (11) and **Dicaine** (12) replaced alkaloids of cocaine in clinical practice by mimicking its pharmacophore –N-(C)_n-X-C(O)Ar without drug addicting property.

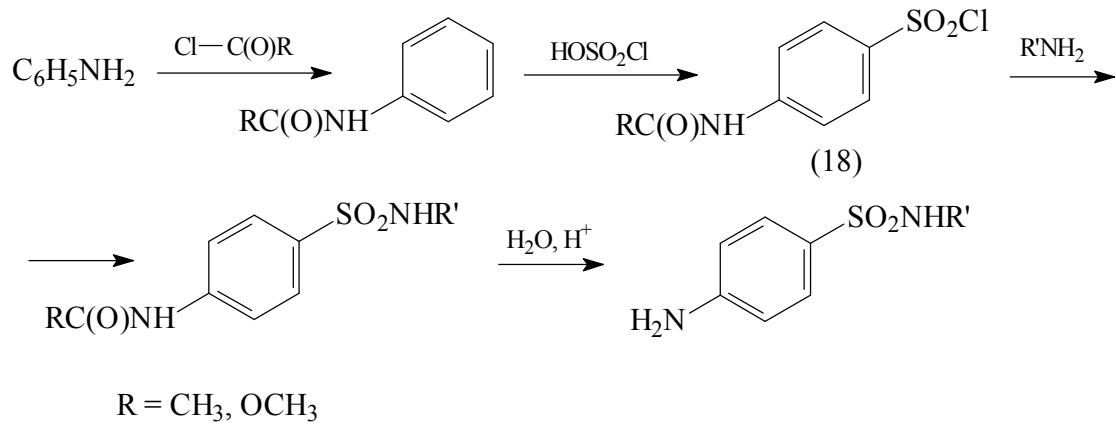
All three compounds are synthesized from *p*-nitrotoluene (13), which is oxidized to nitrobenzoic acid (14). Then in routine reactions of esterification, reduction and re-esterification the compounds are received in the following sequence: ether (15), Anesthesin (10) and Novocain (11). Alkylation of amine (16) with butylbromide with subsequent esterification of butylamine (17) leads to the synthesis of Dicain (12).



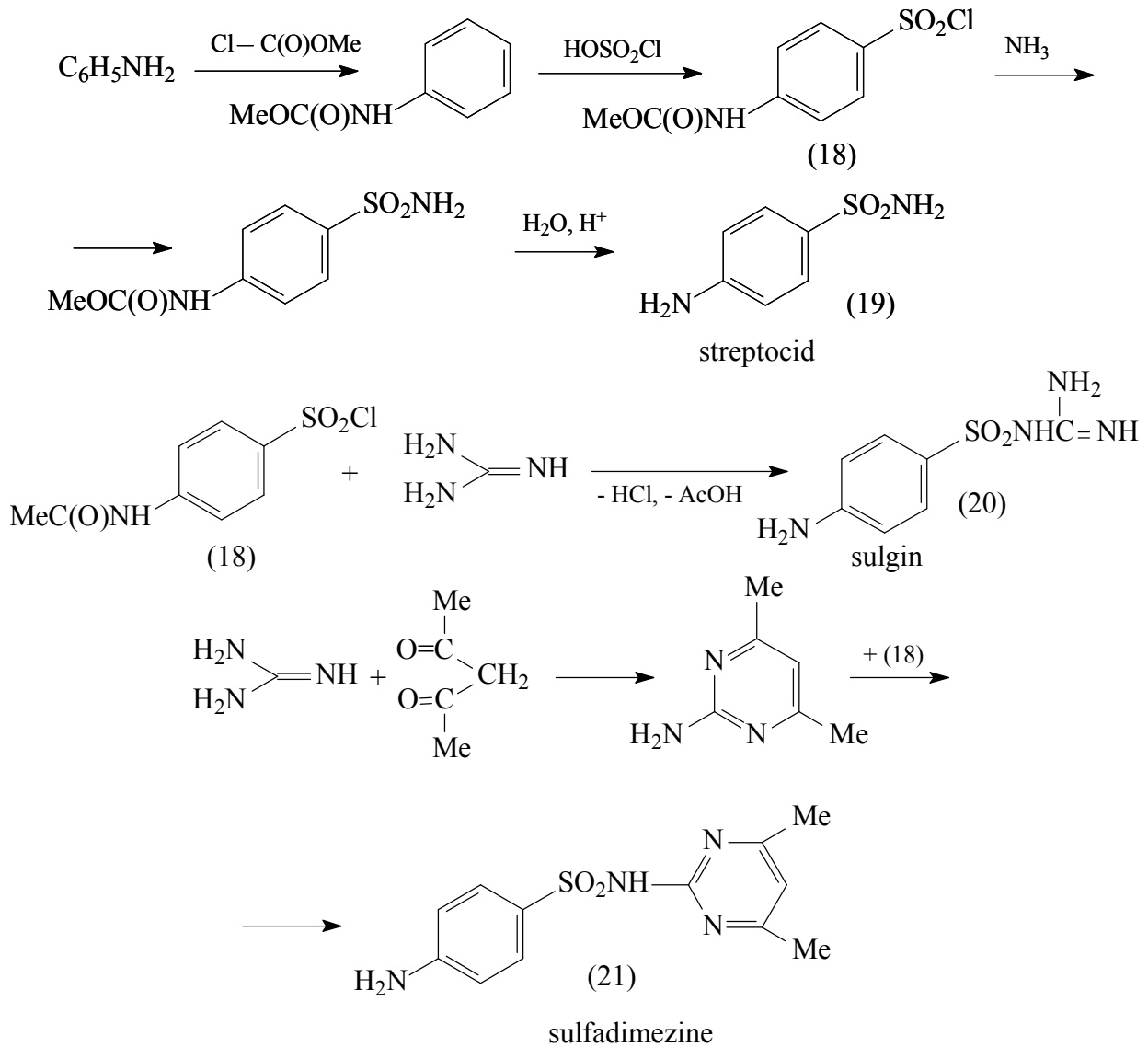
To the group of sulfanilamides (derivatives of *para*-aminobenzolsulfanilamides) belong the remedies with different pharmacological properties: antibacterial, anti-diabetic, diuretic and antiseptic. The structural unit of sulfanilamides is the amide of *para*-aminobenzolsulfonic (sulfanilic) acid.

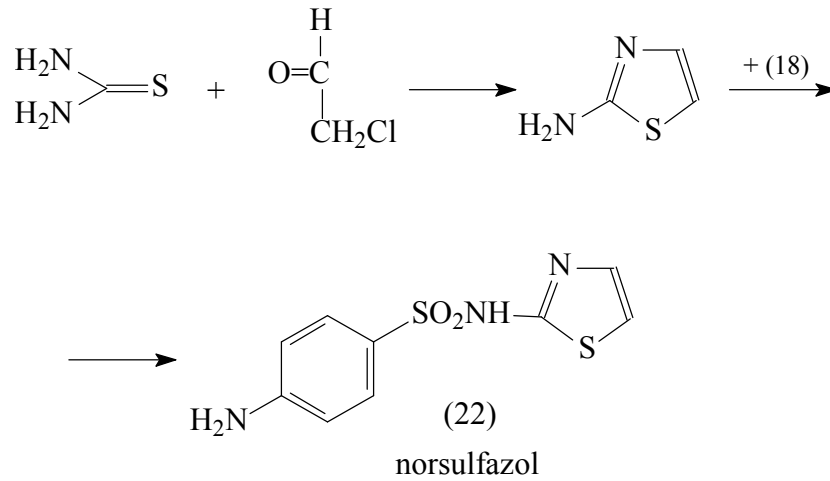


The source product used for synthesis of medicines from this group is aniline. After its amino group is protected by a residue of acetic (or carbonic) acid sulfochlorozation is started. Then the halogen in chloranhydride of substituted sulfanilic acid is substituted by amino group. Finally the protective group is removed via hydrolysis.



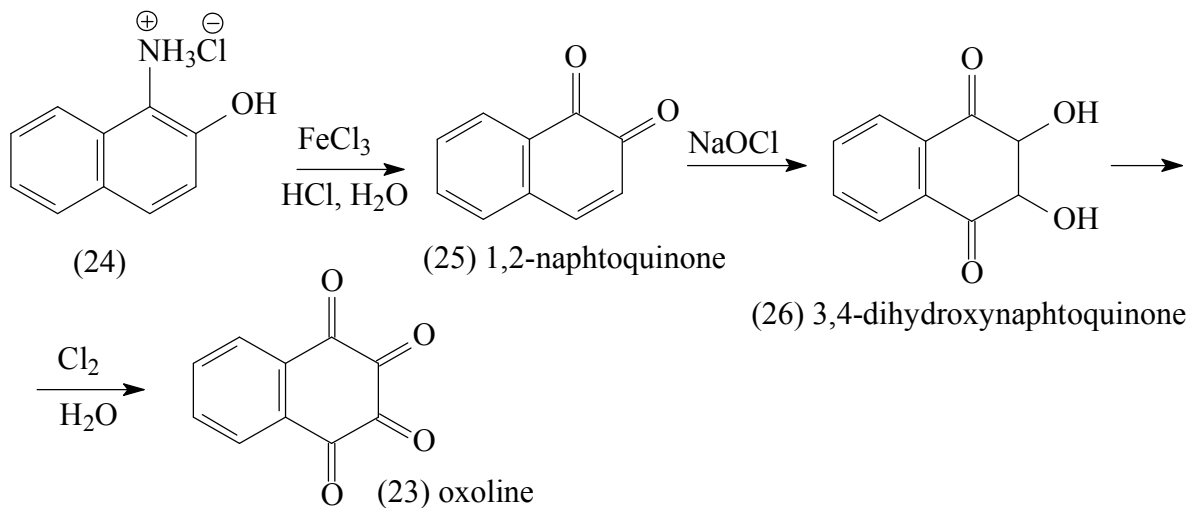
Below are the schemes of synthesis of four sulfanilamides **streptocid** (19), **sulgin** (20), **sulfadimezine** (21) and **norsulfazol** (22), produced by routine condensation of aromatic sulfonilchloride (18) by different amine components.



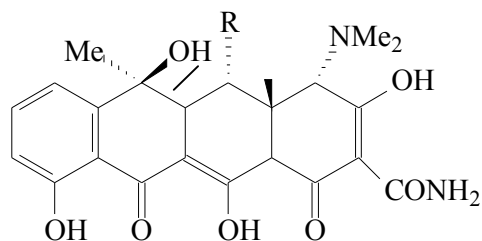


Among synthetic derivatives of naphthalene the most known is the medicine **oxoline** (23), which is used in prophylactics and treatment of flu, viral diseases of eye and skin (as powder for solutions and ointments).

Oxoline (23) is produced by oxidizing the hydrochloride of 1-aminonaphthol-2 (24) in presence of FeCl_3 to 1,2-naphthoquinone (25), which is then further oxidized by sodium hypochlorite in 3,4-dihydroxynaphthoquinone (26). During the latest step chlorine is used as oxidizer, which dehydrates the substrate (21) to oxoline (23).

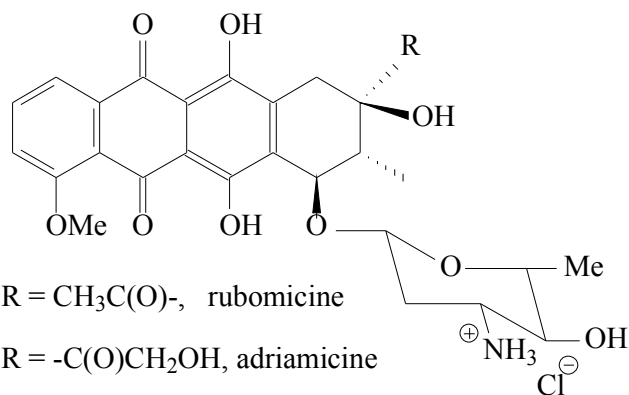


With some assumptions **antibiotics of tetracycline group** can be reckoned among polynucleatic condensed derivatives of naphthalin.



(27) R = H, tetracycline

(28) R = OH, oxatetracycline

(29) R = CH₃C(O)-, rubomicine(30) R = -C(O)CH₂OH, adriamycin

They possess a broad spectrum of action on both gram-positive and gram-negative bacteria, spirochetes, large viruses. They are administered in case of bronchitis, pneumonia, typhus and other diseases.

Lecture VIII. CHEMISTRY OF MEDICINES CONTAINING VARIOUS HETEROCYCLES.

Heterocyclic are the compounds, which molecules contain cycles (rings) containing not only carbon atoms, but also atoms of other elements, most often nitrogen, sulphur and oxygen, which are called heteroatoms (*from Greek "heteros" – different*).

The compounds containing N, S and O in the cycle are widely used and can be easily synthesized. These compounds can have from 3 to 6 and more atoms in the cycle, but heterocycles with 5 and 6 atoms are of higher practical importance. They can contain several same or different heteroatoms. The compounds of heterocyclic series are both of paramount theoretical and practical importance, since many heterocycles are present in molecules of essential medicines both of natural (antibiotics, vitamins, alkaloids, enzymes) and synthetic (analgin, dibazole, metronidazole (Trichopol), quinine, Tubazide, furazolidone, Furacillin and others) origin.

Chemically heterocycles are complex compounds containing along with heterocyclic nucleus other aliphatic and aromatic radicals. They are usually classified according to the original heterocycles from them they are derived.

Compounds containing heterocyclic fragments dominate in the arsenal of medical compounds (more than 60%), and from 25 most sold remedies in 1990 70% were heterocycles. The structure of heterocyclic remedies is usually much more complicated than those without heterocycles, nonetheless, their synthesis is often simpler.

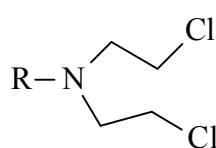
1. Synthesis of anti-neoplastic remedies from ethyleneimine (aziridine) and ethylene oxide (oxirane) group.

History of anti-neoplastic remedies.

First major achievements in the synthesis of anti-neoplastic remedies date back to 40ies. In this time during the World War II the effect of warfare agents (nitrogen mustard and mustard gase) on human organism were intensively studied. Already in 1919 it was known that nitrogen mustard has specific cytotoxic effect on lymphoid tissues and shows anti-neoplastic activity. In 1942 first clinical trials on nitrogen mustard started, that triggered the era of modern tumour chemotherapy.

According to their action the remedies from this group are seen as alkylating agents, they form covalent bond with nucleophilic compounds, including biologically significant radicals like phosphates, amines, sulfhydryl and imidazole groups. Cytostatic and other effects of alkylic compounds are mostly due to alkylation of DNA structural units (purines, pyrimidines).

Chemotherapy of cancer is of paramount importance and aims at suppression of growth and dissemination of malign tumors. Today's international market of anti-neoplastic agents is limited to about 40 compounds. The early therapy of cancer is based on alkylation agents (cytostatics), from those as first was synthesized nitrogen mustard (1) and its analogues (2) and (3), containing as pharmacophore 2,2'-dichloroethylamine, bound to aliphatic, aromatic or heteroaromatic molecule.



(1) R=Me, nitrogen mustard (embichinum)

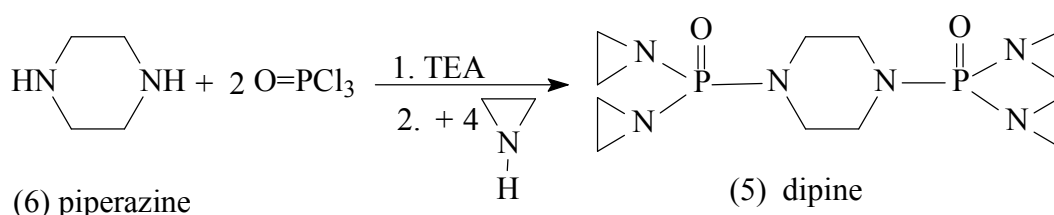
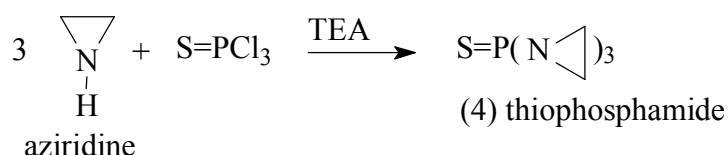
(2) R=MeCH(Cl)CH₂ (novembichinum)

(3) R=C₆H₄CH(NH₂)COOH (sarcolysinum)

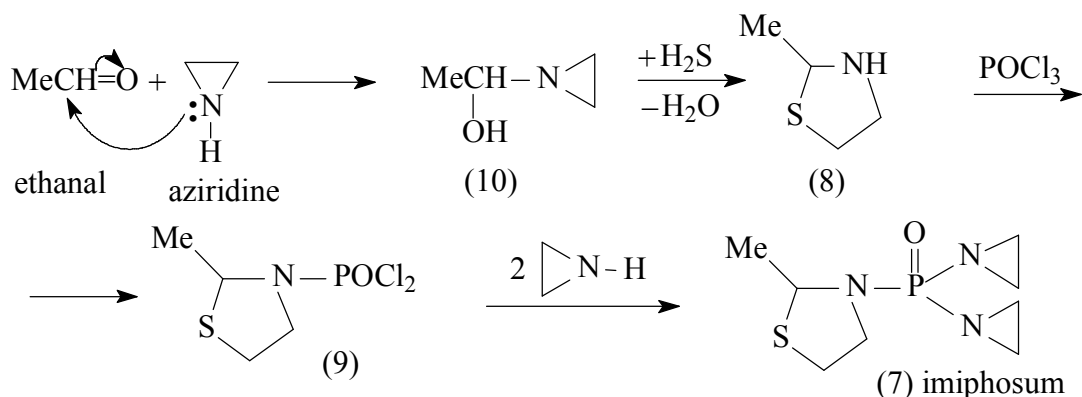
As soon as it was found that dichloroethylamine group in nitrogen mustards is converted into aziridinium (or ethylenammonia) ion the second group of alkylic anti-neoplastic agents was created — ethyleneimines and methylmelamines. These compounds also show cytostatic effect, suppressing the growth of tumour cells through DNA alkylation. Guanine is alkylated most often, that leads to its detaching and cross-linking of DNA molecules in double-strands.

From aziridinium and derivatives of phosphoric acid a new series of amides was synthesized, which were introduced into clinical practice for therapy of different tumours. For instance, thiophosphamide (4) is used in therapeutic protocols of ovary and breast cancers. Dipine (5) is a therapy of choice in case of lympholeucosis or larynx cancer.

The compound (4) is synthesized by the action of aziridine on phosphor thiochloroxide in the presence of triethylenamine as acceptor for HCl. Dipine (5) is synthesized by successive amidation of phosphor chlorooxide by piperazine (6) and aziridine.



Imiphosum (7) is synthesized in analogy to monoamidation of POCl₃ by thiosolidine (6) to dichloramide (9) and further conditioned by aziridine. Thiasolidine (8) is synthesized by electrophilic alkylation of aziridine by ethanal via hydroxiethylaziridine (10), which is recycled on action of hydrogen sulfide that leads to formation of 5-membered ring and water.



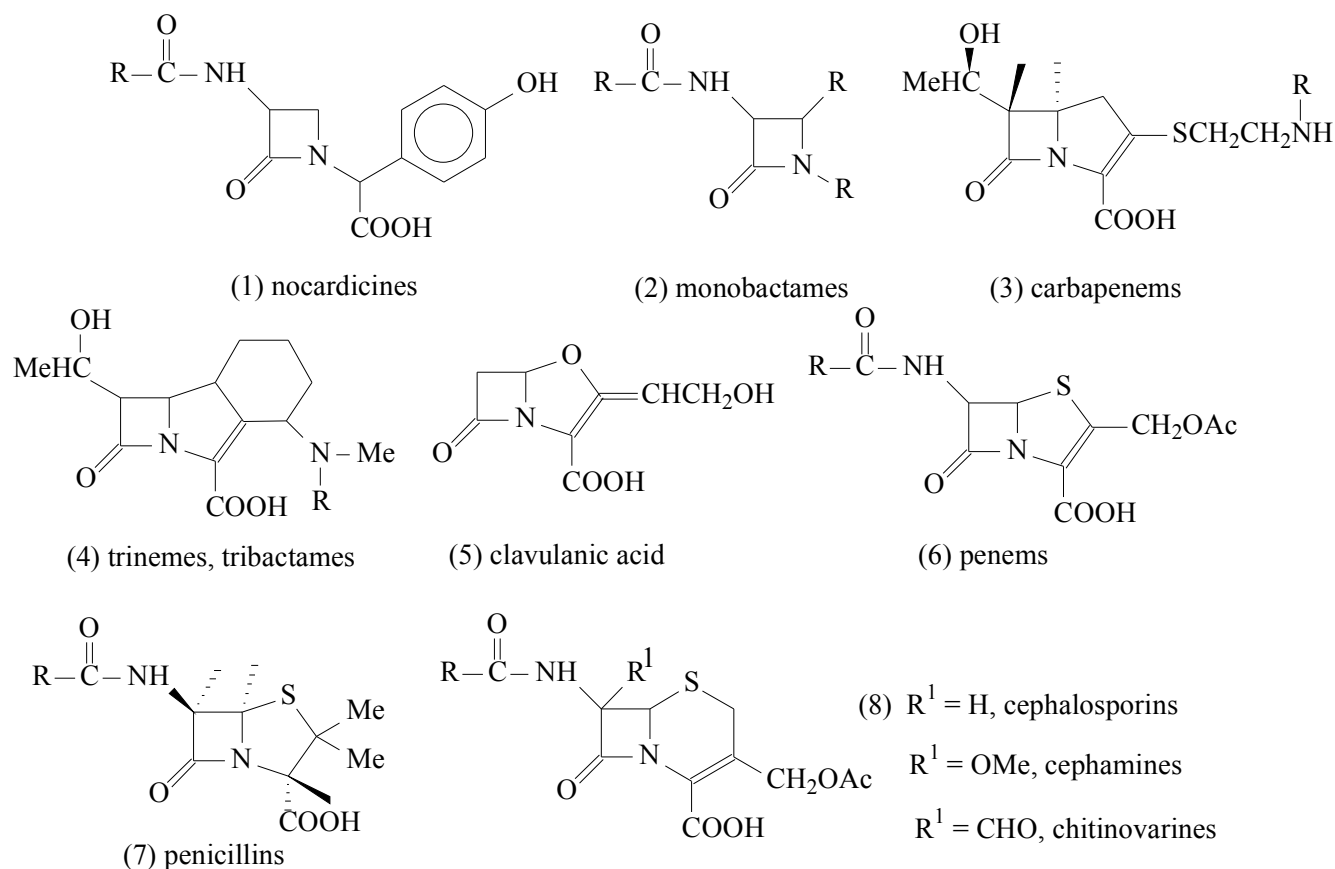
2. Antibiotics, containing tetratomic azetidene ring.

Many microorganisms produce substances which limit growth of microorganisms of other species or kill them. These substances are called **antibiotics** and can be waste products of higher plants and animals and are actually their protective agents. Nowadays more than 10 thousands of natural and synthesized antibiotics are known, more than 100 are in use in medical practice, but also in agriculture with the purpose of plant and animal bioprotection. Their total annual production exceeds 50 thousand tones. Most antibiotics have very complicated structure.

The history of antibiotics starts from first observation that staphylococci are lysed on the borders to the colonies of green mould *Penicillium notatum* (1928, Alexander Flemming) and subsequent isolation and purification of its effective agent penicillin (1940). During the World War II penicillin was used on a large scale (for treating British, American, French or German soldiers), though its structure was defined only in 1945 using X-ray structural analysis. In Russia penicillin becomes publicly available in 1949.

To scientists seemed impossible the fact that this antibiotic contained tetratomic β -lactam cycle, it was generally believed at that time, that azetidene cycles are very unstable.

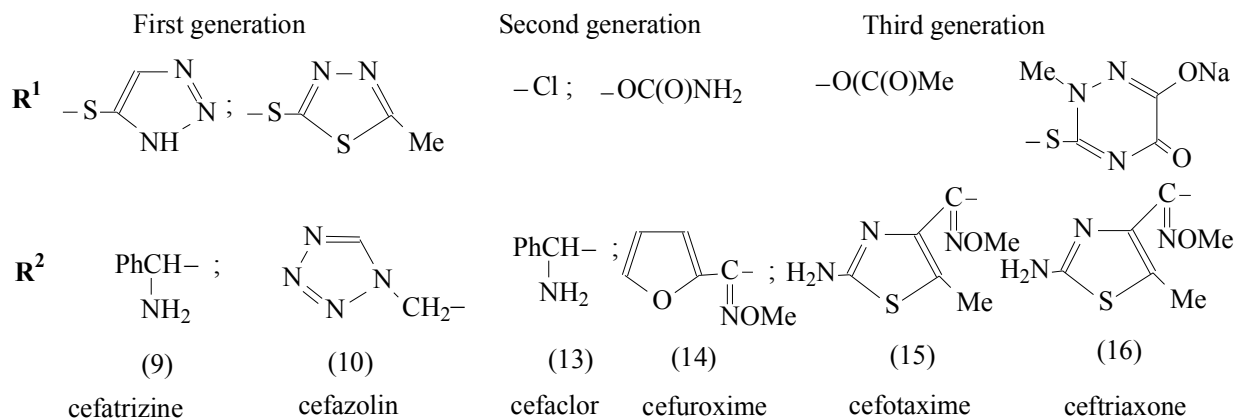
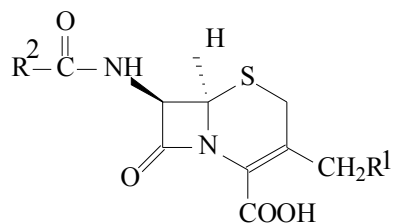
However, it turned out that the very heterocycle is responsible for antibiotic activity not only in case of penicillin, but also in case of other series of antibiotics, which were discovered later, both natural and half-synthetic.



Today one of the most promising antibiotics are cephalosporins (8) [read as [kɛfəlo'spɔrən, sɛfə-]], the metabolite of the fungi *Cephalosporinum*. The investigations of antibiotic and therapeutic properties of cephalosporins were founded in 1948, when the antibiotic activity of the fungi *Cephalosporinum acremonium* from Sardinian sewer was discovered. But only in 1960 cephalosporins entered the medical practice and nowadays a great amount of natural and half-synthetical antibiotics of this group are used in clinical practice.

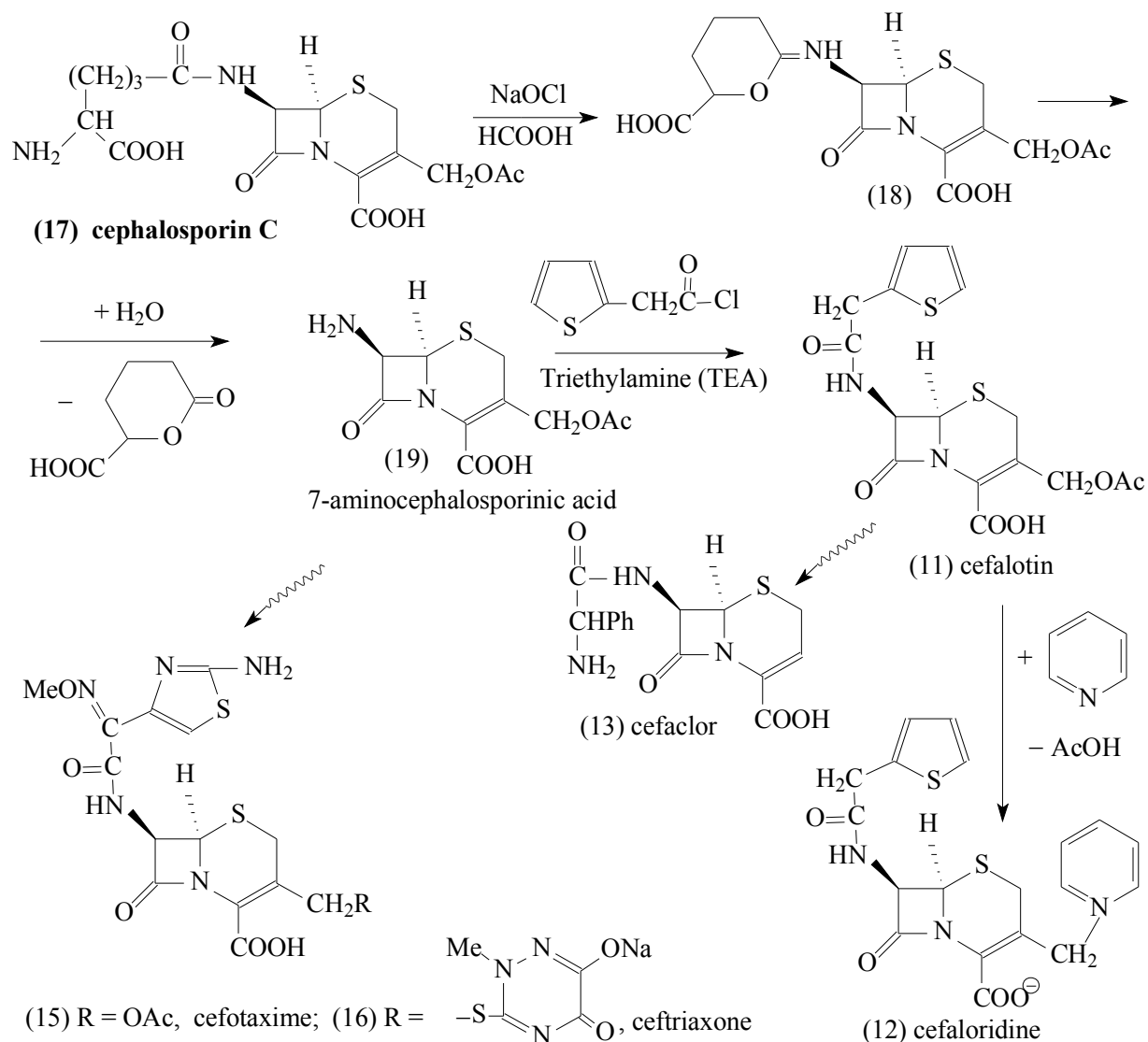
Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins). Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin binding proteins (PBPs).

Structurally cephalosporins are similar to penicillins, but their β -lactam ring is condensed with hexatomic thiazine cycle. Whereas **cephalosporins of the first generation**, such as **cefatrizine** (9), **cefazolin** (10), **Cefalotin** (11), **cefaloridine** (12) etc are effective against gram-positive bacteria, the **second generation cephalosporins** — **cefactor** (13), **cefuroxime** (14) etc suppress some gram-negative bacteria (*E. coli* and others). **Cefotaxime** (15) and **ceftriaxone** (16) belong to **bactericidal third generation**. They have a broader spectrum of activity and effective against bacteria producing lactamases and cephalosporinase (in the beginning of 90ies cephalosporins (9-16) were the mostly sold antibiotics worldwide).



Today cephalosporins of the new **fourth generation** are being actively synthesized, they are not only highly effective against the majority of gram-positive (though less than the first generation) and gram-negative bacteria, but also show high resistance against lactamases.

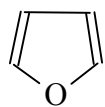
Antibiotics of cephalosporin group are synthesized basing on cephalosporin C (17), which is produced enzymatically. It is oxidized in NaOCl/HCOOH system to iminolactone (18), which is then hydrolysed in 7-aminocephalosporinic acid (19). Then the amino acid is N-acetylated (19) and its acetyloxymethyl group in position 3 is modified, leading to (11), (12), (13), (15) and (16).



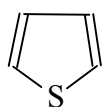
3. Remedies basing on 5-membered heterocycles

The most popular and practically important compounds from the group of 5-membered heterocycles are the following:

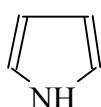
a) with one heteroatom in ring



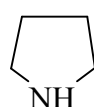
furan



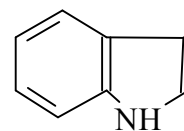
thiophene



pyrrole

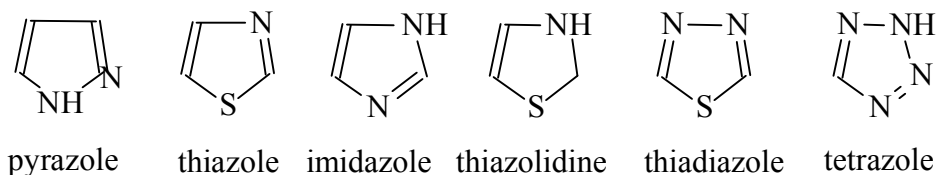


pyrrolidine



indol

b) with two or more heteroatoms



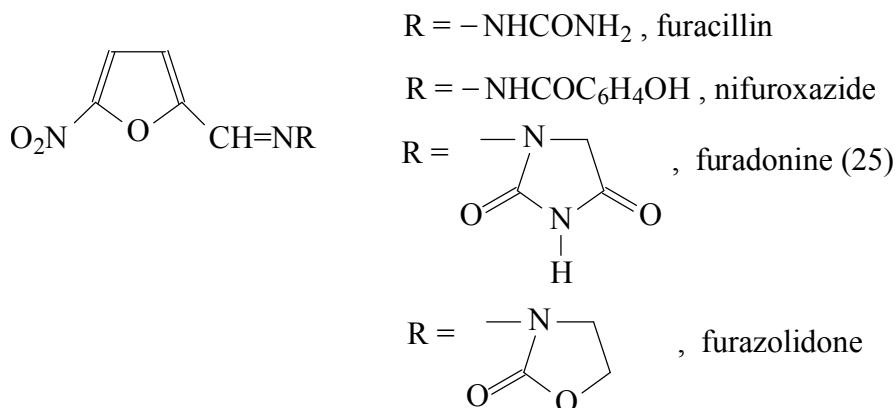
Furan, thiophene, pyrrole and many other heterocycles have the properties of aromatic compounds and thus characterized by substitution reaction, thereby many medical compounds were synthesized.

Nitro-substituted furans are the most interesting in medical practice, especially 5-nitrofuranes, which have very broad spectrum of antibacterial activity and relatively low toxicity.

4. Antibacterial nitrofurans

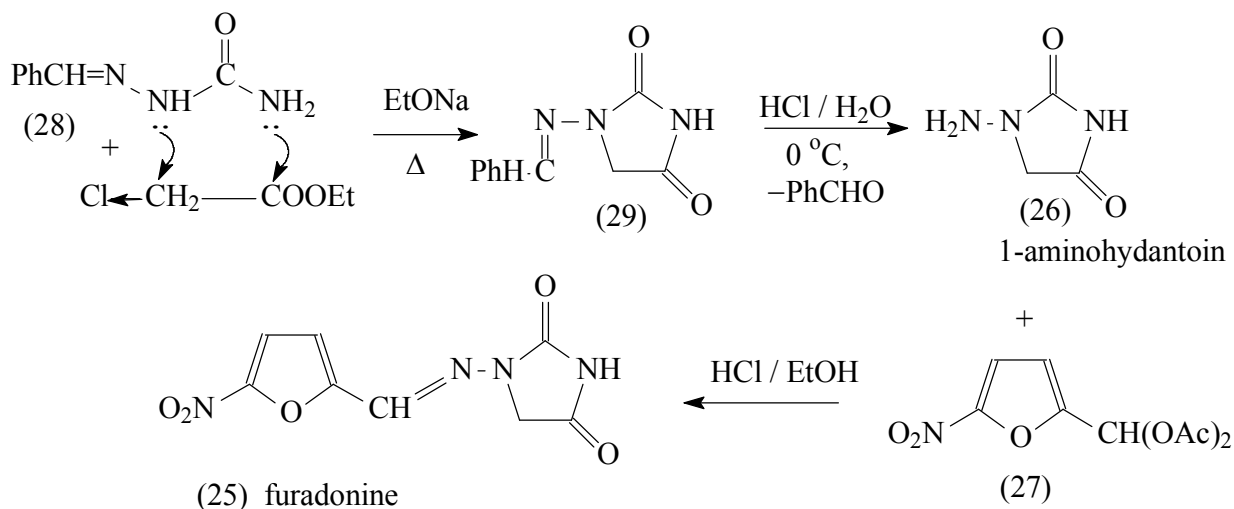
Nitrofurans and their derivatives act both on gram-positive and gram-negative microorganisms, as well as on some viruses and protozoa. Additionally to their bactericidal activity they also act bacteriostatically (*for example, in some cases they inhibit the growth of bacteria, which are resistant to sulfanilamides and antibiotics*).

5-nitro-2-azomethino derivatives of furan form the pharmacological block of antibacterial agents, such as **Furacillin (Nitrofural)**, **nifuroxazide**, **Furadonine (nitrofurantoin)** and **furazolidone**.



First nitrofurans were introduced into clinical practice in 50ies. They are highly effective as regards both gram-positive and gram-negative bacteria and used in therapy of bacterial dysentery, enteric fever, pyoinflammatory processes and other diseases.

Below is the synthesis scheme of one from many similar compounds — **Furadonine (25)**, the last phase in this scheme, the condensation of amino component (26) with nitrofurfurole (27) in acetal form is typical for majority of nitrofurans.



1-aminohydantoin (26) is produced by nucleophilic substitution of chloride in ester of chloroacetic acid with semicarbazone (28) and subsequent intramolecular cycloamidation. This reaction is performed at heat in the presence of sodium ethylate in alcohol. Azomethine group in the newly-synthesized derivative (29) is hydrolysed in acidic medium into free 1-aminohydantoin (26).

Of particular interest is the investigation of the relation between the structure and biological activity of these compounds. It was found, that translocation of NO₂-group from position 5 to position 3 leads to complete loss of antibacterial activity. Introduction of second nitro group into furan ring also diminishes its activity. For antibacterial activity the nature of substituting groups in position 2 of furan ring is of not less importance.

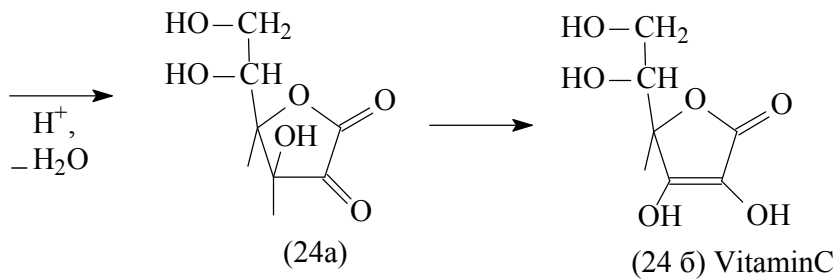
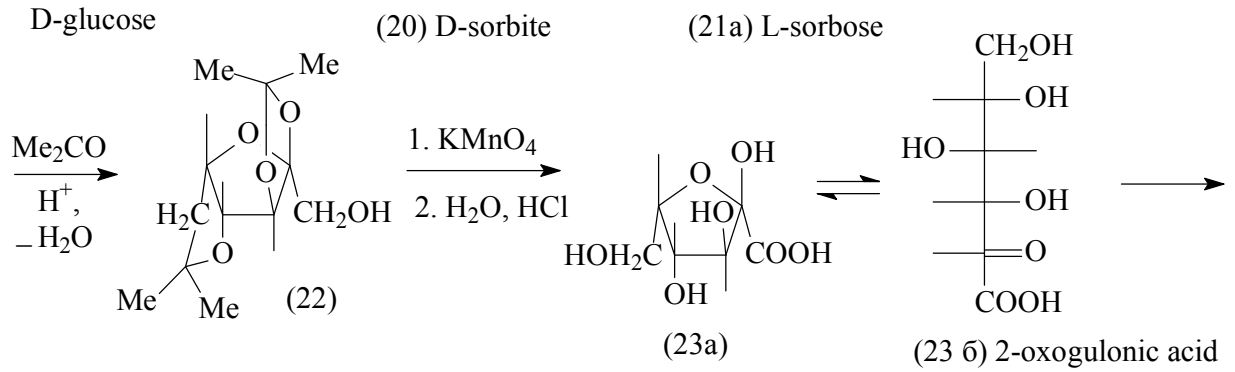
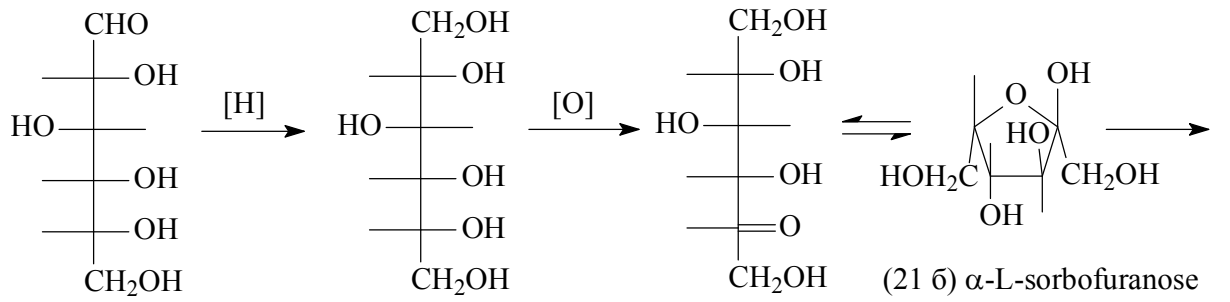
5. Other furan derivatives

Besides antibacterial furans **vitamin C** also belongs to the group of its derivatives with pharmacological activity.

Albert Szent-Györgyi in 1928 isolated from limes, sauerkraut and adrenal cortex a substance with molecular formula C₆H₈O₆ and called it ascorbic acid. The final prove of its structure through chemical synthesis was done by Walter Haworth, Edmund Hirst and (independently from two previous researchers) Tadeus Reichstein in 1934.

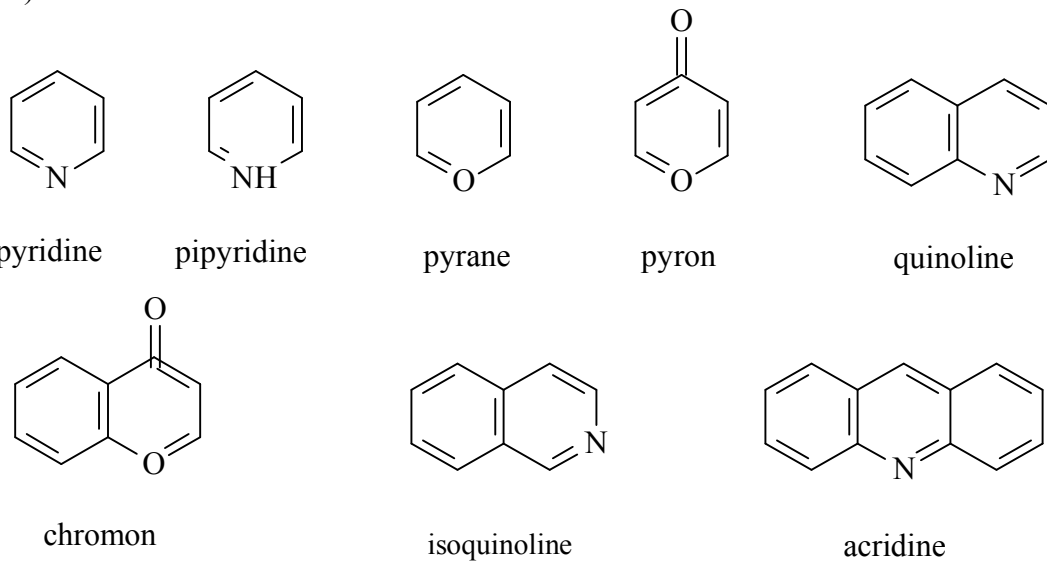
Vitamin C (ascorbic acid) was became popular first as anti-scurvy agent. But later on it turned out that it is also effective in reinforcing the resistance against infections and cold. This vitamin increases the elasticity of blood vessels, dilutes cholesterol plaques and stops the development of atherosclerosis. It has been found recently, that the water-soluble vitamin C acts as antioxidant, inactivating free radicals of cigarette smoke (the latter increases the adhesion of leucocytes and promotes thereby the plaque formation on blood vessel walls, increasing the risk of cardiovascular and pulmonary diseases).

The large-scale production of ascorbic acid is based on conversion of D-glucose, which is reduced electrochemically or catalytically on the first stage (on Reney Nickel) to D-sorbitol (20). This hexatomic alcohol is oxidized microbiologically on *Acetobacter suboxydans* in L-sorbose (21a). Then, after biisopropylidene protection of two *cis*-pairs of hydroxyl groups in α-L-sorbofuranose (21b) the compound is oxidized by potassium permanganate and after removal of protection the mixture of tautomers (23) is obtained. 2-oxogulonic acid (23b) is converted by acid-catalysed cyclodehydration and enolization via 3-oxolacton (24a) to L-ascorbic acid (24b).

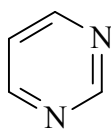


6. Derivatives of 6-membered rings

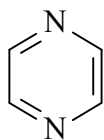
From 6-membered heterocycles most important for medicine are the following:
a) with one heteroatom:



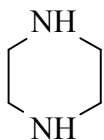
b) with two heteroatoms:



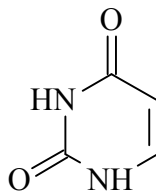
pyrimidine



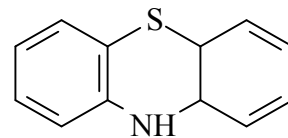
pyrazine



piperazine



uracyl

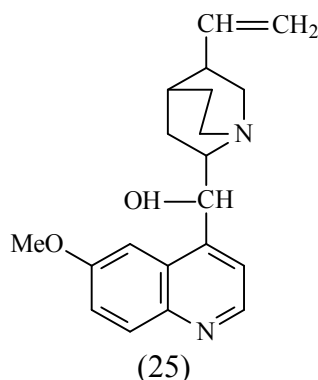


phenothiazine

These heterocycles serve as bases for many natural medical compounds (from the group of alkaloids, vitamins, antibiotics), as well as synthesized remedies (Cordiamine, sedatives from the group of barbituric acid, Aminazine (chlorpromazine) group, ciprofloxacin, antiphthisic remedies – isoniazid, ftivazide (vanizide) and many others).

7. Quinoline derivatives

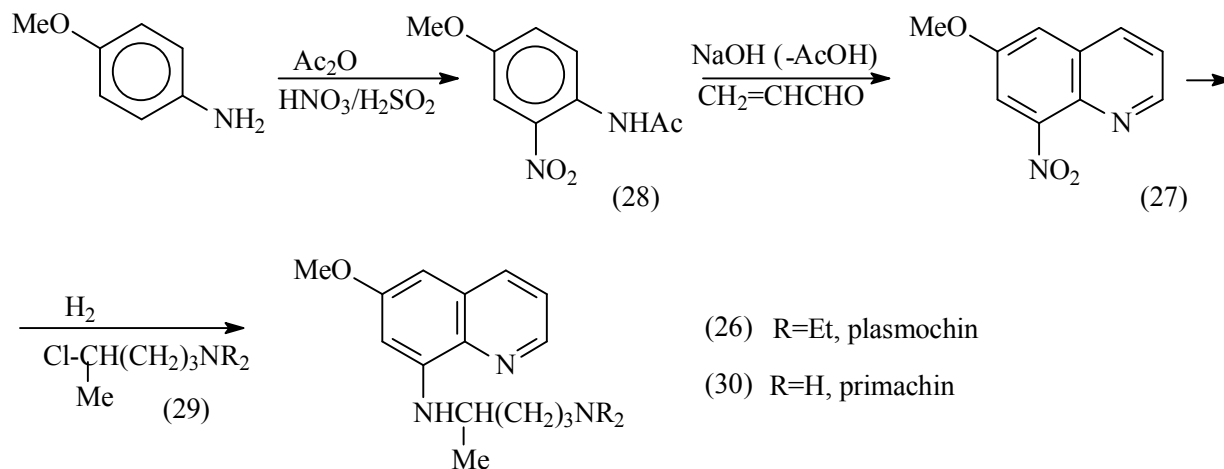
An important place among anti-protozoa remedies is taken by quinoline derivatives. So, the most effective and known remedy against all species of malaria plasmodium is **quinine** (25), alkaloid of the bark (Jesuit's bark) of the cinchona tree (*Cinchona*), which is cultivated in Asia (Indonesia) and South America. Its bark has been used for malaria treatment since 17th century. Purified quinine was isolated in the beginning of 19th century, and its complete synthesis became possible only in 1945. There are more than 20 alkaloids of cinchona tree, from those cinchonine (quinine with MeO-group substituted by hydrogen) is used for the therapy of jungle fever.



After prohibition of vast use of insecticide DDT (due to its ability to accumulate in biological tissues and poisoning) the incidence of malaria dramatically increased (up to several hundred millions per year).

Broad application of synthetic anti-malarial remedies, for example sulfanilamides, lead to formation of resistant strain of malaria (whereas they do not develop resistance against natural quinine!). Today it is known, that in a single mosquito up to 70 different parasite strains can be found. This fact explains the velocity of their conversion towards resistant strains. Therefore the discovery of new, more effective and less toxic remedies (especially those close structurally to natural quinine) can not be overestimated.

First synthetic anti-malarial agent was pamaquine (plasmochin) (26). Quinoline nucleus (27) is obtained in Scaup reaction from 2-nitroacetanilide (28). After reduction of nitro group into amino group the latter is alkylated by chloralkylamines (29), leading to plasmochin (26) or primachin (30).



8. Pyrimidine derivatives with antiviral (anti-HIV) activity

In 20th century medical science passed with flying colors as regards the fight against many diseases, including those, which had been considered incurable, for example plague (the Black Death, St. Sebastian's disease), smallpox, lepra (St. Giles' disease) and other diseases. But the era of transmittable (contagious) diseases is nonetheless far from its decline. Some old seemingly defeated diseases as tuberculosis or malaria got out of control. Simultaneously new infectious diseases are constantly discovered, like AIDS, legionnaires' disease, hantaviral lung syndrome. Nowadays AIDS got pandemic and covers almost all countries of the world. As of 1998 the number of HIV-infected population reached 30 millions (in the USA from 600 to 900 thousands, in Russia from 20 to 100 thousands).

Any virus (virion) consists of nucleonic acid (NA), protected with capsid (cylindrical or spherical protein coat sometimes with lipid and saccharide components). Capsid also helps to interact with host cells, promoting the NA-injection into cells and triggering the synthesis of new viral molecules. In case of HIV the main problem raises from the fact, that this virus integrates into the cell of immune system (leucocytes, phagocytes, lymphocytes), which must confront the invasion of pathogenic microorganisms. As soon as infected organism triggers its immune system on, together with proliferation of proper immune cells it leads to the wanton growth of HIV-particles in the cell and the host cell loses genetic control over its bioprocesses. Immune forces (resistance) get thereby weaker and HIV-patients develop higher risk of other infectious diseases — tuberculosis, pneumonia, leucosis etc.

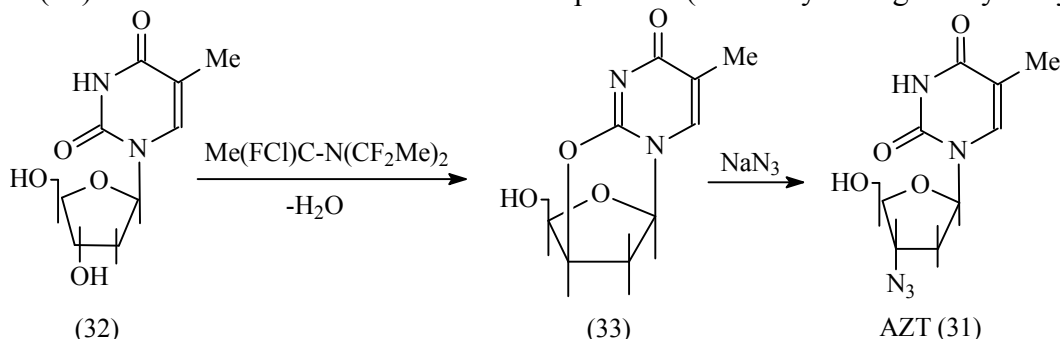
Today for therapy of HIV, which is called “the disease of 21st century” a dozen of synthetic compounds is used, but they all only decrease the viral concentration in blood. Moreover, the virus evolves rapidly, giving one mutation during every reproduction cycle. The rapidly developed resistance of HIV-viruses dictates the necessity to use drug compositions (“cocktails”) of two or three remedies. This dramatically increases the treatment costs (up to more than 20 thousands USD per year).

We should notice, that all known medical compounds used in HIV-therapy are very toxic, that limits the duration of therapy to 2-3 years. However, after stopping of drug intake the concentration of HIV goes up quickly, therefore the therapy must be repeated after some time.

The target points (*biotargets*) of medical compounds in case of HIV can be capsid (its disintegration), nucleonic acid (its mutation, inhibition or disruption) and, ultimately, the enzymes which take part in NA replication.

Some medical compounds used in HIV-therapy, for example **azidothymidine, AZT** (also known as **Zidovudine, INN**) has a nucleoside structure and is considered to be antimetabolite, which can “upset the applecart” of viral NA.

Initially deoxythymidine (32) undergoes intramolecular cyclization in presence of polyhalogenetriethylenamine. Resulted polycyclide (33) is treated with sodium azide in water. Highly nucleophilic N_3^- attacks the electron-deficit C3-atom of ribose from the side, opposite to oxygen (from below). Thereby the ether bond is opened and the azide groups in the molecule (31) becomes to the same stereochemical position (relatively to original hydroxyl).



There are several strategies to decrease toxicity of known remedies, used in HIV-therapy.

One of those is based upon dramatic increase of permeability of AZT and its analogs through lipid membranes. For this purpose their phosphate derivatives are synthesized and these pro-drugs are introduced into artificial liposomes. This “drug + bearer” complex easily trespass the membrane barrier of leucocytes. One should note, that a new drug “phosphasize” is created and is being tested now, which had toxicity several times lower than AZT.

9. Conclusion

All information delivered in these lectures concerning chemistry of medical compounds is just a supplement to the main course of organic and organoelement chemistry and contain the answer to one of the most important questions: what are organic and other chemistries for? In this course of lectures we enlighten the basics of the chemistry of medical compounds, which are used in practical medicine of 20th century.

Industrial drug production of pharmaceutical industry started only 70 years ago. Today the number of remedies in use reaches several thousands, every year only several tens are added to this amount. Due to this fact the attention is mostly paid to the synthesis of widely known and widely approved medical compounds.

Research in the area of drug discovery, especially in last years, reaches vast scale, that is driven first of all by the necessity to solve fundamental problems — for example, elucidation of the correlation between the chemical structure and reactivity, search for new pharmacophores, investigation of chemical and physical-chemical interaction of medical compounds with active components of receptors in biological systems. The issues of chemical bond, kinetic of complex processes, that requires certain body of knowledge in organic, physical organic, analytical and pharmacological chemistry also remain important.

Thereby attention is mostly paid to biologically active compounds and remedies, for those some (proved) information about their action mechanism exists. Therefore, it is natural, that this applied tasks are solved by a formidable army of organic chemists, working in collaboration with pharmacologists, biochemists, medical professionals, professionals in the area of chemical technology. Without tight collaboration of all these scientist there can be no drug discovery research done.

If the information containing in these lectures turns out to be useful for young researchers, eager to reach a high level of excellence in drug discovery, the author’s goal is accomplished.

NARCOTIC SUBSTANCES

Drugs turn a person into a fool, because those, who consume drugs, can not be regarded as clever, so you are a double fool having problems with police.

Lecture IX. and X. NARCOTICS AND ADDICTION. HISTORICAL REVIEW.

The given lecture course is intended for students of chemical faculty, which had not learn the chemistry of narcotic compounds before and are not familiar with addiction.

1. Historical review

Substances which are considered narcotics are known since ancient time. Sumerian knew the dormitory effect of the milky poppy sap. In ancient Egypt they produced somnifacient potions from poppy. They slightly cut non-mature poppy bolls thus obtaining opium, which they took if they wanted to fell asleep or alleviate the pain. Bedoins before long-distance travels provided themselves with dried cannabis blossoms and leaves (marihuana) or its tar (hashish). Cannabis herb and tar were smoked to relax, because of monotonous desert scenery.

Mexican Indians went into ecstasy before their ritual dances by mixing psilocybin-containing mushrooms (*Psilocybe cubensis*, *Psilocybe semilanceata* and *Psilocybe mexicana*) into their food.

Miners in Bolivia since ancient time became their salary partially paid not with real money, but with cocaine-containing leaves of the plant *Erythroxylum coca*, which they smoked and chewed. This helped them to restore their forces after arduous work in mines. Many similar examples can be found and almost every folk consumed narcotics in one or other form.

The majority of narcotics are alkaloids. The name "alkaloid" comes from late Latin word "*alkali*" and Greek "*eidōs*" – "similar to". Alkaloids — nitrogen-containing organic bases of natural origin.

The first narcotic, which was isolated in pure form was morphine. In 1804 it was extracted from opium by the pharmacist of Napoleons Army Friedrich Wilhelm Adam Sertürner and named it after Greek god of dreams Morpheus. The structure of morphine was established by Sir Richard Robinson (1849 – 1928) in 1925 and the complete synthesis was performed only in 1951 - 1956. But three events, which took place in 19th century: the isolation of morphine, invention of injection syringe and heroine synthesis by German chemists in 1898 led to the broad propagation of opiates and their vast application for analgesia. However, the first application of opiates dates back to Sumer civilization and is described in Arabic literature already in 10th century.

In 1821 thein was discovered in tee, caffen in coffee, that turned to be identical. In 1832 codeine was discovered in opium. From the year of 1860 many different alkaloids were isolated, including cocaine from leaves of coca-plant and ephedrine from ephedra. On attempt to synthesize analgetic agents without addicting side-effects such dangerous narcotics as heroine and LSD (lysergic acid diethylamide) were obtained. But the industry of narcotics is not idling, in secret laboratories new narcotics are being developed, that should develop addiction after one or two intakes.

2. Addiction, what is it?

Addiction is not a disease in its usual meaning. Neither is it a vice from those, which even healthy men have.

Addiction is a total (meaning penetrating all the aspects in inner world, relations with other people and the style of living) lesion of personality, with frequent deterioration of health. This means, that the person getting more and more addicted gradually eliminates his best moral qualities, becomes mentally ill, loses his friends, then his family, can not acquire a new profession and forgets his present professional skills and gets fired; he is engaged into criminal medium, bringing suffer to himself and his associates, and finally gradually ruins his own body.

Another peculiarity of addiction is that this pathological state is largely irreversible, the negative changes of human personality as a result of drug consumption stay forever. In this respect addiction is much like disability: if the leg is amputated, there is no chance it will regenerate, in much the same way if mental health and family relations are degenerated by addiction, they will never again come back to normal. The mental “scars” require much more time and effort to disappear, as those on our body.

Moreover, to the regret of addicts, narcotics leave traces not only in our mentality, but also in our body. If the person who put up drug consumption a long ago decides to “fly high” one more time, he or she will have to pass through the hellfire of white plague. That’s why experts in narcology dislike the term “cured drug addict” and prefer to use the term “inactive drug addict” (e.g. those, who do not consume drugs at the moment).

Do you know, what is the most tragic in addiction? This is the fact, that as soon as addicts understand they not just indulge in drugs, but already are addicted to them, it is already too late. The dependancy develops gradually, in half a year or even in a year, but in most cases already after 2-3 months. It is not very seldom though that a person gets addicted already after the first injection of “black agent”. Nobody can predict what results in this or that given situation. And no one should comfort himself saying: “I know, I can try drugs and nothing bad happens”.

That’s the addiction. So, never try drugs. Once you tried it, do not repeat this risky experiment. There are many more other types of pleasure one can find in life, than this artificial chemical substance. Drugs? No, thanks!

3. What are narcotics and what they look like.

What are narcotics? The term “narcotic” comes from Greek verb “*narkoo*”, meaning “to petrify”, “to numb”.

The term “narcotic” is a little bit ambiguous. In medicine it means “agents used for narcosis”, that differs much from the general meaning of narcotics as “agents to get pleasure”. That’s why it was accepted, that in Russia the term “narcotics” applies to the substances included into the official “List N1 of narcotics”, issued by Standing Drug Control Committee (SDCC) of Russian Federation, so the term “narcotic” received a juristical meaning besides “drug”, “psychotropic agent”, “intoxicating agent” etc. In other countries the situation is very much the same (e.g. as narcotics regarded the substances included into an official list of narcotic substances). The legislation of all countries declare heroine, LSD, cannabis, methadone and others as narcotics, “because of their significant social danger and harm for human health” (WHO).

Narcotics are usually qualified according to the following criteria:

- Ability to cause euphoria (good spirit) or at least capable to evoke pleasant feelings;

- Ability to cause dependancy (both physical and/or mental), e.g. a compulsion to take the drug again and again;
- Significant deterioration of mental and/or physical health if taken on a regular basis;
- Ability of wide spread in human population;
- The consumption must not be traditional in this culture, otherwise both tobacco and alcohol would be considered narcotics.

4. Classification of narcotic and psychotropic agents

In one fundamental medical monograph about addiction published recently (“Addiction”, I.N. Pjatnickaja, 1994) the following classification is used:

1. Sedative compounds, including opiates and barbiturates;
2. Stimulators — ephedrine, fenamine, and others.
3. Psychedelic (perception altering) agents — LSD, cannabis and other hallucinogens.

This is a well-suited clinical classification, but for first acquaintance with these substances we chose another classification of these substances, which is not so well-elaborated, but takes into consideration the prevalence of different narcotics in Russian at the end of 20th century. This classification is useful to get an overview about existing narcotics and study some of them in more details.

1. Cannabis (drugs produced from cannabis)
2. Opiates (drugs produced from poppy or artificially synthesized analogues)
3. Sedatives and hypnotics.
4. Psychostimulants.
5. Hallucinogens.
6. Volatile substances.

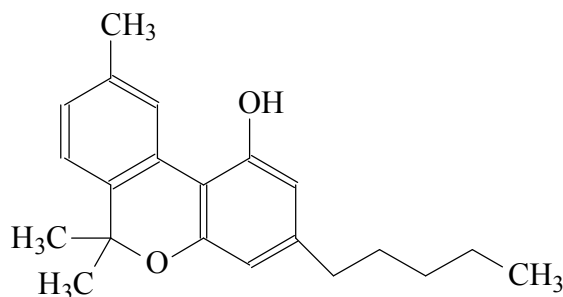
The overview of main groups of narcotics is shown in the table overleaf.

Table 1. Groups of psychoactive drugs.

Psychoactive drugs					
<i>Cannabis</i>	<i>Opiates</i>	<i>Sedatives (hypnotics)</i>	<i>Stimulants</i>	<i>Hallucinogens</i>	<i>Volatile substances</i>
<p><i>Marijuana</i> (buds, shake, brush, bush or leaf)</p> <p><i>Hashish</i> (shit, chocolate, solids or flirty)</p>	<p><i>Poppy straw</i></p> <p><i>Poppy capsules extract</i> (raw opium)</p> <p>Morphine</p> <p>Codeine</p> <p>Heroin</p> <p>Methadone</p> <p>Promedol (Trimeperidine)</p> <p>Omnoponium (Papaverine)</p> <p>Fentanyl</p> <p>Fenadon</p> <p>Pentacozine</p> <p>Prosidol</p>	<p>Barbital sodium</p> <p>Barbital</p> <p>Ethaminal</p> <p>Barbamil</p> <p>Cyclobarbitol</p> <p>Nitrazepam</p> <p>Meprobamate</p> <p>Medinal (barbital-sodium)</p> <p>Trioxazine</p> <p>Hexobarbital</p> <p>Estimal (barbital sodium)</p> <p>Ciklobarbiton</p> <p>Hexanal</p> <p>Diazepam</p> <p>Chlozepidum</p> <p>Phenazepam</p> <p>Oxazepam</p> <p>Reladorm</p> <p>Glutethimide</p> <p>Veronal (Barbital)</p> <p>Luminal</p>	<p><i>Plants:</i> <i>Coca, Kola nut, Ephedra</i></p> <p>Cocain</p> <p>“Crack”-cocain</p> <p>Ephedrine</p> <p>Ephedrone</p> <p>Pseudoephedrine</p> <p>Pervitin</p> <p>Amphetamine</p> <p>MDMA (ecstasy)</p> <p>Caffeine</p> <p>Phenmetrazin (Preludin)</p>	<p>Mescaline (peyote cactus)</p> <p>Psilocybin (magic mushrooms)</p> <p>Harmine (Syrian Rue)</p> <p>Atropine (Solanaceae)</p> <p><i>Synthetic drugs:</i></p> <p>LSD</p> <p>DMT</p> <p>PCP (“Angel dust”)</p> <p>Ketamine</p>	<p><i>Inhalants:</i></p> <p>Petrochemicals:</p> <p>Benzine</p> <p>Kerosene</p> <p>Gasolene</p> <p>Solar oil</p> <p>Solubilizing agents:</p> <p>Benzene, acetone, ether, toluene, xylene</p> <p>Varnishes, dyes, enamels</p> <p>Polieröl</p> <p>Cleansers</p> <p>Aerosols</p> <p>Amyl nitrite</p> <p>Butyl nitrite</p> <p>Varnish remover</p> <p>Rubber cement</p>

5. Cannabis.

The active principle of cannabis is its alkaloid cannabinol (1). There are more than 60 different compounds found in cannabis, which are chemically similar to cannabinol. Cannabinol (6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromen-1-ol) is well-known as the derivative Δ^9 -tetrahydrocannabinol (abbreviated as THC) was discovered in 1945 by Levi and is a substance, which leads to mental impairment both in humans and animals.



(1) Cannabinol

Cannabis flowers are dried and processed to get a tar-like dried hashish (containing 8-12% of cannabinol). In Asia hashish (from Arabic “herb”) is called “bant”. In Western civilization it also got its own names: shit, chocolate, solids or flirty. This is light-gray homogenous substance constituted by small crumbs. From dried cannabis buds — including flowers, upper leaves and fruits (oval-shaped nuts about 2 mm in diameter) — results brown paste, similar to ground herbs or spices. This is marijuana. It contains 1-5% of cannabinol, so its effect is much weaker than that of hashish. Slang words for marijuana are buds, shake, brush, bush or leaf. Similarly to hashish marijuana is mixed with tobacco and smoked, either rolled in a cigarette or in a pipe. Sometimes marijuana is brewed. The pure tar is chewed and smoked in hookah.

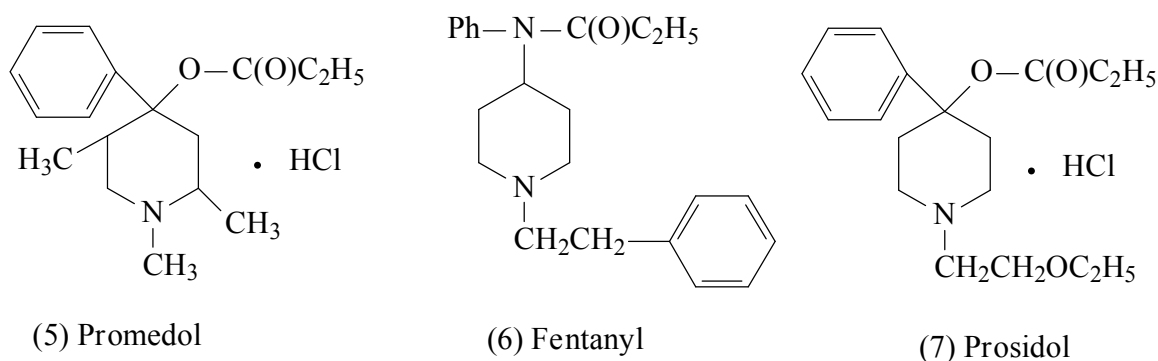
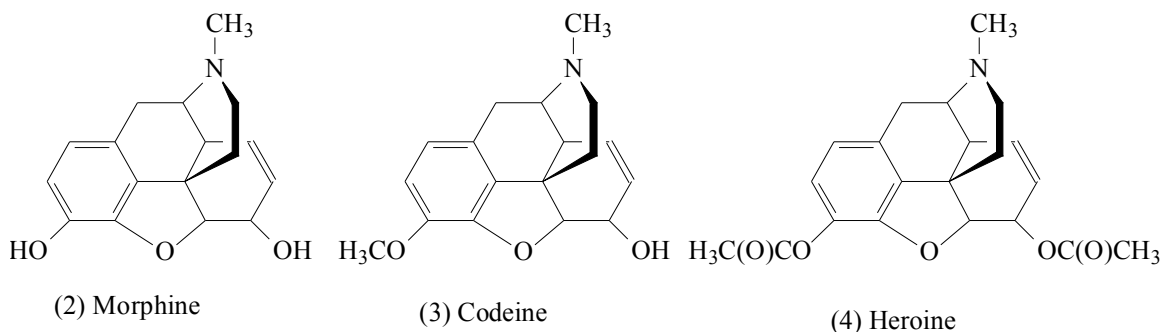
Cannabis is the most abused narcotic today. Its derivatives are the following:

1. Dried or non-dried green herbal part of the plant, which is also called marijuana. It is similar to tobacco and looks like light green or brown ground and dried leaves and stalks. Sometimes it is pressed in clots, it is then called “pot”.
2. The pressed mixture of tar, pollen and ground buds (“pot”, “hashish”, “hash”) is a dark-brown compact substance, similar to plasticine (but less elastic), which leaves fatty traces on paper.

There are other cannabis drugs which are not so popular. All its drugs have rather strong smell and bitter taste. As a rule, they are smoked rolled together with tobacco.

6. Opiate drugs

Narcotics extracted from poppy and their derivatives belong to the group of the most dangerous narcotics, usually called opiates (from Greek “*opion*” – “poppy sap”). Poppy straw contains morphine and codeine; heroine is produced only synthetically from morphine. The most popular opiate drugs are morphine (2), codeine (3), heroine (4), promedol (5), fentanyl (6), prosidol (7), omnopon, dionin, fenadol, methadone, pentazocine:



Opiate drugs (both home-made and industrial) occupy the second place after cannabis drugs as regards their popularity in Russia. They can be also used in the raw state:

1. "Poppy straw" is ground (sometimes to dust) yellow-brown dried parts of plants: leaves, stalks and heads.
2. "Hanukah" is a set dark-brown milky sap of poppy heads (also called gunpowder or raw opium), formed in opium tablets about 1-1.5 cm across.
3. "Binti" (bandage) or "marlja" (gauze) opiated cotton, which turns brown if it was light-colored before. It gets tough by feel and fragile.
4. "Heroin" and "methadone" are the drugs made in clandestine labs. White, grayish or brownish powder consisting of tiny crystals, resembling baking powder by feel. It tastes bitter, mixed up with powdered sugar it has a sweetish smack.

All raw opiates obtained from plant material taste astringent. They contain opiate alkaloids: morphine, codeine and some others.

Raw opiates usually look like solutions:

1. Home-made from plant origins opiate solution has brown color, looking much like weak or strong tea with distinct, sometimes even penetrating scent of acetum. When settled, it gets brighter and more transparent with dark sediment. This is the very ill-famed "black solution" or "the black".
2. Transparent solution in ampules or phials. Phials can be made from dark glass with "morphine hydrochloride" labelling.

Codeine is another opiate, usually distributed in officinal (e.g. industrially produced) cough and headache tablets.

Methadone is a synthetic opiate narcotic. Its production and use for any purpose are prohibited in Russia. Strictly speaking, methadone is not an opium-derivative, it is rather an “opiate-like” narcotic. However clinically methadone addiction does not differ from heroine or opium addictions.

Opiates are usually injected intravenously. The plant material is pretreated with chemical agents — organic solvents and acetic anhydride, powdered narcotics are just diluted. Seldom the straw is brewed like tea or eaten as is. Today (luckily!?) the inhalation of heroine powder became quite popular. Though we do not approve any way of drug intake (since it will anyway have harmful consequences), the inhalation is at least safer as regards transmission of AIDS, hepatitis and syphilis.

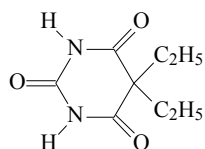
7. Hypnotics and sedatives.

Sleeping pills are available only in their officinal forms, often tablets. Not every sleeping pill is an official narcotic, but almost every sleeping pill can cause addiction (those, which cause it dramatically quickly are included in the SDCC list) and can reveal narcotic properties.

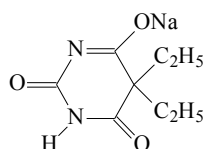
Barbiturates are barbital (8), sodium barbital (9), sodium ethaminal (nembutal) (10), cyclobarbital (11), luminal (phenobarbital), hexobarbital, barbamil (amital-natrium), estimal medinal and others.

Tranquilizers (psychotropic agents to reduce stress and anxiety) are seduxen (12) (synonyms are subazon, relanium, diazepam), phenazepam (13), elenium, tazepam (nozepam), as well as tranquilizers of other chemical groups — trioxasin (14), meprobamate (15) etc.

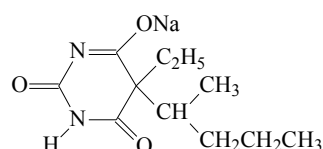
Benzodiazepine **hypnotics** — radedorm (16) (nitrazepam, neozepam);



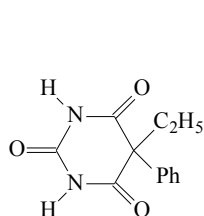
(8) Barbitital (veronal)



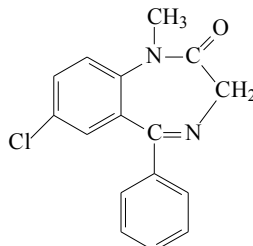
(9) Sodium Barbitital



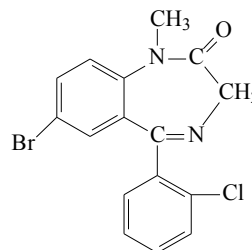
(10) Sodium ethaminal (nembutal)



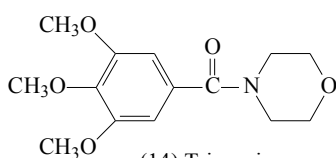
(11) Cyclobarbitital



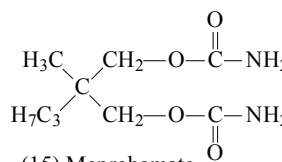
(12) Seduksen (diazepam)



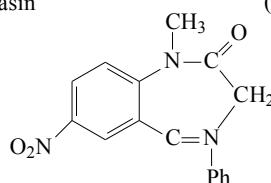
(13) Phenazepam



(14) Trioxasin



(15) Meprobamate



(16) Radedorm

The most dangerous are the derivatives of barbituric acid (barbiturates), for example barbamil, phenobarbital etc. But other tranquilizers, including relatively freely sold drugs (phenazepam, radedorm, relanium, elenium) can lead to physical and psychological dependencies if used regularly and in overdoses. That means, that the patient will have to gradually increase the amount of drug.

The most often used sleeping pills used by addicted people are radedorm. One should consider, that this drug contains cyclobarbitital – a barbiturate, so radedorm addiction is the same as any other drug addiction.

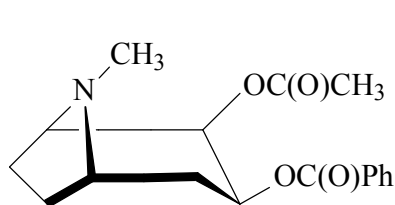
Nowadays drug in tablet form are usually taken orally. The intravenous injection of chapped tablets becomes less popular.

Since all sleeping pills are produced industrially, they are always adequately labelled. The label includes generic name, content and sometimes even short description (which can be as a rule found on the drug inlay). Read all these prescriptions carefully!

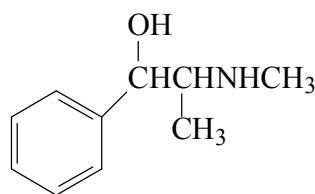
8. Psychostimulants

Psychostimulants are quite inhomogeneous group of drugs, which have one common property: on their intake the brainwork tempo increases (thereby the reasoning becomes shallow, facile and less deliberate). Some agents from this group are also able to distort perception, that is quite close to hallucinogens. There are psychostimulants of plant origin (coca, ephedra, cola), though they are usually consumed in the form of chemical substances (powders) or tablets.

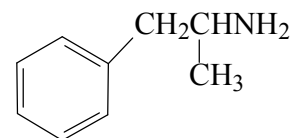
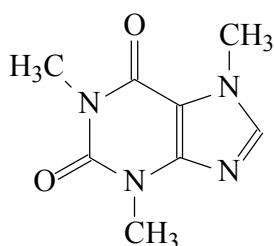
To this group belong cocaine (17), ephedrine (18), amphetamine (benzedrin, phenamin) (19), caffeine (20) (in case of theism with extra strong tee or coffe), ecstasy (MDMA, 3,4-methylenedioxy-N-methylamphetamine) (21), pervitin (metedrin) (22), ephedron, preludine (gracidine) etc.



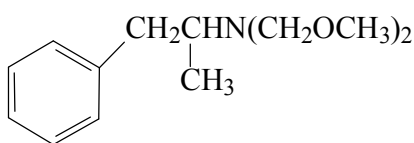
(17) cocaine



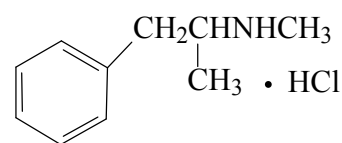
(18) ephedrine

(19) amphetamine
(benzedrin, phenamin)

(20) caffeine



(21) ecstasy

(22) pervitin
(metedrin)

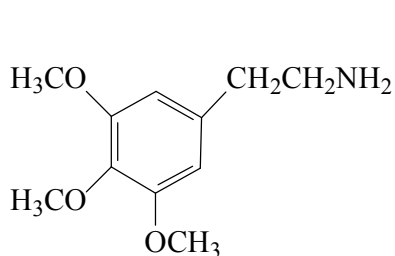
1. **Ephedrine** is a white powder with bitter taste consisting of oblong crystals. It can also be in the form of solution in ampules labelled "ephedrine". It is also present in the ill-famed drug "solutan" and ointment "sunoref".
2. **Pseudoephedrine** and **ephedron** are ephedrine derivatives. They are not sold in pure forms and are usually home-made by addicts *ex tempore* using potassium permanganate and acetic acid. In this case they look like transparent solution (slang "the white", "white solution") with acetic scent. They are injected intravenously.
3. **Phanamin** or **amphetamine** (generic name) is the drug, which is sold in tablets or as a powder, sometimes can be prepacked in capsules. It is taken orally and intravenously. Amphetamine and similar agents can be components of "slim pills", be careful!
4. **Ecstasy**, HTC is a group of amphetamine derivatives (3,4-methylenedioxy-N-methylamphetamine, MDMA; 3-methoxy-4,5-Methylenedioxyamphetamine, MMDA and others more complicated names), which is marketed under the enticing name "ecstasy". It is sold as parti-colored tablets with different shapes, taken only orally.
5. **Cocaine** is an alkaloid, which can be found in the leaves of tropic coca bush. Pharmacologically can be classified as psychostimulant with euphoric effect, which increases on every intake. Chemically cocaine is white crystal powder, similar to the baking powder. Sprinkle on a tongue it leads to numbing (similarly to novocaine). Cocaine is usually inhaled ("sniffed"), sometimes administered intravenously in diluted form. Some cocaine derivatives are heated on a foil to inhale the smoke. The euphoric effect lasts for 25-40 minutes, followed by loss of strength, apathy and damp. "**Crack**"-cocaine is smoked, it is a very dangerous drug.

9. Hallucinogens

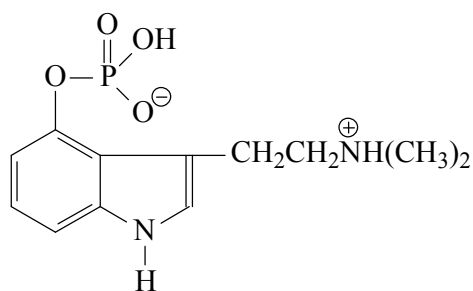
Hallucinogens are chemical compounds of natural or artificial origin which cause mind alterations — hallucinations (acoustic or light effects, abstract visualities, dream-like visions of complex geometrical compositions, loss of sense for reality and ability to orientate in space,

deterioration of reasoning and habitual perception). They are characterized by the state of "diluting in the space". Addicts usually call hallucinogens "acid". Hallucinogens comprise over 100 natural and synthesized drugs.

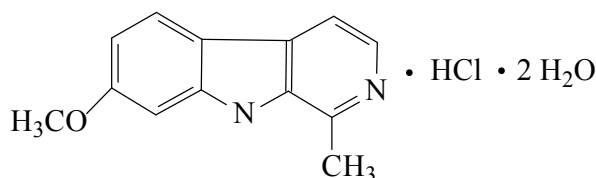
Natural psychedelics are found in many plants. The most known are the alkaloid mescaline (23), obtained from Mexican peyote cactus (*Lophophora williamsii*); psilocybine (24), the alkaloid of Mexican magic mushrooms ("shrooms") or *teonanácatl* ("divine flesh"), the alkaloid **harmin** (25), contained in **Syrian rue**, whose seeds were used by ancient Greeks for inebriety; alkaloid **atropine** (26), obtained from solanaceous plants. Indigent nations of North (Chuckchee, Tungus, Inuites) use cooked toadstools as hallucinogens. From synthetic hallucinogens the most popular are **LSD** (lysergic acid diethylamide) (27) (its hallucinogenic activity is hundred times higher than any other drug of natural origin), **butophenin** (28), DPT (dipropyltryptamine), as well as phencyclidin (PCP) and amphetamine analogues. Here are some formula:



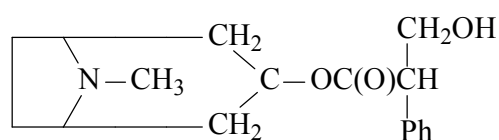
(23) Mescaline



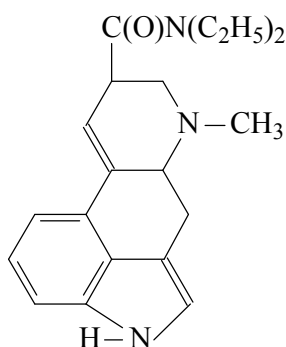
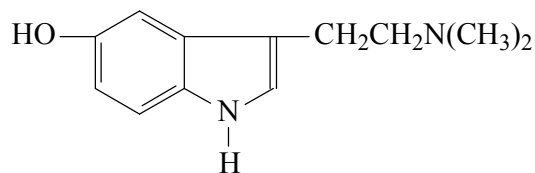
(24) Psilocybine



(25) Harmin



(26) Atropine

(27) Lysergic acid diethylamide
(LSD)

(28) Butophenin

1. Mushrooms of the *Psilocybe* genus contain psilocybin and psilocin. This is one of the most popular hallucinogen in Russia. They are available only in the end of summer and look like small brown fairy-mushrooms with thin stalk and caps having violet shade. Usually consumed fried, cooked or even raw.

2. LSD (lysergic acid diethylamide) is a “reference” hallucinogen. It is extremely toxic, the consequences of its intake are described in lecture 11. LSD is sold as transparent solution, powder or different stamps, resembling postage ones (their material is imbued with drug solution). LSD is taken orally as a rule, though some addicts tend to inject it intravenously.
3. PCP (read as [pi: si: pi:], sometimes mispronounced as [pi: es pi:]), or phencyclidine. It is quite rare in Russia, usually in powder form. Sometimes is also injected intravenously.

We would like to emphasize, that all hallucinogens are extremely harmful for mental health. More details are available in the next lecture.

10. Volatile substances (volatile addictions)

Inhalation agents are volatile narcotizing agents contained in household and technical chemistry products and used for inebriation.

There is no need to describe the volatile narcotic substances in details. These are different glues, liquids used in lighters and varnish remover, kerosine, gasoline, dye solvents, varnishes, enamels, cleansers, polieröls etc. Chemically they are usually benzine, acetone, bezol, xyloles, ketones, ethers and esters, different alcohols, aromatic and aliphatic hydrocarbons, halogen-substituted hydrocarbons.

Lecture XI. PHYSIOLOGICAL EFFECTS OF DRUGS

Often teenagers try drugs for the very first time just out of curiosity or “solidarity” with friends. Those who consume drugs voluntarily usually expect two types of effects. The first one is the opportunity to relax, to go away from daily routine, sometime really annoying problems or tragic memories. The second effect expected is the opportunity to test new, novel feelings, to stimulate imagination, creative abilities.

We start from the second effect. As always, narcotics cheat those, who count on inextinguishable firework of astonishing discoveries and spirits. However, world-known authorities, including famous “rock giants” as “Rolling Stones” or “Beatles”, Zen and Krishna masters recommend hard work and self-cultivation to reach this marvelous state. Those, who tried to falsify this work or stimulate it by drug intake ended tragically. Marilyn Monroe, Elvis Presley, Mikhail Bulgakov, Jim Morris – you can continue this list on your own. Despite all expectations drugs hinder creative work and concentration. As regards artistic ideas, they do not come because of drugs, but thanking to previous experience and knowledge. As a result of regular drug intake the active, ever-wondering, vivid personality is suppressed, loses its energy. Artistic interests are replaced by worries about money and the picture of the precious “kaif”-dose obtrusively raises before the mind.

Though there are some situations when it is not possible to “create” without drugs. Yes, there is such a situation. This is the situation when an addict has to “create” something. He can not even raise his head from the pillow without drugs, to say nothing about work — he is in possess of withdrawal. This is the back side of the former “creative ecstasy”.

As concerns the first effect expected, it is true, that the majority of drugs can “switch off problems” for short period of time. It is true, that this time is really very short, and even on first intake it rarely last for more than 12-18 hours. Thereby the problems do not go away, but often even worsen. But the irony of the fate is that drugs themselves soon become a huge problem for those, who tried them once.

There are several types of **dependencies** which could develop. The biological mechanism of dependancy is mediated through biochemical, biophysical, membrane, cell and

tissue reactions taking place in human body. This dependence is called “physical dependence”. It is mostly typical for opiate, hypnotic addiction or alcohol.

Physical dependence develops as a result of organism “tuning” to drug intake and their involvement in its biochemical processes. There is no way to explain in a nutshell what really happens. **The main principle is simple: drugs — every single drug in particular manner — become to function as substances, formerly synthesized by the organism itself. Therefore organism stops or drastically reduces the production of these substances to spare some internal resources.** You may remember hormones as norepinephrine, epinephrine etc. Besides, on drug intake the balance of many other less known but not less important substances, like serotonin (neuromediator), acetylcholine and dopamine, DNA-bricks is upset, that leads to increased permeability of cell walls for Calcium ions and many other effects.

If the process of organism physiological “re-tuning” to drugs went too far, drug withdrawal leads to abstinence or withdrawal syndrome (colloquially called “breakage” or “wrecking” in Russian).

Another peculiarity of this process: drugs are constantly broken up by enzymatic systems and excreted through kidneys, intestine and lungs. Therefore the “drug depot” in organism must be renewed on a regular base. So the developed physical dependence forces the addict to consume drugs regularly, without big pauses. Subjectively, e.g. by the addict himself, it is very difficult.

Once the due time for the next dose is missed, the addict is doomed to suffer cruelly. This is not just pain, but also hardly bearable shivering — “internal icy cold” without even slender hope to warm up, cold sweat, abdominal pains with persistent diarrhea, nausea and vomiting, permanent cold, fatigue, acute pains in joints. If you have never experienced withdrawal just remember the debut of the most severe flu you have ever suffered add a food poisoning and that will be approximately one fourth of that the poor addict feels besides cruel pains, which are often seen in the motion films with addicted people. Alcoholic physical dependence is characterized besides all that also by tremor, well-known as “shivering”, when not only hands, but the whole body shivers and quivers.

Abstinence, as usual, is accompanied by marked anxiety with more or less pronounced (during not less than 7-10 nights) insomnia. That is why addicts must get the next dose till due time by right or wrong. And it often turns not to be so easy.

But that’s not all. Besides physical dependence addicts also develop psychological dependence. It can be hardly described, since it is not well felt on constant drug consumption and young addicts refuse to believe it. Often then they come to doctors they beg only to cope withdrawal (or at least to alleviate it), being sure that they can easily put up taking drugs afterwards without much effort. Many therapists who deal with alcoholic and drug abuses nonetheless consider the psychological dependence be the result of pleasant reminiscences about euphoria. It is true at least for young addicts, who are able to reach this euphoria.

It is evident, that the motive which underlies the formation of psychological dependence is the very unwillingness to face the problems, which we mentioned in the beginning of the lecture. Addict, who has been taking drugs for long time and then one day puts that up undergoes dramatic stress. This stress is due to drastic changes of accustomed lifestyle. If before the addict could “flee” to his internal world of pleasant dreams or at least do not percept so sharply the necessity of vital and urgent, but not always easy decisions (which often force him to sacrifice one or another personal values), now he feels unprotected. That’s why many “experienced” addicts resume drug intake after therapy. They perfectly realize this “rat race” and would like to escape it, to re-learn how to live without fair and drugs.

The tragedy of the fate here is that this skill is lost for ever. And the problem here is that these persons started to consume drugs being quite careless about possible negative consequences and mistakenly thinking that will never happen to them.

Sure, there are many factors that contribute to the formation of psychological dependence in every single case, there is no way to consider them all.

That's why the best protection even against addiction is the coward, stupid, ridiculous, silly, obstinate and flat **refusal** to "just try it".

And now to the **harm** the drug consumption causes to the physical **health** of an addict. All drugs, independent from the way of administration damage more or less the following:

- Nervous system (including brain);
- Immune system
- Liver;
- Heart;
- Lungs;

What is the usual lifetime of an addict? If drugs are consumed intravenously it comprises 7-10 years of narcotization. There are of course come, who live 15, 20 and even longer being addicted. But there are some, who die after 6-8 months of regular consumption.

What are the causes of death of addicts? What factors lead to high mortality? The most common ones are: traumas (in road accidents, through negligence, in rumbles), overdose, poisoning with low-quality drugs; diseases — sepsis, pneumonia, chronic hepatic failure. The factors, leading to high mortality also include the higher involvement in criminality, negligence and flippancy when drunk, disregard of hygienic rules and sterility of injections, and many others.

To get an overview we will briefly describe the negative side-effects of the main drug groups. More information can be found in specific manuals.

1. Cannabis

This is the most frequent narcotic. The main narcotic substance of cannabis is cannabinol. Cannabinoids are characterized by their ability to bind lipids, that facilitates the permeation of the drug through lipid membranes into brain cells. As a result of this the cannabis metabolites are accumulated and stored for long time in brain cells. This explains the fact why cannabis metabolites require much more time to be eliminated from human body than other drug metabolites. Several weeks are needed to eliminate the traces of one dose. Since cannabis drugs are most often smoked the first organ injured are lungs. Many addicts think that marijuana is less dangerous than tobacco and has less risk of lung cancer. It should be considered, however, that cannabis has not less tars and phenanthrenes, than tobacco, and this is what causes chronic bronchitis and lung cancer.

Even though that cannabis is only smoked, its alkaloids injure liver, as follows from the last monograph of Pjatnickaja I.N.

The heart also is afflicted by cannabis intoxication, because it causes acceleration of heart rate, that leads to the overload of heart muscle (myocardium). The overload then rapidly exhausts the resources of myocardium and leads to its degeneration. Besides, cannabis intoxication leads to deterioration of nerve ganglia, responsible for eurhythmia of heart beats, thus causing arrhythmia. This can remain unnoticed by the addict, by is clearly seen on a routinely made ECG-recording.

Specialists in drug abuse treatment unanimously warn, that cannabis intake leads to severe brain injury. This is due to the fact, that cannabis, as every hallucinogen (which group it belongs strictly speaking), impair the mediator metabolism in the brain. This impairment is similar to that in schizophrenia patients. After the intoxication is gone the normal functioning of the brain is usually regained, but not all effects are completely reversible. Tiny lesions, called "defects" in psychiatry, remain forever. Depending on the intensity of cannabis abuse these changes accumulate, so formerly cheerful "man of action" turns into dreamy, apathetic, slow-witted, worrying about every minor problem and enormously burdensome both for

himself and for his family. These addicts are ready to put up cannabis consumption, but the state is already irreversible.

2. Opiates

Opiates are the major cause of death and disability among addicts. The situation with opiate addiction is so critical, that the most efforts of medical professionals are concentrated on the prevention of the complication of opiate addiction. What is then so terrible in opiate addiction?

First of all one should consider, that opiates are usually injected intravenously. This means, that those, who inject them have a higher risk of AIDS, syphilis and hepatitis (“jaundice”) contamination. This risk is real and quite high. According to different surveys up to 95% of opiate addicts are infected with hepatitis. Hepatitis together with permanent intoxication by solvents and acetic anhydride leads to liver dystrophy with ensuing consequences.

The incidence of syphilis contamination grows up. The worst here is that the disease is usually recognized when it is already advanced and serious nerve system complications (usually paralysis) can not be prevented anymore.

Previously AIDS was very rare. But in summer 1996 bad news came from Ukraine, the outbreak with more than 7 thousands contaminated with AIDS was reported. In Kaliningrad there are currently several thousands, in Tver from 3000 officially registered addicts more than 100 are infected with AIDS, that makes more than 30 infected per 1000 addicts. One should not rely only on disposable syringes — sometimes addicted people just do not have enough time to get them.

As concerns liver, besides hepatitis other problems can result from opiate addiction. Historically in Russia — probably because of the cheapness — the drugs are usually produced by addicted themselves from raw material (e.g. poppy). This technology requires organic solvents (previously acetone was widely used for it, today it is supplanted by “bottled solvents” labelled with code numbers, usually 646, 647 and 649, sometimes benzol or toluene are used for this purpose) and acetic anhydride. Thereby due to general primitivity of the methods used for the purification, from 1 to 5% of the solvents and anhydride are contained in the final product. This explains why it has acetic scent. The solution is injected into blood, so the solvents go directly to the liver. Do not forget, that the liver can be already compromised by hepatitis.

What happens to the delicate liver cells once they are “immersed” into the solvent? They just dissolve. And if we immerse them into acetum? They will burn.

Another important issue. Liver is a “protein factory” of the body. That also applies to the proteins, which are responsible for immunity, e.g, for resistance against infectious diseases. Liver also produces proteins responsible for blood clotting, as well as other important proteins. As a result of liver cell degeneration and necrosis the production of these proteins dramatically decreases.

That is why the natural immunity fails. Another reason for compromised immunity is the fact that opiate addicts usually add dimedrole to the final solution. Dimedrole was specially designed to suppress the overreaction of organism to a disease, thus to suppress immunity. It leads to the situation, where immunity-responsible proteins lack and the immune response is suppressed by dimedrole. As a result of this suppression the patient can not withstand the infection accompanying drug addiction (sepsis, trombophebitis, pnegmons, pneumonia etc).

The immune deficiency is so high, that it can be compared to that in case of AIDS.

For those, who are not addicted: do not use dimedrole, this is an obsolete medicine. If you want to cope your allergy use more specific (and thus less toxic) remedies: ketotiphen, tavegil (klemastin) and many others.

One should not cherish the illusion that solvents and acetic anhydride damage only liver. They damage also heart, lungs, brain to the same extend. But addicted people usually do not notice it, since the pain is usually coped by drug intake and withdrawal pains are outshine these problems. The addicts get aware of the problem in two cases:

1. if the problem becomes critical — suppurative inflammation, for example, or
2. if the consciousness is cleared as a result of the addiction therapy.

We would like to notice, that the most common problem of opiate addiction is the lesion of bone tissue. This is due to the opiate (morphine, heroine, codeine and methadone) ability to intervene (and impair) the Calcium metabolism in the body. And because Calcium is the main part of bone and tooth tissues, they both are very much affected by the addiction. The bone just gets softer what usually remains unnoticed. But the teeth get destroyed very intensively, sometimes 2 years of addiction are enough that only dark stubs are left in the mouth. By the way, broken or crumbling teeth is one of the most reliable sign to spot an addict among your friends.

The brain is impaired both by organic solvents or acetic anhydride. Besides there are other indirect factors, which affect the “head” of every addict:

1. Life full of problems. As a result of many not so romantic adventures (street fights, falls and police) brain concussion and other more serious trauma are unevitable.
2. Any, even slight overdose of opiates leads to respiratory failure (opiate suppress the center of breathing), and thus to insufficient brain oxygen supply. This logically leads to cell death. Brain cells normally can not regenerate in adults. The higher is the intoxication the more cells die.
3. Opiate drugs are predominantly produced at home, so they can not be sterile. The conditions of their production are also far from sterile. As a result of their injection not only sepsis (blood inflammation), quite often and very threatening complication, but also another unavoidable complication called “quivering”. Correctly this state is called “hypertoxic reaction”, which develops if too many alive or dead microorganism are injected into blood. “Quivering” is accompanied by abrupt temperature rise, chill, nausea, dizziness, fatigue and sometimes by pain in the back and joints. This state is extremely dangerous and can end lethally. High temperature seriously damages the brain.

All this leads to the health problem, called “encephalopathy”, when the majority of brain cells are damaged or dead.

The main conclusion: opiate abuse leads to hepatitis, AIDS, hepatic failure, cardiac failure, lung dystrophy and brain degeneration, critical immune status, which is referenced to as “chemically-induced AIDS” and very high risk of suppurative inflammation. Therefore the expected lifetime of those who take drugs regularly is about 7-10 years after the first dose.

3. Barbiturates

Isolated barbiturate abuse is quite rare. Barbiturates are often combined with opiate drugs. Today the most popular barbiturate drug used is reladorm, which is used by opiate addicts as a sleeping pill.

Barbiturates cause intoxication similar to the alcoholic one. Even higher similarity share the complications of their abuse (with the only exception that complication of barbiturate addiction are usually more severe and occur earlier). So, everyone can guess the spectrum of damaged targets: brain, liver and heart. Barbiturate withdrawal is similar to alcohol abstinence.

If taken regularly barbiturates lead to phycological and physical dependence after 1 to 3 months. The physical dependence manifests not only as withdrawal sickness, but mainly as constant and long-lasting insomnia.

Moreover every psychiatrist knows, that barbiturate addicts are the most uncivil, sensitive and aggressive patients. Barbiturates are the only drugs, whose intoxication makes one not complacent but rather aggressive.

On long-term (more than 6 months) abuse barbiturate addicts develop psychoses, which manifest either as imperative hallucinations ordering them to make something ridiculous or dangerous, or as persecution complex and jealousy. Since the addicts are usually very aggressive in this state the consequences of these psychoses can be very tragic.

Cardiovascular system is greatly impaired by barbiturates, to the same extent as alcohol does impair it. Especially during the abstinence, when the blood pressure sharply rises. During this period the risk of myocardial infarction is extremely high. Besides possible infarction heart muscle also suffers degeneration.

Barbiturates like other drugs are very toxic especially for liver and cause its dystrophy. Fortunately, barbiturate addicts do not live long enough for this dystrophy to develop, similar to alcoholics they die of encephalopathy or related complications (convulsive attacks or incidents during psychoses). According to the literature data the incidence of suicide among barbiturate-addicted people is 60-80 times higher than in average population.

4. Psychostimulants

Every psychostimulant is a doping, destroying your soul and body. They have two common features: 1) they sharply increase metabolism in the whole body, including brain and 2) they increase the heart beat rate and blood pressure. The energy needed for higher level of functioning is taken from reserve storages, which can not be restored in between intakes.

Every psychostimulant (though the manifestations are usually clearer in case of intravenous injections) has a characteristic course of addiction development. It is similar to alcoholic "boozing". If an addict has enough drugs (or money to buy them), and he does not want (or can not) decrease the dose he starts to increase the dose of the "potion" taken. At the end of "boozing" the in-between time can be as little as 20 minutes. This "boozing" can last for several days, during all this time the addict is awake. But body resources inevitably get depleted, and one day the next dose does not maintain the stimulatory effect. The addict falls asleep and sleeps for one-two days. He wakes up jaded, weak, depressed and irritable. He does not feel need for further drug intake, his primary goal is to recuperate. Several days later he is back to normal and it starts all over again.

As a result of psychostimulants addiction a severe lack of energy-containing substances develops (due to accelerated metabolism). This manifests as extreme emaciation, skin ageing and cachexia.

Regular intake of stimulators damages the cardiovascular system. First manifestation of this damage is usually a severe arrhythmia (*abnormal heart beat rhythm*). These addicts often die of heart arrest. If not so, myocardial dystrophy develops. The incidence of myocardial infarction is higher in this population, even relatively young addicts can develop it.

Of course patients suffering on cachexia and myocardial dystrophy have not only the problems to re-integrate into the society, but simply to move.

The psychological profile also reveals the traces of the abuse. In drug-induced accelerated state the addicts are very enthusiastic. Addicts can not keep sitting quietly in this state, but rarely accomplish something. As a result of long-lasting intake of psychostimulants severe depression can develop. They often lead to psychosis, e.g. force the addicts to behave ridiculously, in unexplainable manner, to commit tragic things (for example, suicide) only because of their depressed or dispirited state.

There also develop psychoses of other origin. During intoxication the addicts are so wrought-up and strained, that good mood can rapidly change to anxiety, alertness and pathological suspiciousness. This happens so often, that it is colloquially called "desertion".

“Desertion” is accompanied by hallucinations and delirium. The addicts suspect being watched, that they are going to be killed, mugged or arrested. Resultingly, they try to flee, to protect themselves. Because sometimes they try to use knives to protect themselves or escape through the window on the 5th floor, it can end up tragically.

Another fatal type of psychosis is when during the culmination of intoxication they believe they can fly, and they try it, usually from the tops of high blocks or top floors.

Different drugs from this group can have different specific complications. Until recently the most popular drug from this group was ephedrone. Ephedrone is produced domestically from ephedrine or other medicines containing ephedrine. The domestic technology requires the use acetic acids and potassium permanganate. Permanganate causes the paralysis of lower extremities, and if thighs and shanks can be moved with some effort, the footsteps are completely paralyzed. Concurring with distal leg paralysis the manganate-induced dementia develops. As many other complications of addiction, neither paralysis nor dementia can be cured, they are irreversible. M.A. Lapickij, the specialist on ephedron addiction describes also Parkinson’s syndrome in addicts: *loss of coordination, reduced facial expression, blurred speech, tremor (shivering) of head and extremities*.

We would like to tell a little bit more about cocaine, which is getting popular among young people today. It seems to me, that similarly to the cellular phone brand you have, intake of cocaine is regarded as a sign of well-being. But those, who take cocaine usually do not know, that American doctors call it (and especially its derivative “crack”) “*fast killer*”.

The cardiovascular complications (arrhythmias and heart arrests) are not rare.

We should also mention the “cocaine psychosis”, called after french psychiatrist Valentin Magnan, which develops in the patients who take cocaine for long time. This psychosis, besides anxiety and fear, is also accompanied by delirium, hallucinations. Patients suffer on painful itching, the patients feel as if small stinging insects infest under their skin, or somebody “poured some sand” under the skin. Hallucinations can be both visual (many small dark object, “flies”), and, more often, acoustic (patient hears the voice which threatens, scolds, insults). These hallucinations are usually accompanied by persecution complex.

Another seemingly little detail is that cocaine leads to vessel contraction. And since it is usually inhaled through nose, it leads to the constriction of nose mucus vessels. Therefore the blood supply decreases and some ulcerous aphthae appear. Some health care professionals wrote in the beginning of 20th century, during the world-wide cocaine fad, that those, who sniff cocaine for long time develop holes in nasal septum and alae.

5. Hallucinogens

Principally the complications of hallucinogens are similar to those of cannabis, because the latter belongs to this group. Nonetheless, speaking of hallucinogens in general (mainly about so-called “acid” or LSD, PCP and some toxic mushrooms), they usually do not damage lungs as cannabis, because they are not smoked. To the less extend other organs, except for the brain, are damaged.

Hallucinogens are extremely aggressive against the brain. Actually, every hallucinogen intoxication is an induced psychotic disorder. That is why the drugs of this group are called “psychodisruptics” (*e.i. “destroying the psyche”*). The very LSD, which is taken by addicted people, is used as an antipersonnel chemical warfare agent. The report about military testing of LSD and its analogous BZ by Pentagon convulsed the world. In this short film people eat grass like muttuns, because they were told that they are muttuns. You probably have seen this episode, it is shown in the documentary about intelligence service “Dead season”¹¹.

¹¹ A similar documentary about LSD-testing on soldiers can be seen here: <http://video.google.com/videoplay?docid=517198059628627413&q=lsd+troops>

LSD, as other hallucinogens, get involved into the functioning of several types of synapses (*tiny structures in nerve cells, enabling information transfer from one cell to another*), completely disorganizing it. After LSD elimination from the brain many cells fail to restore the normal functioning of their synapses.

Single LSD injection can irreversible damage the brain and leave the traces, which can not be distinguished from schizophrenia. Of course, the low dose will hardly take effect if the person is healthy. But the damages, caused by LSD, PCP or “magic mushrooms” accumulate and aggravate. After some time the addict loses the energy, the animal spirits, the ability to act purposefully, similarly to a schizophrenia patient. PCP and magic mushrooms are somewhat less toxic for the brain than LSD. But they also often cause psychoses and lead to the irreversible damage of psyche if taken regularly.

By the way, please, bear in mind that eating mushrooms is not safe as well. The substances contained in them are more dangerous for the liver than even solvents. One-time poisoning with a bad mushroom can end lethally in the intensive care unit because of acute hepatic failure.

6. Volatile substances

Colloquially they are called “solvents”. According to health care professionals both solvents, and household products, containing them (for example resin-based adhesives), and benzine, and dyes belong to this group. Everybody knows, that they can be “sniffed”, e.g. inhaled, but not everybody knows that follows this whim.

Volatile substances *per se* do not belong to the group of drugs, the same is valid for nicotine and alcohol. The intoxicant effect of volatile substances is only then possible, if the sniffed amount of substance is very high (compared to other types of real drugs). Surely everyone of us many times felt the smell of benzine or acetone, but never felt drunk. But exactly due to the fact, that the high amount of the substance is needed, these substances are very dangerous.

Volatile substances are able to damage every organ and tissue in human body. Their toxicity is higher than that of any known drugs, sleeping pills and even the ill-famed “crack”.

Volatile substances are often taken by children and preteens. Their retardation is usually clearly seen, especially compared to their counterparts.

Fortunately, substance abuse is not as addictive, as other types of abuse, and the therapy is easier. Consequently the teenagers usually do not abuse substances for long. Those, who nonetheless continues to abuse them, soon becomes mentally impaired.

**Lecture XII. SYMPTOMS OF DRUG ABUSE.
LIFE-THREATENING CONDITIONS AND EMERGENCY CARE.
CRIMINAL LIABILITY FOR DRUG SYNTHESIS, PURCHASE, DEALING
AND ABUSE.**

1. Symptoms of certain drug abuses.

The symptoms specific for certain groups of drugs will be reviewed in the descending order of their popularity among people.

Drug abuse can be suspected during both intoxication and during withdrawal, though withdrawal symptoms are less specific.

2. Cannabis

The most often seen addiction is the cannabis addiction. Cannabis is usually smoked, stuffed into cigarettes in the mixture with tobacco.

The symptoms of cannabis intoxication depend greatly on the dose and the overall quantity of consumed drug. Intoxication by low and medium doses is characterized by pupils dilatation, lip, sclera and face reddening. In this intoxicated state the addicts are agile and agitated. They are quick and light-headed in decisions. The speech is often speedy, wordy and hasty. Cannabis and its derivatives are often called “group drug”, because the whole group of addicts shares one mood: if somebody laughs then everyone laughs, somebody cries — everybody cries. If somebody feels danger the whole group immediately panics. Or it can well be a feckless gaiety just apropos of nothing of silly thing. But the gaiety can immediately turn into peevishness or aggression. A characteristic trait of cannabis intoxication is voracious, canine appetite. During intoxication a teenager can easily eat a full pot of soup or several loaves of bread.

If the dose was high, the face can turn pale, the pupils become as small as pinholes, lips get dried. The addict is usually apathetic, inhibited, thoughtful. His speech is usually blurred. If asked he answers with delays, sometimes off the mark, curtly. In some cases a specific cannabis smell can be felt. His movements are usually non-coordinated and sweeping, space orientation is impaired. In this state addicts usually try to seclude themselves, so that nobody could disturb them or bother with conversations and requests.

Intoxication is followed by withdrawal, “hang-over”. This state is similar to alcoholic hang-over manifesting in the form of apathy, indisposition, sometimes dizziness. The addicts are touchy, choleric, maudlin, capricious. The higher is the dose taken the worse is the fatigue after intoxication. Abstinence is characterized by constraint, anxiety, insomnia. The addicts suffer from chill, cold sweat, acute pains in bones. Sometimes psychoses with so-called “pseudohallucinations” (typical for schizophrenia patients) can manifest.

3. Opiates

These are the signs of opiate intoxication:

1. Unusual drowsiness. If the intoxicated is left alone, he or she starts to fall asleep and to nod, taking long naps and waking up. If addressed they keep the conversation as if they were not sleeping.
2. Speech is usually slowed and drawled, addicts often start to speak on the topic already discussed and closed and tend to repeat several times what they are saying. Alternatively, the addicted person can be very lively, witty and livable.
3. Addicts are amiable, easy, compliant and obliging.

4. They can forget about the lighted cigarette in their hand and drop it or burn the hand.
5. They tend to seclude themselves, preferably in a separate room, switching on the TV-set there and falling asleep. Sometimes contrarily, they try to be in the public eye despite possible repugnance, very obtrusive and importunate.
6. The pupils are abnormally pinned and do not dilate in darkness, therefore the acuity of vision dramatically decreases in twilight. The skin is pale, dry and warm.
7. The sensitivity to pain is decreased, they can get burned by cigarette or hot frying pan without feeling any pain.
8. It is difficult to make them go to bed, they are up until 2 or 4 am.

This state lasts for no longer than 8-12 hours, sometimes only for 4-5 hours. It is followed by withdrawal.

During withdrawal the addicts are anxious. They are strained, touchy for no particular reason and nervous. They must find new dose, so they leave home or start to call the dealers and to speak with unfinished, short and enigmatic phrases. "So, how is it going?", "I need it", "Everything ready?" etc. If asked they flare up and hector. They usually try to go away from home.

Not-experienced addicts ("students") without severe physical dependence do not have very pronounced picture of withdrawal. They then can mimic a cold. Light form of opiate withdrawal is really similar to a cold or stomach upset.

The withdrawal starts with sudden pupil dilatation, apathy, indisposition, chill and profuse sweating, bad mood. Addicts wrap warm clothes around themselves, switch on the heaters, even if it is not cold at home. Their noses run, some constantly sneeze. They nauseate, sometimes vomit. Stomach aches, the stool becomes loose. Only those who abuse drugs for very short time or enjoy the support and care from their kith and kin can endure this state, lasting for at least 3-4 days, sometimes even longer. That is why the addicts usually give up and if on the third day the "disease" suddenly gives up it means that the addict just "booted" and now feels best.

The most universal signs of opiate abuse are the following:

1. Sudden and frequent changes in mood, general activity, often irrespectively of the current situation.
2. Abnormal sleep rhythm (go late to bed, rise early).
3. Abnormally pinned pupils.

4. Psychostimulants

We would like to remind you, that psychostimulants include the following more or less widespread drug, as ephedrone, benzedrine, "ecstasy", cocaine, methamphetamine. These substances are quite different chemically, but they lead to similar symptoms and behavioral changes. These changes are the following:

During intoxication the addicts are best characterized by slang word "brisky", they are extremely agitated, quick in decisions and deeds. The movements are jerky and abrupt. They try to accomplish all possible tasks, they can not wait even a minute. From time to time they start to pick up things as if they were going to leave, though they rarely manage to really get off. They speak quickly, jumping from one subject to another. They change their mind every minute and never manage to accomplish what they start. The pupils are dilated, the skin is dry, the pulse is accelerated and (if measured) the blood pressure is elevated.

If the addict has enough money or drugs, the intoxication can last for several days. During all this time the addicts do not sleep. After such a long sleep deprivation they have a characteristic look.

Intoxication then goes to the next phase, the addicts become flat, slow and touchy. They feel depressed, but in the same time are anxious and alerted, startle if hear loud or sometime

even soft sounds. This clinical picture is typical for those, who are addicted only for relatively short period of time. Those, who abuse drugs regularly, can develop intimidating hallucination and delusion of persecution. The skin is pale, damp with sweat, the coordination is impaired, movements are uncertain. Pulse rate is usually accelerated.

Those addicts, who abuse ephedrone or ephedrine (which remains one of the most widespread psychostimulants) often have smooth, somewhat edematous crimson tongue.

As regards “ecstasy”: because its narcotic effect is somewhat weaker than that of ephedrone, benzedrine or cocaine and the “ecstasy”-tablets are quite expensive (so can hardly be bought in numbers), the intoxication picture will not be so characteristic as in case of other psychostimulants. Holland became the main vendor and manufacturer of ecstasy in the last years. These are tablets, containing 120 mg of 3,4-methylenedioxy-N-methylamphetamine (MDMA) each, sometimes together with marijuana and rarely also cocaine. Ecstasy is usually taken by those, who would like to dance on a disco all the night long. These tablets, which are distributed in clubs, usually have different colors and pictures on their coating, the last fad are the tablets in the form of a bunny. These tablets mainly evoke the following feelings: hunger for movements, sex, euphoria. The effect lasts for 3 to 8 hours. The death can be due to water depletion or heart arrest during the dance. To avoid this one should make short breaks every 40-60 minutes, drink more water, and dance without stimulants.

5. Sleeping pills

Sleeping pills comprise the large group of drugs, clinical picture is quite universal and resembles the clinical picture of alcoholic intoxication with the exception that there are no alcohol vapours.

Generally the clinical picture depends on the consumed dose. Low doses usually have very vague symptoms and can not be determined with certainty. Therefore we describe here the clinical picture of a frank intoxication. The intoxication is usually characterized by perceptive loss (in psychiatry this phenomenon is called “torpor”), transient inhibition of thinking abilities and loss of moral values. This loss manifests as sassy and tactless behavior, impoliteness, hasty and frivolous decisions. Unlike other drug intoxications, on intoxication with sleeping pills the addicts are often aggressive and often show hackles.

The pupils are usually dilated. Unlike in case of alcohol intoxication the skin is usually pale, pulse rate is accelerated, coordination is significantly impaired: the movements are sweeping, excessive and clumsy. Their attention is not constant and they quickly hop from one topic to another. The speech is slurred, blurred and excessively loud.

This state lasts for 2-4 hours and known as excitement stage.

Then the addicts get apathetic, drowsy and finally drop asleep. The sleep is usually rugged, with heavy snoring, similar to alcohol-induced sleeps. On wake-up they suffer of headache, general fatigue and indisposition. They are usually depressed, irritable and moody.

6. Volatile substances.

The group of volatile substances is constituted by different solvents, resin-based glue, benzin, acetone etc. They are not drugs by themselves, but are extremely dangerous for physical and mental health.

The intoxication by volatile substances manifests very similarly to alcohol intoxication. There are only subtle differences, which we enumerate below:

1. The intoxication by volatile substances can be suspected, if addicts are in the age between 10 and 14 years (though sometimes “occupational” addiction is seen in drivers, house painters and patients with other occupations dealing with hazardous chemical substances)

2. Teenagers intoxicated with low dose of volatile substances usually behave extremely brassily and loudly: they speak loudly; hoot with laughter; scuffle;
3. There are no alcohol vapors, but sometimes a subtle scent of solvent, acetone or benzine can be smelled, coming from their hairs or clothes.
4. Systematic abuse of volatile substances is usually noticed by relatives, who see the significant mental retardation, sluggish reasoning, worsening of school notes and behavioral problems. This is often noticed only in advanced phase, because these changes are very gradual and usually overseen even by closely living relatives.
5. Systematic abuse of volatile substances leads to facial changes: the skin gets earth shade, the bridge is edematous, hairs get dry and brittle.

7. Life-threatening conditions and emergency care.

Complication of regular drug abuse usually manifest as life-threatening conditions, which require urgent medical intervention. Every addict can develop these conditions, the longer is the addiction, the higher is the risk of their development.

a) Most often complications

What can one do in order to recognize these complication and to help?

The most efficient help one can do is to carry the patient immediately to health care professionals (the easiest way is just to call an ambulance). Usually there are special health teams to deal with such complications.

b) Drug overdose.

Drug overdose is the main reason for developing of life-threatening conditions. This complications is most often in case of opiate addiction (since it is the most widespread addiction nowadays), though ephedrone and cocaine addiction are not less dangerous.

Opiate overdoses directly leads to respiratory arrest, no indirect mechanisms are involved here. The respiratory arrest does not happen all of a sudden; it usually develops over time with breathing becoming less deep and slowing down. Exteriorly it looks as if the addict is just sleeping very deeply. The skin is usually pale, cold by feel, lips, fingertips and ear tips get cyanotic.

How can one recognize the respiratory arrest? The best way is to listen to the breathing. The ear should be placed near the addict's face. The correct breathing when asleep must be rhythmic and deep, with breathing rate not less than 12 times per minute. If you hear, that

1. The addict does not breath at all during one minute.
2. The addict is breathing less than 10 times or more than 30 times per minute;
3. His breathing is arrhythmic, with 30-60 sec pauses followed by soughing;
4. The breathing is very rare and is hardly heard during 10 minutes or more;
5. The breathing is accompanied by gurgling;

- this means, that the adduct needs urgent medical aid and you should call an ambulance.

If you revealed a sleeping addict with rare and shallow breathing, you should immediately start to shake and to slap him. If as a result of your efforts he wakes up, sits up or springs to his feet and starts to scold you then everything is ok. You can scold him in reply and calm down. If he does not wake up, or just can not wake up completely, if he remains apathetic, **immediate call an ambulance**. It is recommended to beg somebody to call an ambulance and to keep shaking and slapping the addict. If he answers something try to make him walk, do not stop talking to him until the ambulance is there.

If despite all your efforts he does not react or can not reply something, immediately start the mouth-to-mouth ventilation (colloquially called "kiss of life"). This is not something

complicated, but it requires considerable physical efforts, so try to have a healthy and strong male do this.

Overdose of psychostimulants (ephedrone, benzedrine, cocaine) is dangerous not only due to development of pathologic hallucinatory delirium. These substances can directly cause severe abnormalities of heartbeat rate (in the following way: tachycardia → ciliary arrhythmia → ventricular fibrillation → **heart arrest**). Ventricular fibrillation is accompanied by respiratory arrest. In this case the respiratory arrest occurs suddenly, compared to developing respiratory arrest in case of opiate overdose.

So, if you diagnose a respiratory arrest you should immediately feel the pulse of carotid artery (it is usually felt on the front part of neck, somewhat below the lower jaw angle, try to feel your own pulse and compare). Simultaneous heart and breathing arrests are called “**clinical death**”. In this case besides calling an ambulance you should also start the complex of urgent reanimation – artificial mouth-to-mouth ventilation and closed-chest cardiac massage.

These arrangements can last for quite a long time. If you are not sure that the addict is breathing normally keep doing them until the ambulance comes. Do not slack off! In manual on reanimation they write that these arrangements can sustain life for more than 30 minutes.

Further complication is **sepsis**, or blood poisoning. Before we describe its symptoms we would like to show its development.

As we mention above, addicts unpreventably develop immune deficiency, e.g. the ability to resist an infection. Practically it means, that they easily (and quite often) develop various purulent infections. They are especially characteristic for those, who inject drugs intravenously. Needles used for injections are rarely sterile, the injection place is never antiseptized, and the drug solution itself is far from sterile. Thereby disease-producing bacteria invade various tissues, causing following complications:

- **thrombophlebitis** is an inflammatory process inside a vein. Damaged internal vein wall leads to formation of blood thrombus containing microorganisms. These microorganisms start to proliferate in these optimal conditions. This results in reducing of blood outflow through this vein and consequently the arm (or leg) gets swollen. Because the swelling is accompanied by inflammation, the limb also gets red and hot by feel. Skin reddening propagates along the vein. If the infection is not treated adequately, the infection is disseminating along the blood vessels, that ultimately leads to sepsis. Another danger of thrombophlebitis is the damage of femoral vein, which can require leg amputation. This vein is the only outflow vein in leg and the complete arrest of blood circulation in this vein leads to necrosis (*death*) of lower limb.
- **abscess** is an enclosed purulent infection. The bacteria, which manage to get under the skin, start to proliferate rapidly and unopposedly. They “digest” the tissues and lead to formation of a “sack” filled with pus. Exteriorly the abscess looks like a dolorous, ruby and edematous area of skin in the place of drug injection. The abscess often leads to fever. “Sack” bursting into deeper tissues can lead to phlegmona, if it floods out into a blood vessel it causes sepsis.
- **phlegmona** is almost the same as abscess is, but it is not confined to a “sack”, the pus propagates freely along the intramuscular spaces. Exteriorly it looks similar to an abscess, but it is not confined to a certain area, but rather propagates over considerable part of limb. As an abscess it has all manifestations of an inflammation: edema, fever, impaired functioning of the extremity (*functia lesa*). Its dangers is not only sepsis, but also purulent destruction of nerves, vessels, muscles, bones and everything on its way.

As you see, every purulent inflammation can lead to sepsis. Sepsis is very severe and dangerous state, which often ends lethally if not treated, treated at home and even if treated in a hospital. **Its (sepsis’) symptoms** are pronounced fatigue, fever heat, which quickly alternates

from normal to 39,5 °C and higher, profuse sweating, low blood pressure. An optional symptom is skin blotching. Usually the “entry gate” of septic infection are the places where initial inflammations, e.g. thrombophebitis, phlegmone or abscess, started.

There is another complication, experienced by almost every addict with regular drug abuse. On addicts’ slang it is called “shivering” or “quivering”. In a medical literature it is called “hyperthermic reaction” or hyperthermia. Hyperthermia is called by large amount of microorganisms, which invade blood together with drug solution. It means, that in case of hyperthermia the sepsis can (in rare occasions) develop instantly, without initial thrombophlebitis, abscess or phlegmon.

If the addict tells you, that immediately after drug injection he felt not well and developed shakings, indisposition, fatigue, joint pains, nausea, headache, it means that he injected low-quality drug solution and he is suffering of **hyperthermic reaction**.

This is perhaps the only situation, when an immediate injection of habitual drug in sufficient dose is vitally indicated, because developing hyperthermia can lead not only to sepsis, but also to severe damage of heart and kidneys. Drug injection should cope these complications. But do not fall for possible simulation; the fever must be above 38 °C. And be cautious, if the addict discovers that he can thereby get drugs from you, he can start to use that up. So, take into account, that hyperthermia rarely happens two times in a row, and it is very improbable that it develops weekly. If the situation is not so critical, you may try to give him aspirin or analgin with tavegyl. Alternatively intravenous injection of antibiotics together with steroid hormones (for example prednisolone) can be used to cope the overdose, but this can be done only in a hospital.

Hyperthermia is usually short, especially if coped. If the suspected hyperthermia lasts for more than 6 hours and the addict does not get better during 6 hours, the ambulance should be immediately called.

Pneumonia in addicted people is characterized by rapid development and severe course. It is often complicated by pulmonary edema, which is one of the most dangerous life-threatening conditions. Besides, the risk of tuberculosis is very high in these patients. Cough with fever in addicted people should be carefully investigated. Due to compromised immunity these cough and fever can quickly turn into serious disease.

8. Criminal liability for drug synthesis, purchase, dealing and abuse.

In Russia all illegal drug operations (synthesis, purchase, storage, transportation, shipment and marketing) are prosecuted under criminal law. There is no way to abuse drugs legally. The new criminal code in Russia has several assets which strictly prohibit the above-mentioned operations.

In USA the criminal law also lists different types of criminal punishment for drug abuse.

21 USC 13.I.D § 841 states:

§ 841. Prohibited acts A

(a) Unlawful acts

Except as authorized by this subchapter, it shall be unlawful for any person knowingly or intentionally—

(1) to manufacture, distribute, or dispense, or possess with intent to manufacture, distribute, or dispense, a controlled substance; or

(2) to create, distribute, or dispense, or possess with intent to distribute or dispense, a counterfeit substance.

(b) Penalties

Except as otherwise provided in section 849, 859, 860, or 861 of this title, any person who violates subsection (a) of this section shall be sentenced as follows:

(1)

(A) In the case of a violation of subsection (a) of this section involving—

(i) 1 kilogram or more of a mixture or substance containing a detectable amount of heroin;

(ii) 5 kilograms or more of a mixture or substance containing a detectable amount of—

(I) coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed;

(II) cocaine, its salts, optical and geometric isomers, and salts of isomers;

(III) ecgonine, its derivatives, their salts, isomers, and salts of isomers; or

(IV) any compound, mixture, or preparation which contains any quantity of any of the substances referred to in subclauses (I) through (III);

(iii) 50 grams or more of a mixture or substance described in clause (ii) which contains cocaine base;

(iv) 100 grams or more of phencyclidine (PCP) or 1 kilogram or more of a mixture or substance containing a detectable amount of phencyclidine (PCP);

(v) 10 grams or more of a mixture or substance containing a detectable amount of lysergic acid diethylamide (LSD);

(vi) 400 grams or more of a mixture or substance containing a detectable amount of N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide or 100 grams or more of a mixture or substance containing a detectable amount of any analogue of N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide;

(vii) 1000 kilograms or more of a mixture or substance containing a detectable amount of marihuana, or 1,000 or more marihuana plants regardless of weight; or

(viii) 50 grams or more of methamphetamine, its salts, isomers, and salts of its isomers or 500 grams or more of a mixture or substance containing a detectable amount of methamphetamine, its salts, isomers, or salts of its isomers;

such person shall be sentenced to a term of imprisonment which may not be less than 10 years or more than life and if death or serious bodily injury results from the use of such substance shall be not less than 20 years or more than life, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$4,000,000 if the defendant is an individual or \$10,000,000 if the defendant is other than an individual, or both. If any person commits such a violation after a prior conviction for a felony drug offense has become final, such person shall be sentenced to a term of imprisonment which may not be less than 20 years and not more than life imprisonment and if death or serious bodily injury results from the use of such substance shall be sentenced to life imprisonment, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$8,000,000 if the

defendant is an individual or \$20,000,000 if the defendant is other than an individual, or both. If any person commits a violation of this subparagraph or of section 849, 859, 860, or 861 of this title after two or more prior convictions for a felony drug offense have become final, such person shall be sentenced to a mandatory term of life imprisonment without release and fined in accordance with the preceding sentence. Notwithstanding section 3583 of title 18, any sentence under this subparagraph shall, in the absence of such a prior conviction, impose a term of supervised release of at least 5 years in addition to such term of imprisonment and shall, if there was such a prior conviction, impose a term of supervised release of at least 10 years in addition to such term of imprisonment. Notwithstanding any other provision of law, the court shall not place on probation or suspend the sentence of any person sentenced under this subparagraph. No person sentenced under this subparagraph shall be eligible for parole during the term of imprisonment imposed therein.

(B) In the case of a violation of subsection (a) of this section involving—

(i) 100 grams or more of a mixture or substance containing a detectable amount of heroin;

(ii) 500 grams or more of a mixture or substance containing a detectable amount of—

(I) coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed;

(II) cocaine, its salts, optical and geometric isomers, and salts of isomers;

(III) ecgonine, its derivatives, their salts, isomers, and salts of isomers; or

(IV) any compound, mixture, or preparation which contains any quantity of any of the substances referred to in subclauses (I) through (III);

(iii) 5 grams or more of a mixture or substance described in clause (ii) which contains cocaine base;

(iv) 10 grams or more of phencyclidine (PCP) or 100 grams or more of a mixture or substance containing a detectable amount of phencyclidine (PCP);

(v) 1 gram or more of a mixture or substance containing a detectable amount of lysergic acid diethylamide (LSD);

(vi) 40 grams or more of a mixture or substance containing a detectable amount of N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide or 10 grams or more of a mixture or substance containing a detectable amount of any analogue of N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide;

(vii) 100 kilograms or more of a mixture or substance containing a detectable amount of marihuana, or 100 or more marihuana plants regardless of weight; or

(viii) 5 grams or more of methamphetamine, its salts, isomers, and salts of its isomers or 50 grams or more of a mixture or substance containing a detectable amount of methamphetamine, its salts, isomers, or salts of its isomers;

such person shall be sentenced to a term of imprisonment which may not be less than 5 years and not more than 40 years and if death or serious bodily injury results from the use of

such substance shall be not less than 20 years or more than life, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$2,000,000 if the defendant is an individual or \$5,000,000 if the defendant is other than an individual, or both. If any person commits such a violation after a prior conviction for a felony drug offense has become final, such person shall be sentenced to a term of imprisonment which may not be less than 10 years and not more than life imprisonment and if death or serious bodily injury results from the use of such substance shall be sentenced to life imprisonment, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$4,000,000 if the defendant is an individual or \$10,000,000 if the defendant is other than an individual, or both. Notwithstanding section 3583 of title 18, any sentence imposed under this subparagraph shall, in the absence of such a prior conviction, include a term of supervised release of at least 4 years in addition to such term of imprisonment and shall, if there was such a prior conviction, include a term of supervised release of at least 8 years in addition to such term of imprisonment. Notwithstanding any other provision of law, the court shall not place on probation or suspend the sentence of any person sentenced under this subparagraph. No person sentenced under this subparagraph shall be eligible for parole during the term of imprisonment imposed therein.

(C) In the case of a controlled substance in schedule I or II, gamma hydroxybutyric acid (including when scheduled as an approved drug product for purposes of section 3(a)(1)(B) of the Hillary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000), or 1 gram of flunitrazepam, except as provided in subparagraphs (A), (B), and (D), such person shall be sentenced to a term of imprisonment of not more than 20 years and if death or serious bodily injury results from the use of such substance shall be sentenced to a term of imprisonment of not less than twenty years or more than life, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$1,000,000 if the defendant is an individual or \$5,000,000 if the defendant is other than an individual, or both. If any person commits such a violation after a prior conviction for a felony drug offense has become final, such person shall be sentenced to a term of imprisonment of not more than 30 years and if death or serious bodily injury results from the use of such substance shall be sentenced to life imprisonment, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$2,000,000 if the defendant is an individual or \$10,000,000 if the defendant is other than an individual, or both. Notwithstanding section 3583 of title 18, any sentence imposing a term of imprisonment under this paragraph shall, in the absence of such a prior conviction, impose a term of supervised release of at least 3 years in addition to such term of imprisonment and shall, if there was such a prior conviction, impose a term of supervised release of at least 6 years in addition to such term of imprisonment. Notwithstanding any other provision of law, the court shall not place on probation or suspend the sentence of any person sentenced under the provisions of this subparagraph which provide for a mandatory term of imprisonment if death or serious bodily injury results, nor shall a person so sentenced be eligible for parole during the term of such a sentence.

(D) In the case of less than 50 kilograms of marihuana, except in the case of 50 or more marihuana plants regardless of weight, 10 kilograms of hashish, or one kilogram of hashish oil or in the case of any

controlled substance in schedule III (other than gamma hydroxybutyric acid), or 30 milligrams of flunitrazepam, such person shall, except as provided in paragraphs (4) and (5) of this subsection, be sentenced to a term of imprisonment of not more than 5 years, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$250,000 if the defendant is an individual or \$1,000,000 if the defendant is other than an individual, or both. If any person commits such a violation after a prior conviction for a felony drug offense has become final, such person shall be sentenced to a term of imprisonment of not more than 10 years, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$500,000 if the defendant is an individual or \$2,000,000 if the defendant is other than an individual, or both. Notwithstanding section 3583 of title 18, any sentence imposing a term of imprisonment under this paragraph shall, in the absence of such a prior conviction, impose a term of supervised release of at least 2 years in addition to such term of imprisonment and shall, if there was such a prior conviction, impose a term of supervised release of at least 4 years in addition to such term of imprisonment.

(2) In the case of a controlled substance in schedule IV, such person shall be sentenced to a term of imprisonment of not more than 3 years, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$250,000 if the defendant is an individual or \$1,000,000 if the defendant is other than an individual, or both. If any person commits such a violation after one or more prior convictions of him for an offense punishable under this paragraph, or for a felony under any other provision of this subchapter or subchapter II of this chapter or other law of a State, the United States, or a foreign country relating to narcotic drugs, marihuana, or depressant or stimulant substances, have become final, such person shall be sentenced to a term of imprisonment of not more than 6 years, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$500,000 if the defendant is an individual or \$2,000,000 if the defendant is other than an individual, or both. Any sentence imposing a term of imprisonment under this paragraph shall, in the absence of such a prior conviction, impose a term of supervised release of at least one year in addition to such term of imprisonment and shall, if there was such a prior conviction, impose a term of supervised release of at least 2 years in addition to such term of imprisonment.

(3) In the case of a controlled substance in schedule V, such person shall be sentenced to a term of imprisonment of not more than one year, a fine not to exceed the greater of that authorized in accordance with the provisions of title 18 or \$100,000 if the defendant is an individual or \$250,000 if the defendant is other than an individual, or both. If any person commits such a violation after one or more convictions of him for an offense punishable under this paragraph, or for a crime under any other provision of this subchapter or subchapter II of this chapter or other law of a State, the United States, or a foreign country relating to narcotic drugs, marihuana, or depressant or stimulant substances, have become final, such person shall be sentenced to a term of imprisonment of not more than 2 years, a fine not to exceed the greater of twice that authorized in accordance with the provisions of title 18 or \$200,000 if the defendant is an individual or \$500,000 if the defendant is other than an individual, or both.

(4) Notwithstanding paragraph (1)(D) of this subsection, any person who violates subsection (a) of this section by distributing a small amount of marihuana for no remuneration shall be treated as provided in section 844 of this title and section 3607 of title 18.

(5) Any person who violates subsection (a) of this section by cultivating a controlled substance on Federal property shall be imprisoned as provided in this subsection and shall be fined any amount not to exceed—

(A) the amount authorized in accordance with this section;

(B) the amount authorized in accordance with the provisions of title 18;

(C) \$500,000 if the defendant is an individual; or

(D) \$1,000,000 if the defendant is other than an individual; or both.

(6) Any person who violates subsection (a) of this section, or attempts to do so, and knowingly or intentionally uses a poison, chemical, or other hazardous substance on Federal land, and, by such use—

(A) creates a serious hazard to humans, wildlife, or domestic animals,

(B) degrades or harms the environment or natural resources, or

(C) pollutes an aquifer, spring, stream, river, or body of water,

shall be fined in accordance with title 18 or imprisoned not more than five years, or both.

(7) Penalties for distribution.—

(A) **In general.**— Whoever, with intent to commit a crime of violence, as defined in section 16 of title 18 (including rape), against an individual, violates subsection (a) of this section by distributing a controlled substance or controlled substance analogue to that individual without that individual's knowledge, shall be imprisoned not more than 20 years and fined in accordance with title 18.

(B) **Definition.**— For purposes of this paragraph, the term “without that individual's knowledge” means that the individual is unaware that a substance with the ability to alter that individual's ability to appraise conduct or to decline participation in or communicate unwillingness to participate in conduct is administered to the individual.

(c) Offenses involving listed chemicals

Any person who knowingly or intentionally—

(1) possesses a listed chemical with intent to manufacture a controlled substance except as authorized by this subchapter;

(2) possesses or distributes a listed chemical knowing, or having reasonable cause to believe, that the listed chemical will be used to manufacture a controlled substance except as authorized by this subchapter; or

(3) with the intent of causing the evasion of the recordkeeping or reporting requirements of section 830 of this title, or the regulations issued under that section, receives or distributes a reportable amount of any listed chemical in units small enough so that the making of records or filing of reports under that section is not required;

shall be fined in accordance with title 18 or imprisoned not more than 20 years in the case of a violation of paragraph (1) or (2) involving a list I chemical or not more than 10 years in the case of a violation of this subsection other than a violation of paragraph (1) or (2) involving a list I chemical, or both.

(d) Boobytraps on Federal property; penalties; “boobytrap” defined

(1) Any person who assembles, maintains, places, or causes to be placed a boobytrap on Federal property where a controlled substance is being manufactured, distributed, or dispensed shall be sentenced to a term of imprisonment for not more than 10 years or fined under title 18, or both.

(2) If any person commits such a violation after 1 or more prior convictions for an offense punishable under this subsection, such person shall be sentenced to a term of imprisonment of not more than 20 years or fined under title 18, or both.

(3) For the purposes of this subsection, the term “boobytrap” means any concealed or camouflaged device designed to cause bodily injury when triggered by any action of any unsuspecting person making contact with the device. Such term includes guns, ammunition, or explosive devices attached to trip wires or other triggering mechanisms, sharpened stakes, and lines or wires with hooks attached.

(e) Ten-year injunction as additional penalty

In addition to any other applicable penalty, any person convicted of a felony violation of this section relating to the receipt, distribution, manufacture, exportation, or importation of a listed chemical may be enjoined from engaging in any transaction involving a listed chemical for not more than ten years.

(f) Wrongful distribution or possession of listed chemicals

(1) Whoever knowingly distributes a listed chemical in violation of this subchapter (other than in violation of a recordkeeping or reporting requirement of section 830 of this title) shall be fined under title 18 or imprisoned not more than 5 years, or both.

(2) Whoever possesses any listed chemical, with knowledge that the recordkeeping or reporting requirements of section 830 of this title have not been adhered to, if, after such knowledge is acquired, such person does not take immediate steps to remedy the violation shall be fined under title 18 or imprisoned not more than one year, or both.

§ 842. Prohibited acts B**(a) Unlawful acts**

It shall be unlawful for any person—

(1) who is subject to the requirements of part C to distribute or dispense a controlled substance in violation of section 829 of this title;

(2) who is a registrant to distribute or dispense a controlled substance not authorized by his registration to another registrant or other authorized person or to manufacture a controlled substance not authorized by his registration;

(3) who is a registrant to distribute a controlled substance in violation of section 825 of this title;

(4) to remove, alter, or obliterate a symbol or label required by section 825 of this title;

(5) to refuse or negligently fail to make, keep, or furnish any record, report, notification, declaration, order or order form, statement, invoice, or information required under this subchapter or subchapter II of this chapter;

(6) to refuse any entry into any premises or inspection authorized by this subchapter or subchapter II of this chapter;

(7) to remove, break, injure, or deface a seal placed upon controlled substances pursuant to section 824 (f) or 881 of this title or to remove or dispose of substances so placed under seal;

(8) to use, to his own advantage, or to reveal, other than to duly authorized officers or employees of the United States, or to the courts when relevant in any judicial proceeding under this subchapter or subchapter II of this chapter, any information acquired in the course of an inspection authorized by this subchapter concerning any method or process which as a trade secret is entitled to protection, or to use to his own advantage or reveal (other than as authorized by section 830 of this title) any information that is confidential under such section;

(9) who is a regulated person to engage in a regulated transaction without obtaining the identification required by 830(a)(3) of this title.

(10) negligently to fail to keep a record or make a report under section 830 of this title; or

(11) to distribute a laboratory supply to a person who uses, or attempts to use, that laboratory supply to manufacture a controlled substance or a listed chemical, in violation of this subchapter or subchapter II of this chapter, with reckless disregard for the illegal uses to which such a laboratory supply will be put.

As used in paragraph (11), the term “laboratory supply” means a listed chemical or any chemical, substance, or item on a special surveillance list published by the Attorney General, which contains chemicals, products, materials, or equipment used in the manufacture of controlled substances and listed chemicals. For purposes of paragraph (11), there is a rebuttable presumption of reckless disregard at trial if the Attorney General notifies a firm in writing that a laboratory supply sold by the firm, or any other person or firm, has been used by a customer of the notified firm, or distributed further by that customer, for the unlawful production of controlled substances or listed chemicals a firm distributes and 2 weeks or more after the notification the notified firm distributes a laboratory supply to the customer.

(b) Manufacture

It shall be unlawful for any person who is a registrant to manufacture a controlled substance in schedule I or II which is—

(1) not expressly authorized by his registration and by a quota assigned to him pursuant to section 826 of this title; or

(2) in excess of a quota assigned to him pursuant to section 826 of this title.

(c) Penalties

(1)

(A) Except as provided in subparagraph (B) of this paragraph and paragraph (2), any person who violates this section shall, with respect to any such violation, be subject to a civil penalty of not more than \$25,000. The district courts of the United States (or, where there is no such court in the case of any territory or possession of the United States, then the court in such territory or possession having the jurisdiction of a district court of the United States in cases arising under

the Constitution and laws of the United States) shall have jurisdiction in accordance with section 1355 of title 28 to enforce this paragraph.

(B) In the case of a violation of paragraph (5) or (10) of subsection (a) of this section, the civil penalty shall not exceed \$10,000.

(2)

(A) If a violation of this section is prosecuted by an information or indictment which alleges that the violation was committed knowingly and the trier of fact specifically finds that the violation was so committed, such person shall, except as otherwise provided in subparagraph (B) of this paragraph, be sentenced to imprisonment of not more than one year or a fine under title 18, or both.

(B) If a violation referred to in subparagraph (A) was committed after one or more prior convictions of the offender for an offense punishable under this paragraph (2), or for a crime under any other provision of this subchapter or subchapter II of this chapter or other law of the United States relating to narcotic drugs, marihuana, or depressant or stimulant substances, have become final, such person shall be sentenced to a term of imprisonment of not more than 2 years, a fine under title 18, or both.

(C) In addition to the penalties set forth elsewhere in this subchapter or subchapter II of this chapter, any business that violates paragraph (11) of subsection (a) of this section shall, with respect to the first such violation, be subject to a civil penalty of not more than \$250,000, but shall not be subject to criminal penalties under this section, and shall, for any succeeding violation, be subject to a civil fine of not more than \$250,000 or double the last previously imposed penalty, whichever is greater.

(3) Except under the conditions specified in paragraph (2) of this subsection, a violation of this section does not constitute a crime, and a judgment for the United States and imposition of a civil penalty pursuant to paragraph (1) shall not give rise to any disability or legal disadvantage based on conviction for a criminal offense.

§ 844. Penalties for simple possession

(a) Unlawful acts; penalties

It shall be unlawful for any person knowingly or intentionally to possess a controlled substance unless such substance was obtained directly, or pursuant to a valid prescription or order, from a practitioner, while acting in the course of his professional practice, or except as otherwise authorized by this subchapter or subchapter II of this chapter. It shall be unlawful for any person knowingly or intentionally to possess any list I chemical obtained pursuant to or under authority of a registration issued to that person under section 823 of this title or section 958 of this title if that registration has been revoked or suspended, if that registration has expired, or if the registrant has ceased to do business in the manner contemplated by his registration. Any person who violates this subsection may be sentenced to a term of imprisonment of not more than 1 year, and shall be fined a minimum of \$1,000, or both, except that if he commits such offense after a prior conviction under this subchapter or subchapter II of this chapter, or a prior conviction for any drug, narcotic, or chemical offense chargeable under the law of any State, has become final, he shall be sentenced to a term of imprisonment for not less than 15 days but not more than 2 years, and shall be fined a minimum of \$2,500,

except, further, that if he commits such offense after two or more prior convictions under this subchapter or subchapter II of this chapter, or two or more prior convictions for any drug, narcotic, or chemical offense chargeable under the law of any State, or a combination of two or more such offenses have become final, he shall be sentenced to a term of imprisonment for not less than 90 days but not more than 3 years, and shall be fined a minimum of \$5,000. Notwithstanding the preceding sentence, a person convicted under this subsection for the possession of a mixture or substance which contains cocaine base shall be imprisoned not less than 5 years and not more than 20 years, and fined a minimum of \$1,000, if the conviction is a first conviction under this subsection and the amount of the mixture or substance exceeds 5 grams, if the conviction is after a prior conviction for the possession of such a mixture or substance under this subsection becomes final and the amount of the mixture or substance exceeds 3 grams, or if the conviction is after 2 or more prior convictions for the possession of such a mixture or substance under this subsection become final and the amount of the mixture or substance exceeds 1 gram. Notwithstanding any penalty provided in this subsection, any person convicted under this subsection for the possession of flunitrazepam shall be imprisoned for not more than 3 years, shall be fined as otherwise provided in this section, or both. The imposition or execution of a minimum sentence required to be imposed under this subsection shall not be suspended or deferred. Further, upon conviction, a person who violates this subsection shall be fined the reasonable costs of the investigation and prosecution of the offense, including the costs of prosecution of an offense as defined in sections 1918 and 1920 of title 28, except that this sentence shall not apply and a fine under this section need not be imposed if the court determines under the provision of title 18 that the defendant lacks the ability to pay.

§ 844a. Civil penalty for possession of small amounts of certain controlled substances

(a) In general

Any individual who knowingly possesses a controlled substance that is listed in section 841 (b)(1)(A) of this title in violation of section 844 of this title in an amount that, as specified by regulation of the Attorney General, is a personal use amount shall be liable to the United States for a civil penalty in an amount not to exceed \$10,000 for each such violation.

(b) Income and net assets

The income and net assets of an individual shall not be relevant to the determination whether to assess a civil penalty under this section or to prosecute the individual criminally. However, in determining the amount of a penalty under this section, the income and net assets of an individual shall be considered.

(c) Prior conviction

A civil penalty may not be assessed under this section if the individual previously was convicted of a Federal or State offense relating to a controlled substance.

(d) Limitation on number of assessments

A civil penalty may not be assessed on an individual under this section on more than two separate occasions.

(e) Assessment

A civil penalty under this section may be assessed by the Attorney General only by an order made on the record after opportunity for a hearing in accordance with section 554 of title 5. The Attorney General shall provide written notice to the

individual who is the subject of the proposed order informing the individual of the opportunity to receive such a hearing with respect to the proposed order. The hearing may be held only if the individual makes a request for the hearing before the expiration of the 30-day period beginning on the date such notice is issued.

(f) Compromise

The Attorney General may compromise, modify, or remit, with or without conditions, any civil penalty imposed under this section.

(g) Judicial review

If the Attorney General issues an order pursuant to subsection (e) of this section after a hearing described in such subsection, the individual who is the subject of the order may, before the expiration of the 30-day period beginning on the date the order is issued, bring a civil action in the appropriate district court of the United States. In such action, the law and the facts of the violation and the assessment of the civil penalty shall be determined de novo, and shall include the right of a trial by jury, the right to counsel, and the right to confront witnesses. The facts of the violation shall be proved beyond a reasonable doubt.

(h) Civil action

If an individual does not request a hearing pursuant to subsection (e) of this section and the Attorney General issues an order pursuant to such subsection, or if an individual does not under subsection (g) of this section seek judicial review of such an order, the Attorney General may commence a civil action in any appropriate district court of the United States for the purpose of recovering the amount assessed and an amount representing interest at a rate computed in accordance with section 1961 of title 28. Such interest shall accrue from the expiration of the 30-day period described in subsection (g) of this section. In such an action, the decision of the Attorney General to issue the order, and the amount of the penalty assessed by the Attorney General, shall not be subject to review.

(i) Limitation

The Attorney General may not under this subsection commence proceeding against an individual after the expiration of the 5-year period beginning on the date on which the individual allegedly violated subsection (a) of this section.

(j) Expungement procedures

The Attorney General shall dismiss the proceedings under this section against an individual upon application of such individual at any time after the expiration of 3 years if—

- (1) the individual has not previously been assessed a civil penalty under this section;
- (2) the individual has paid the assessment;
- (3) the individual has complied with any conditions imposed by the Attorney General;
- (4) the individual has not been convicted of a Federal or State offense relating to a controlled substance; and
- (5) the individual agrees to submit to a drug test, and such test shows the individual to be drug free.

A nonpublic record of a disposition under this subsection shall be retained by the Department of Justice solely for the purpose of determining in any subsequent proceeding whether the person qualified for a civil penalty or expungement under this section. If a record is expunged under this subsection, an individual concerning whom such an expungement has been made shall not be held thereafter under any provision of law to be guilty of perjury, false swearing, or making a false statement by reason of his failure to recite or acknowledge a

proceeding under this section or the results thereof in response to an inquiry made of him for any purpose.

9. Conclusion

Drugs is an enemy, guileful and ruthless. The easiest way to avoid a drug problem is to **never start using them**. You will soon understand that you did it right if you put them up, you will see how they can change people who frivolously abused them.

We would also like to encourage those, who already tried drugs. Do not think that addiction is invincible. It is true, that the ratio of those who permanently put them up is not higher than 40% from all patients finished the therapy. But you always has a hope to escape from the resting 60%.

Yes, it is not easy. It requires time. This is a long way full of stops and recessions. Sure, you will never get back to the state before addiction. But if you are persistent and patient, you can put them up.

PESTICIDES IN MODERN AGRICULTURE.

Lecture XIII. and XIV. WHAT ARE PESTICIDES? MAIN CLASSES AND MODERN ARMORY.

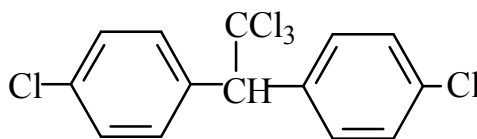
The need for pesticides appeared in the ancient time together with origination of agriculture. As soon as wild animals were domesticated by ancient men and they started to plant crops, to build housings, appeared organisms, who struggled against humans for food and living space – the pests. These are insects and rodents, who ruin the harvest, weeds and unwanted “house animals” – flies, cockroaches, mosquitoes, moths, ticks, ants, bugs and other living beings. It is widely accepted that about a half of the global harvest is ruined by weeds, insects, fungal and viral infections.

How did these ancient men struggle against this pest? The ancient Greek poet Homer mentions “divine and purificatory” smudging with sulfur to repel noxious insects. Sulfur dioxide SO₂, which can be obtained by sulfur burning was probably the first pesticide (from Latin *pestis* – “pest” and *caedo* “to kill”), i.e. the first substance to eliminate pests. Some advice of how to use different substances to eliminate pests and plant diseases were included into their works by ancient Greek philosophers Democritus and Plinius the Senior. Compounds of arsenic and quicksilver were used since the 19th century as pesticides, though their use was quite limited, because they were not only dangerous for pests, but also for men.

First synthetic pesticides were synthesized in 20th century, today more than 1000 different pesticides are routinely used worldwide.

Today more than 70 000 different species of pests are known, they do harm to humans, to domesticated animals, plants and materials. Chemical ways of protection turned out to be the most effective against these pests. In 2002 about 450 g of pesticides were worldwide averagely used on every hectare of farmland. The total production costs of these pesticides were higher than 14 billions USD that is close to the total production costs of fertilizers.

The era of common use of synthetic organic pesticides was triggered in 1939, when the Swiss chemist Paul Hermann Müller (1899-1965) discovered unique insecticide properties of DDT (*in 1948 this discovery was awarded with Nobel Prize in physiology and medicine*) - **dichloro-diphenyl-trichloromethylethane** [IUPAC 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane] which is highly toxic against all insect species and relatively low toxic for humans and other warm-blooded animals.



DDT was produced by chlorobenzol condensation with chloral in presence of concentrated sulfuric acid. The compound was relatively cheap and available.

DDT saved millions of human lives: it was used to eliminate insects – transmitters of many dangerous diseases, including malaria and typhus. The invasions of voracious locust which completely marauded crops were considered plague since ancient times. Plagues of rapacious locust are described in Bible as one of the Ten Plagues of Egypt.

However we should remind you, that in the majority of countries (including Russia) the use of chloroorganic pesticides is strictly prohibited or limited, new achievements in the development of organic chemistry allowed to synthesize more effective and less toxic substitutes.

Armory of pesticides is being completely updated. First of all, newly synthesized pesticides are less toxic and safer for humans and environment. But this is not the only reason. After several treatments with pesticides it loses its efficacy and the population of pests explodes. Domestic flies, for example, developed resistance against DDT already in the second year of its application. This can be explained by the fact, but only those insects, which can survive the treatment can lay eggs and sire. During last 40 years appeared several populations of completely DDT-resistant insects.

The synthesis and industrial production of pesticides today is an ample scientific and research niche. Every year about 50 new pesticides are synthesized. From 10 000 tested compounds on average only one turns out to be suitable for practical application, highly-selective action can be found in one out of 70 000 tested compounds. Nevertheless already in the first year the economical effect is on average 6 times higher than all expenses. Unfortunately as regards pesticide research Russia is not among the most developed countries.

Despite all protective actions the total economical losses in agriculture due to pests are about 20% of the total collected harvest.

Pesticides are chemical compounds to eliminate microorganisms, plants and animals, considered to be harmful or undesired from economical or health care viewpoint.

The protective compounds are subdivided in several groups: insecticides (against insects), miticides (against acari), herbicides (against higher plants), fungicides (against fungi), bactericides (against bacteria), molluscicides (against slugs and snails), nematocides (against nematodes), zoocides (against vertebrates) etc.

To pesticides also belong defoliant (including the ill-famed “Agent Orange”, they cause a premature ageing of leaves leading to artificial leaf fall (defoliation)), dessicants (they cause dehydration of plants and increase their maturation), which facilitate the mechanized harvest of several types of crops, plant growth regulators (auxins, gibberellins, retardants), dye additives against ship fouling.

To the group of pesticides also belong **seed treatment agents**, **repellents** (compounds used to repel insect-pests, mites, mammals and birds, **attractants** (compounds used to attract the arthropods with the aim of their elimination), **chemosterilants** (compounds, which do not kill insects, rodents and mites, but cause to their sterility). There are pesticides showing mixed effects, for example seed treatment agents contain fungicides, bactericides and insecticides. The use of these pesticides helps decrease the labor expenditures for storage and processing.

In some cases the pesticides are classified according to the development phase of pests. For example **ovicides** are poisons, which kill the eggs of insects and mites, **larvicides** kill larvae.

Table 2. Main classes of pesticides

<i>Pesticides</i>		
Insecticides	Fungicides	Herbicides
<p><i>Pyrethroids:</i> Decis Trebon Permethrin Phenvalerate</p> <p><i>Organophosphorus:</i> Carbophos Chlorophos Metaphos Dimethyldichlorvinylphosphate (dichlophos) Diazinone Phozalone</p> <p><i>Carbamates:</i> Carbofuran Dimilin Imidaloprid</p>	<p><i>Triazoles:</i> Bileton Bitan Tilt Topaz</p> <p><i>Morpholines:</i> Corbel Dimetomorph (Acrobat)</p> <p><i>Dimethylanilines:</i> Ridomyl Oxadixyl</p> <p><i>Other derivatives:</i> Polycarbacin Copper chloroxide</p>	<p><i>Sulfonyl urea derivatives:</i> Glin Oust Elai Harmonie</p> <p><i>Derivatives of phenoxypropionic acid</i></p> <p>Fusilad-super</p>

Pesticides belong to various classes of organic and inorganic compounds. The majority of them are organic substances obtained chemically. The most important here are chloroorganic and phosphororganous pesticides, derivatives of carbamic acid, pesticides of plant origin, triazines, urea derivatives. From inorganic compounds of importance are copper and sulfur containing compounds. Pesticides are the base of plant chemical protection, they are the most effective compounds for crop pest control and allow significant decrease of yield losses in agriculture, forestry and carpentry. Their production expenses are paid off in 5-12 times.

Pesticides must comply with following requirements:

1. Being highly toxic against certain pests the pesticide must be low toxic ($LD_{50} > 1000$ mg/kg) for humans, domestic animals and crops, desired insects and microorganisms.
2. The environmental resistance of the compound must be high (up to 6 months). Ideally the compound must completely degrade in environment before harvesting.
3. Particular attention should be paid to possible effects of pesticides on the genetic material of humans, animals, desired insects and plants and carcinogenic activity.

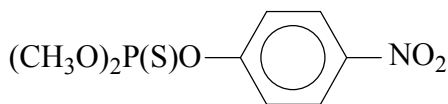
Several representatives of main pesticide classes are given in the Table 2.

1. Modern armory of pesticides. Organophosphorus compounds.

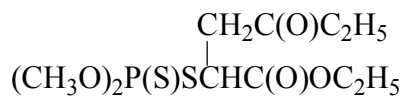
Chloroorganic pesticides were supplanted by organophosphorus compounds: the derivatives of phosphoric, thiophosphoric, dithiophosphoric and phosphonicacids. The compounds of this class act as phosphorilating agents, which phosphorilate the pest enzymes (acetylcholinesterase), impairing his vital functions. Their common drawback is the toxicity for warm-blooded animals, though for the majority of them the toxicity is quite low. The replacement of one oxygen atom through the atom of sulfur in the group of phosphoric acid usually reduces toxicity, but not the insecticide activity.

All numerous derivatives of this class are rapidly deactivated in environment due to hydrolysis and oxidation. The metabolic processes are also quite quick. Below on the figure we should some widely used organophosphorus insecticides—ethers of thio- and dithiophosphoric, phosphoric and phosphonic acids.

For example, *Metaphos* ($LD_{50} = 20$ mg/kg) is a contact insecticide and acaricide with relatively high toxicity, *Carbophos* ($LD_{50} = 1200$ mg/kg) eliminates the pests of fruit trees and vegetables, as well as mosquitoes. *Dichlophos* ($LD_{50} = 65$ mg/kg) is a compound used against domestic insects. *Chlorophos* ($LD_{50} = 650$ mg/kg) is a contact insecticide with middle toxicity. These and similar compounds are highly toxic not only for insects, but also for warm-blooded animals and humans.



Metaphos



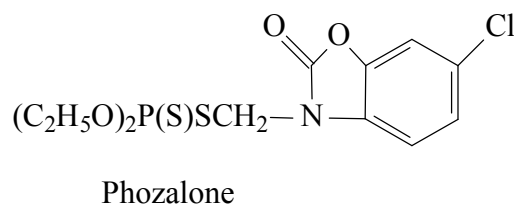
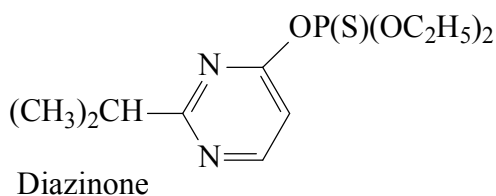
Carbophos



Chlorophos



Dichlophos



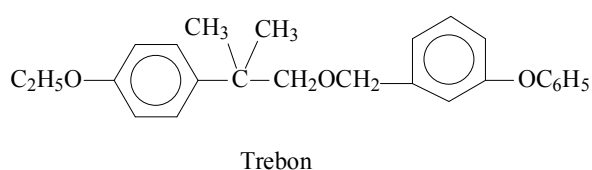
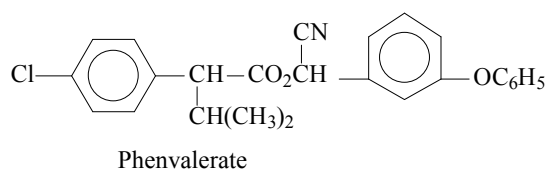
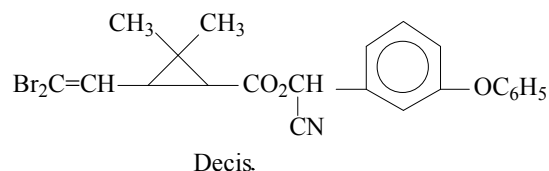
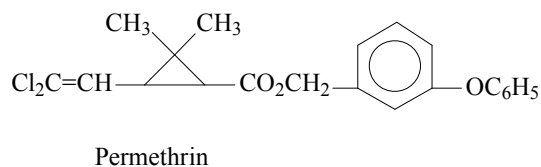
“Close relatives” of popular insecticides chlorophos, metaphos, carbophos and dichlophos, as we will see later, were until recently used as chemical warfare agents in many countries (sarin, somane, tabun, V-gas).

It has been known since ancient time that some plants, for example certain species of *Pyrethrum* which are poisonous for insects are harmless for humans. They were widely used as natural pesticides. Thereby basing on *pyrethrins*, compounds found in feverfew (*pyrethrum*), a new class of their synthetic analogues (insecticides) called *pyrethroids* was synthesized. They are effective in small amounts and rapidly degrade in environment.

Pyrethrins are the only group of insecticides for those no resistance was reported, although they are in use since 1830! Besides, pyrethrins are almost non-toxic for warm-blooded animals. Unfortunately, they are very unstable and can not be stored for long time.

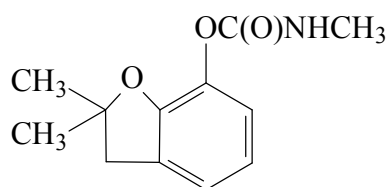
Chemical properties of pyrethrins were thoroughly investigated by outstanding organic chemists of 20th century Hermann Staudinger (1881-1965, Germany) Nobel Prize Winner (1953) and Lavoslav (Leopold) Ružička (1887-1976, Croatia), a Nobel Prize Winner (1939) either.

Pyrethroids are produced industrially since 80ies of 20th century. Insecticides against insects-pests turned out to be the most stable during storage and resistant against solar radiation, their activity and efficacy is close to their natural analogues.



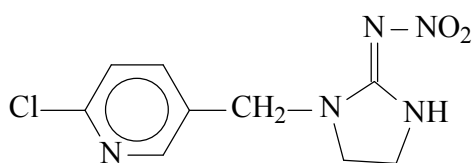
Today they are widely used for garden treatment. Wool socks are usually impregnated with these substances to protect them against moth. The global production of pyrethroids rapidly grows. They are significantly less toxic than organophosphorus compounds. The only disadvantage of pyrethroids is their high production costs.

2. Derivatives of carbamic acid

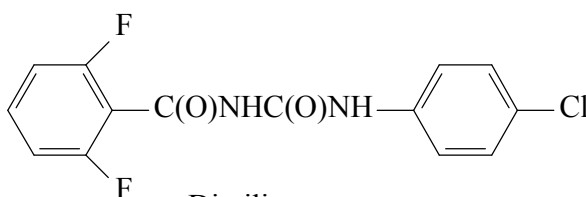


Furadan

This is relatively new group of *insecticides*, including a systemic insecticide imidaloprid and hormonal insecticide dimilin

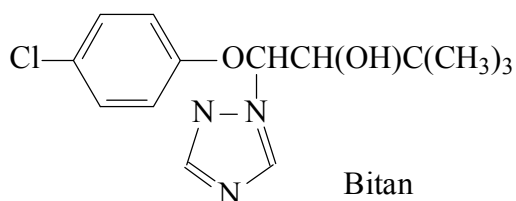


Imidaloprid

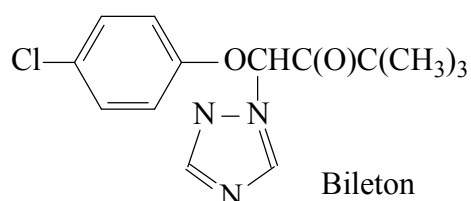


Dimilin

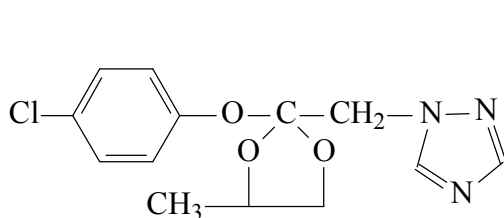
From lately developed fungicides with systemic action we would like to mention the *derivatives of triazole*



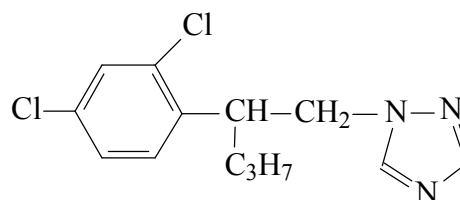
Bitan



Bileton

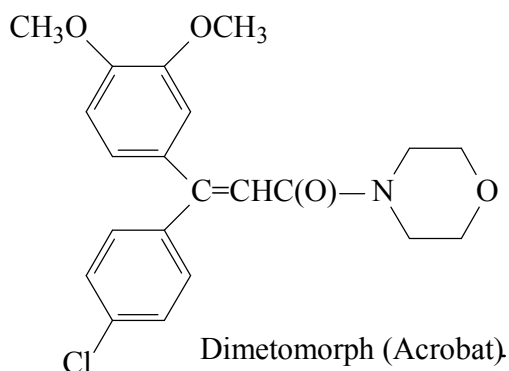


Tilt

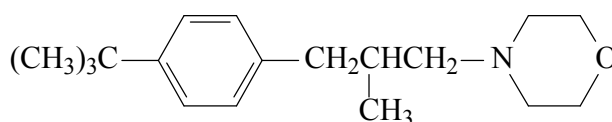


Topaz

3. Derivatives of morpholine

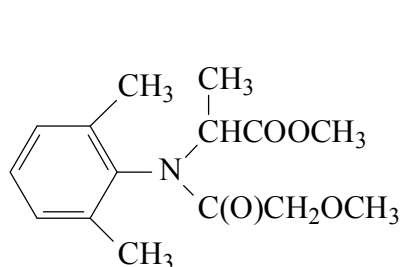


Dimetomorph (Acrobat)

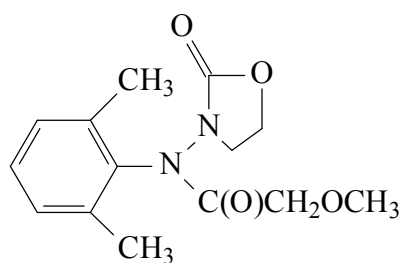


Corbel

And derivatives of **dimethylaniline**:



Ridomyl

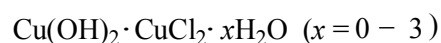


Oxadixyl

Fighting against resistant strains of fungi the mixtures of above-mentioned substances with contact **fungicides**, for example polycarbacin, copper chloroxide.

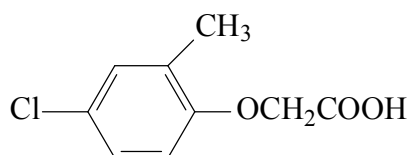


Polycarbacin

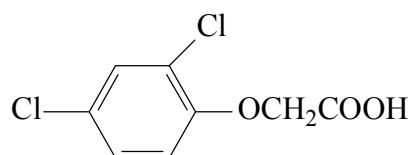


Copper chloroxide

Following **herbicides** are still actual nowadays: the derivatives of chlorophenoxy-acids (2M-4X, 2,4-D) and their mixtures.



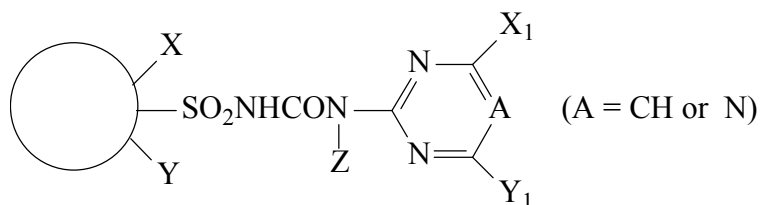
2M-4X



2,4-D

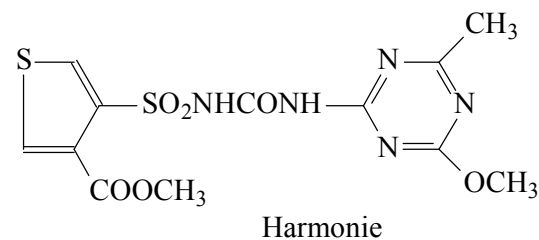
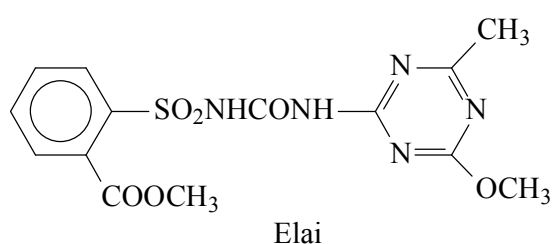
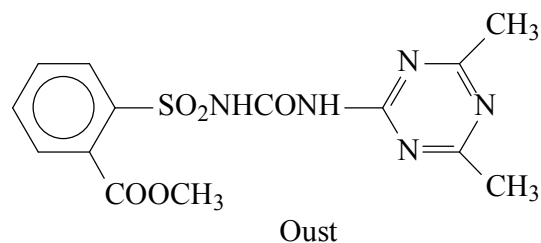
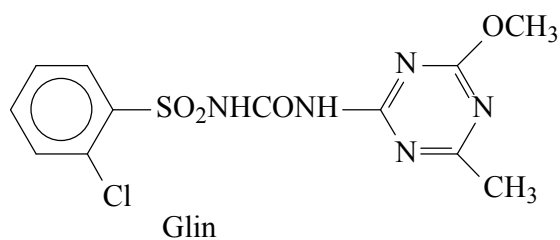
These herbicides, which are used to eliminate unwanted plants (weeds) usually contain small amounts of extremely toxic dioxins, that is why their use is officially prohibited in some countries. Uncontrolled use of them is even more dangerous. Thereupon we would like to mention the grave consequences of the “Agent Orange”, which was used by USA Navy during Vietnam war as a defoliant. It was sprayed from crop-dusters onto Vietnam jungle to cause artificial leaf fall and reveal the guerillas hiding in exuberance of vegetable growth.

Special attention should be paid to a relatively new group of **herbicides**, known under group name “**sulfonylureas**”. The representers of this group are characterized by low consumption rate (about 10 – 50 g/ha) and can be described by the following formula:

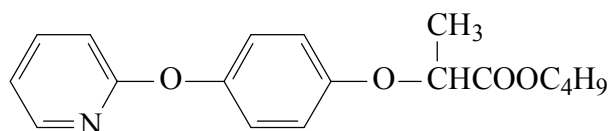


Subtle changes in the formulas of these compounds lead to different selectivity of their action against certain plant species, that is owed to different stability of this compound in tissues of certain plants.

Nowadays some derivatives of sulfonylurea become widely distributed:



From another relatively new group of **herbicides** we can mention the derivatives of phenoxypropionic acid. A characteristic representer of this group is a well-known herbicide used to fight against weeds in sugar beet plantings fusilad-super.



Fusilad-super (R-enantiomer)

From **plant growth regulators** worth to mention is 2-chloroethylphosphonic acid (etephon).



In order to decoy the “harmful” insects and small animals to the places of their mass elimination special substances, called **pheromones** are used. These are chemical substances, produced by endocrine glands (or special endocrine cells) of animals which serve as transmitters of information to the animals of the same species. Pheromones are sexual attractants, alarm agents, collection agents etc.

Humans use speech to exchange information. Animals can also convey a lot of information from one to another using sounds. But this is not the only way of communication. Dogs, cats and other animals communicate using special “labels”, which they leave on plants and other things. That is why dogs when walked muzzle every tree — it gets messages left by other dogs and leaves its own messages.

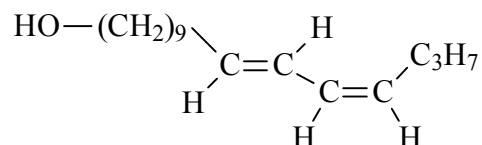
Pheromones are at most important for insects which have a developed chemical “speech”. Pheromones with various effects are known. For example, sexual attractants are the substances, which attract males to females. An ant if in danger releases an alarm pheromone. Other ants in the vicinity rush to him to help and start to produce alarm pheromones on their own. Soon the whole ant-hill is in the combat ready status. The way to forage is paved with tracing pheromones, there are other substances which signal the swarming and other actions.

Insects reveal a marvelous sensitivity towards pheromones. For example, male butterfly of the silkworm detect the sexual pheromone if its concentration in air is about 10^{-12} mg/l. The

champions among insects seem to be cockroaches, which are able to detect the sexual pheromone in the concentration of 10^{-14} mg/l.

It is interesting to compare the olfactory acuity of insects and men. The so-called wine lacton (cyclic ester of tartaric acid, which tincture a special bouquet to wine), studies in 1996, can be smelled by humans in the concentration 10^{-14} mg/l.

According to their chemical structure pheromones are a heterogeneous class of organic compounds. Non-saturated hydrocarbons with one or several olefinic bonds, non-saturated alcohols, aldehydes, acids and other compounds can serve as pheromones. It is important to notice, that biological activity highly depends on molecular geometry, that can be seen on the example of bombycol – the sexual hormone of silkworm.



This is *trans-cis*-hexadecanediene-10,12-ol-1. Interestingly, if the spatial interposition arrangements of substitutes around olefinic bond slightly changes (for example, if we take *cis-cis*-isomer), the compound fails to attract butterflies.

One should remember, that every biologically active substance, used for elimination of “harmful fauna” are almost never used in pure form, but rather serve as bases for wetting powders, emulsion concentrates, crop dusts, solutions, granules, microcapsules, aerosols etc. These products also contain solid or liquid thinners, surface-active agents and sometimes special adjuvants (adherents, anti-oxidants, anti-evaporating agents, densifiers). Every firm market the products under their own generic names, that give rises to many synonyms. Many products contain 2-3 active agents, that increases their efficacy and broadens the spectrum of their effects.

Representers of the main classes of pesticides are shown in the table 2.

According to their **routes of administration** to the body of vermins **pesticides** are classified in the following way:

Enteral -- pesticides, which are administered through mouth and bowels.

Contact – pesticides act through contact with body surface, e.g. through cutaneous covering.

Fumigants – administered in vaporous or gaseous state through respiratory ways

Systemic – easily penetrating into plants and animals, they mostly act on vermins, which feed themselves with plant moistures or animal blood.

Depending on the rate of decomposition in soil pesticides are divided into six groups, with decomposition time:

More than 18 months (chloroorganic compounds, Selenium compounds);

About 18 months (triazine herbicides, pikloram, diuron and some others)

About 12 months (derivatives of haloidbenzoic acids and some amides of aminoacids)

Up to 6 months (nitriles of acids, derivatives of aryloacetic acids, treflan and its analogues, nitrophenoles etc).

Up to 3 months (derivatives of arylcarbaminic, alkylcarbaminic acids; some derivatives of urea and heterocyclic compounds);

Less than 3 months (organic phosphorus compounds).

In agriculture it is preferred to use the compounds which completely decompose during one cropping season, on airfields long-lasting compounds are the agents of choice to fight against ramping.

According to their toxicity for humans and warm-blooded animals pesticides are divided into 4 groups *superpotent*, *high-toxic*, *middle-toxic* and *low-toxic*. LD₅₀ (a dose at which 50% of subjects will die) for pesticides of these groups is respectively less than 50, 50-200, 200-1000 and more than 100 mg/kg. This classification is rather tentative, since the pesticide toxicity for humans and animals depends not only upon the absolute amount of pesticide: some of them have follow-up consequences if subjects are exposed to them for a long time, their other properties, like oncogenic (causing tumors), mutagenic (deteriorating gene material), embryotoxic (affecting the fetus development), teratogenic (leading to congenital deformities), allergenic (hypersensitivity against pesticides) etc.

Mechanisms of action for different classes of pesticides is quite variant and not thoroughly studies yet. For example, organic compounds of phosphorus and esters of alkylcarbaminic acids inhibit acetylcholinesterase of arthropods, derivatives of thiourea block redox processes in insect body. Depending upon the properties of pesticides and their mechanisms of action from 0.2 to 40 kg (usually from 0.5 to 2 kg) of active substance per hectare are needed. In order to evenly distribute such a small amount of pesticides they are used in special preparative form (wetting powders, emulsion concentrates, crop dusts, water solutions, solutions in organic solvents, aerosols, granules), which are introduced in different way (spraying, dusting, fumigation, poison baits, treatment). Preparative form besides pesticide itself also contains adjuncts, solvents and emulsifiers. The most promising are spray products (wetting powders, emulsion concentrates, water and organic solutions), and granules for plant dusting and soil application. Of great interest are solutions in involatile organic solvents used for ultrasmallvolume spraying, the consumption is about 0.5-10 l/hectare here. The crop dusting with pesticides is usually done with terrain vehicles and planes.

By overdosage or overconcentration of pesticides, inappropriate ways and time of their use without paying attention to weather conditions, pesticides can cause plant injury, decrease of pollen vitality and pistils failure. All these can diminish the yield. Crops can be contaminated with pesticides and get unpleasant scent and taste (for example, by using hexachlorane), as well as accumulate them on their surface in a form of poisonous coat dangerous both for animals and humans. If pesticides are used systematically crop pests can develop resistance against them. In order to avoid the “breeding” of new resistant strains of pests broad spectrum of pesticides with similar activity must be used with alternative use of different compounds.

The influence of pesticides on biocenoses is complex and multiform. Especially extensive damage is noted by systematic use of stable high-toxic pesticides (mostly insecticides and miticides). Due to elimination of parasites and harmful insects the population outbreaks of other insects and mites are often observed. For example, massive population outbreak of harvest red mites after DDT treatment that has been observed in many countries including Russia is owed to the elimination of mites predators, and wooly apple aphids population increased due to elimination of their natural parasites *Aphelinus*. The adverse effects of pesticides on humans, bees, bumblebees and other insect pollinators, fishes (if drained into water systems), birds, wild animals, domestic animals, and on environment in general are well known. It is important to thoroughly control the residual quantities of pesticides in food, storage, transportation and usage precautions. These precautions are mandatory for every agency and every person working with pesticides.

Much attention is given to purification, investigation, synthesis and development of new methods of pesticides application, finding new mechanisms of their action, which would be more specific, — sexual attractants (pheromones), feeding repellents, chemosterilants,

substances that mimic juvenile hormone of insects. Administration of juvenile hormone or its analogues on a certain development stage (when the hormone is not produced) leads to impaired and lethal metamorphosis. High specificity of these pesticides seems to allow selective elimination of certain insect species without impact on the whole biocenosis. Pesticides should not be the agents to eliminate pests, but to agents helping to control their population. The least danger for useful insects (entomophagues, pollinators, honeybees) despite the use of pesticides can be reached by presowing treatment of seeds and planting materials with highly selective pesticides which are less toxic for entomophagues than for phitophagues.

Pesticides are introduced into human body mainly through respiratory tract, skin, gastrointestinal tract. The most dangerous are the poisonings occurred during pesticide spraying in enclosed space and by seeds treatment.

Chloroorganic pesticides have a systemic toxic effect on human organism, they usually damage inner organs (liver, kidneys) and nervous system. The symptoms of intoxication are non-specific: general fatigue, dizziness, nausea, conjunctival irritation and irritation of higher respiratory tract.

The majority of organophosphorus pesticides easily penetrate to human organism through skin and have pronounced anticholinesterase effect. The signs of acute intoxication are rather specific here: salivation, myosis, muscular twitching, convulsions. Acute intoxications with pesticides containing quicksilver are characterized by salivation, metallic aftertaste, nausea, sometimes vomiting, diarrhea with slime, headaches, syncopal state. Any type of work with pesticides must be performed only using special individual protective equipment (protective garment and shoes, respirator, gas mask, eye shields etc).

One should not forget that every pesticide decomposes in natural environment during certain time which can be undesirably long in some cases. Several decades of pesticides active use turned into unqualified disaster for every living being. These pesticides are drained into water systems, into World's water and propagated through entire earth globe. For example, unregulated use of DDT allowed detecting it in the liver of penguins (along the food chain through fishes and seaweed). They accumulate in living organisms, many (lipophilic) pesticides can enter human organism via gastrointestinal tract with ordinary food and get accumulated in concentrations dangerous for life and health. Increases concentration of pesticides (and other noxious substances) in fish brought about the death of several waterfowl populations.

That is why today in many countries the use of pesticides is strictly regulated by appropriate institutions and is under government control. Acute and chronic toxicity, long-term effects and the maximal allowed residual quantities of pesticides in food are constantly monitored.

Therefore a logical question rises: do we need pesticides at all? Unfortunately we do, we can not put up using chemical agents in agriculture so far otherwise the crop losses will be too high. But the use of these quite dangerous substances must be very prudent and only in the cases where it is really necessary. Else pesticide can turn from intime friend to treacherous enemy.

Lecture XV. METABOLIC PATHWAYS OF PESTICIDES TRANSFORMATION IN NATURAL ENVIRONMENT AND LIVING BEINGS

We would like to investigate the metabolism of pesticides in natural environment and to analyse their biochemical transformation from original substances to their decomposition products.

1. Organophosphorus pesticides

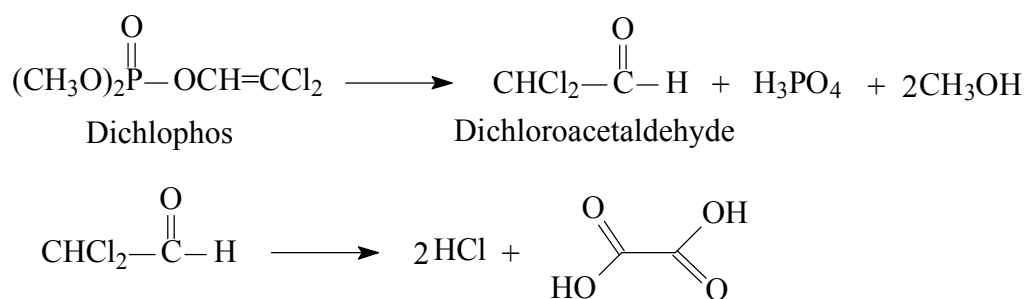
From all modern pesticides organophosphorus compounds are the most used ones, they constitute the groups of insecticides, miticides, nematocides, fungicides, herbicides and growth-regulating chemicals. These are phosphoric, thiophosphoric, dithiophosphoric and phosphonic acids, their salts, complex esters, amides of these acids and other derivatives whose ester parts contain molecules of different substituents.

From esters of phosphoric acids most often used are Dichlophos and chlorpheninfos, esters of thiophosphoric acids – terbuphos, phozalone, carbophos (melathion) and others, from phosphonates — chlorphos, glihosat.

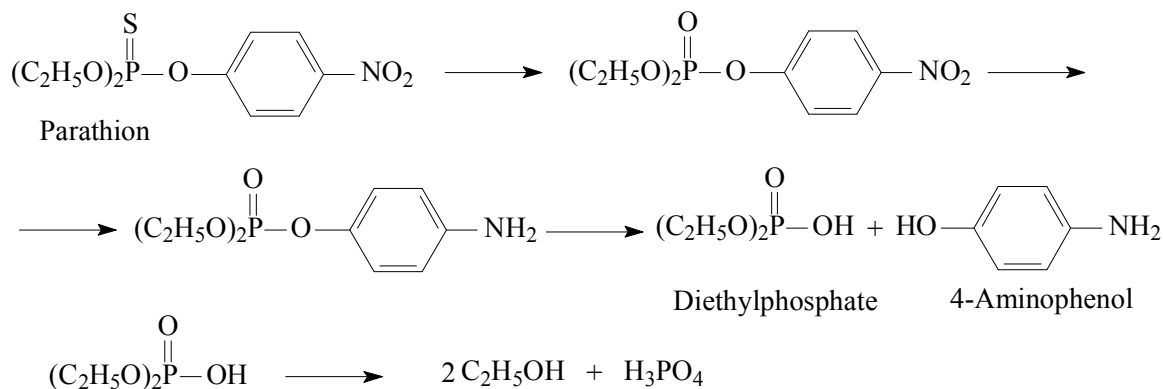
Metabolic products of these compounds are phosphoric acid and substances formed by degradation of ester parts. In natural environment they can undergo following transformations: oxidation of thio-forms into oxo-forms, sulfides to sulfoxides and sulfones with subsequent transformation into sulfoacids, aliphatic parts of molecules turn into hydroxyl and carboxyl groups, the reduction of nitro groups into amino groups, hydrolysis of esters, interaction with the enzyme glutathiontransferase, formation of carbohydrates interaction products in plants, glucuronic and humic acids in soil and sulfates in the organisms of mammals.

Let us take a good look at transformation of most known pesticides from this group.

Dichlophos is a quite unstable substance and easily hydrolyzed with water at low temperature (4-12 °C). Its degradation in living organisms, for example in fish, yields phosphoric acid and dichloroacetaldehyde, which is then hydrolyzed and oxidized into chlorohydric and oxalic acids.



From esters of thiophosphoric acids became common use parathion and metylparathion. The former is more stable (it decomposes in soil during 30-45 days). Methylparathion decomposes twice as fast. Metabolism of parathion in different living beings is deliberately studied:

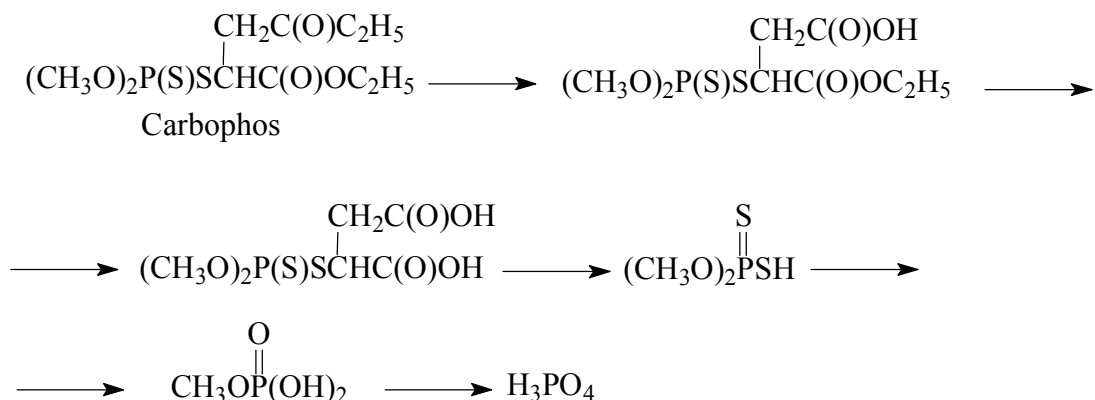


Following enzymes take part in parathion metabolism: oxidases, nitroreductases, phosphatases, aryltransferases, glutathiontransferase. Soil microorganisms use metabolism

products as source of carbon and phosphorus. The end-items of decomposition are carbon dioxide and orthophosphoric acid. Thionic sulfur turns into sulphuric acid or sulfates.

Metabolism of derivatives of dithiophosphoric acids in natural environment depends upon the structure of ester radicals of dithiophosphate. In this respect similar behavior demonstrate carbophos, terbuphos and phozalone. They are characterized by hydrolyzation and oxidation of sulfidic sulfur until sulfoxides and sulfones. Oxidation of thionic sulfur and hydrolysis to phosphoric acid are also possible. The complete decomposition of these compounds in soil happens within 63-120 hours.

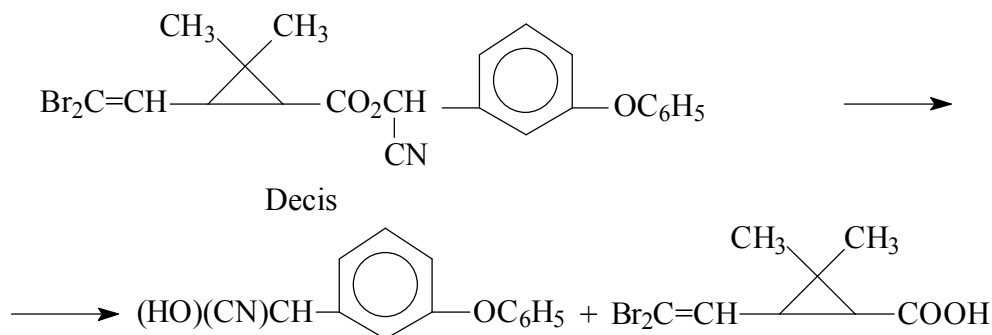
The mostly used contact insecticide is carbophos. It is low-toxic for mammals and decomposes relatively quickly in natural environment via following metabolic stages:

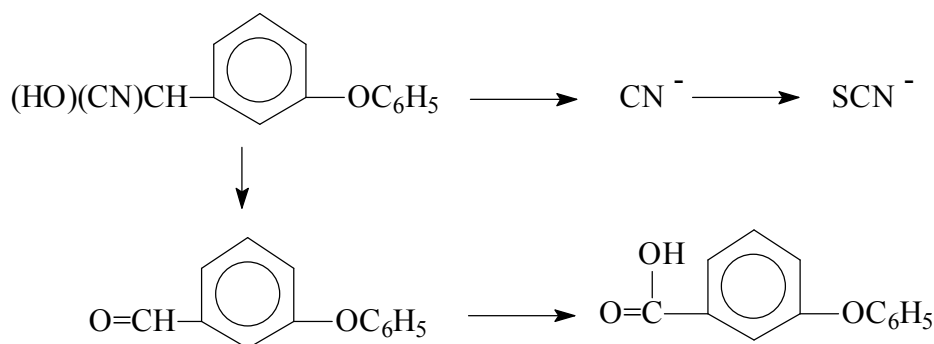


Carbophos decomposition rate in natural environment is quite high and it is rapidly eliminated from plants and animals. For example, it can not be detected anymore in cherry and red currant 6-8 days after treatment.

2. Synthetic pyrethroids

From this group of pesticides only 15 are used as regular pesticides, the most important representers are permethrin, cipermetrin and decis. Pesticides from this group possess moderate toxicity for mammals and birds. They have quite low expenditure rates (10 – 20 g/hectare). Being chemically esters synthetic pyrethroids are relatively easily hydrolyzed, especially in alkaline conditions. The enzymatic degradation in soil is even faster, same applies for enzymes of commensal bacteria enzymes. Temperature increase boosts decomposition. Metabolism of decis happens in the following way:





Pyrethroid decomposition products are well soluble in water, thus rapidly excreted from living organisms with products of vital functions. The decomposition products are less toxic than original substances.

Pyrethroid metabolism in plants leads to formation of conjugates with glucose and other carbohydrates. These conjugates can be involved into the global metabolism of plants.

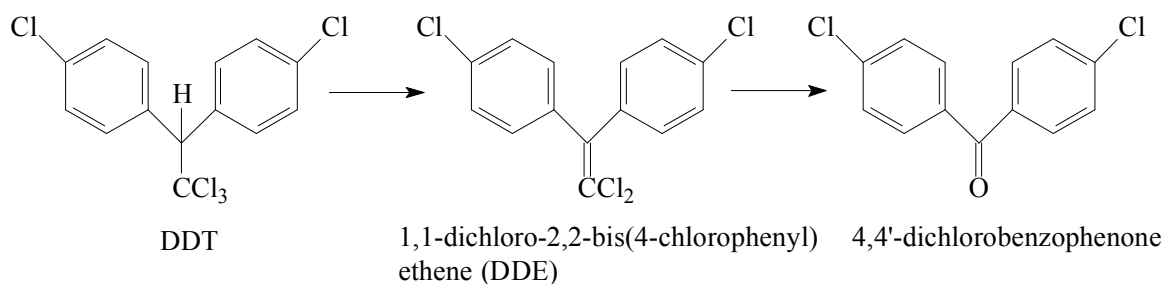
In soil the complete decomposition of pyrethroids until elementary chloro and nitro compounds and carbon dioxide is possible.

3. Chlorohydrocarbons

From chloroorganic insecticides the practical application in agriculture found following compounds: DDT, metoxichlor, hexachlorocyclohexane, aldrin, dieldrin, heptachlor, endrin etc. Let us explore the transformation of the first two compounds.

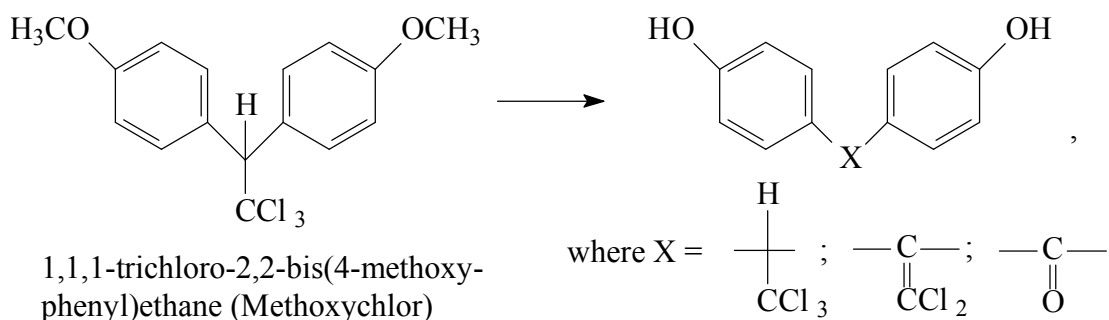
It is known from literature that DDT and products of its degradation virtually can not be eliminated from organism, since they are poorly soluble in water and accumulate in fatty tissue. That is why their concentration in the body of fish is much higher than in water, its habitat, and in the body of a waterfowl eating predominantly fish it can be millions times higher than in water. Thereby DDT along food chains for several decades propagated through entire globe.

These aversive long-term consequences of DDT use made scientists from all around the world investigate the processes of its degradation. It has been shown that transformation of DDT follows the following scheme:



On the first stage the compound is dehydrochlorized, then the resulted product is oxidized in the place of its olefinic bond. Both stages are performed by enzymatic systems in target organisms. None of these three groups contain a hydrophilic groups but only the hydrophobic ones. Thus they accumulate in fatty tissue.

Methoxychlor does not accumulate in mammals. The reason for this is the formation of metabolites with hydrophilic groups.



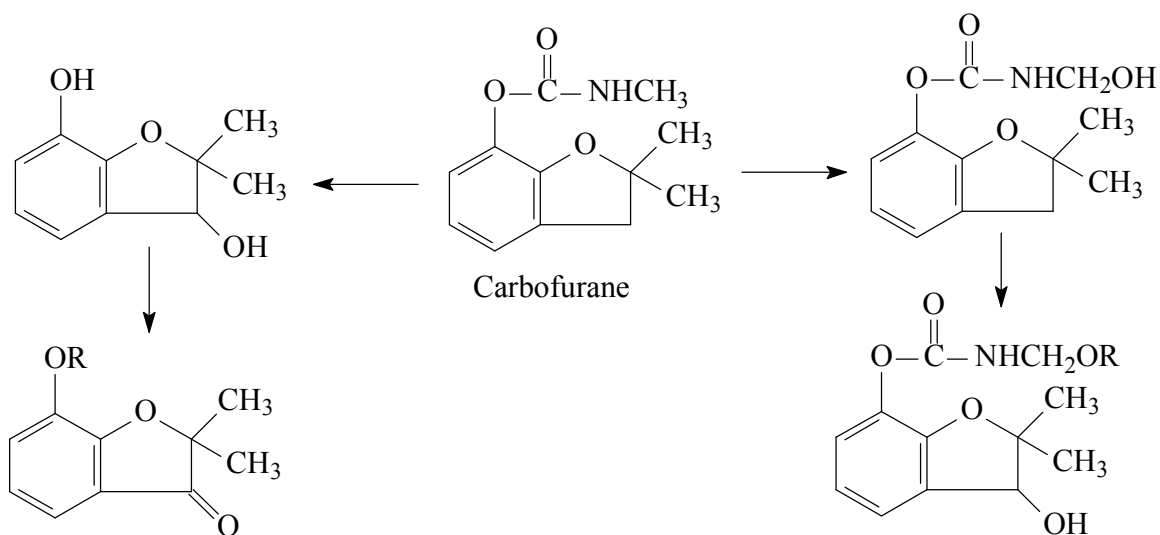
Metabolism of methoxychlor goes through substitution of methoxy groups with hydroxy groups. This substitution is done by hydrolysis in the place of etheric bond between the carbon atom of methyl group and oxygen. Central trichloroethane bridge group can undergo the same transformations as in case of DDT metabolism. The 4,4'-dihydroxy-derivatives which are produced during these transformations turn in the organism of animals into soluble sulfates and glucuronates (salts of glucuronic acid). These converted substances are rapidly excreted from organism.

4. Derivatives of carbamic acid

Up to now more than 40 derivatives of carbamic acid are used in agriculture. Mostly used are the derivatives of N-methylcarbamic acid as insecticides and esters of arylcarbamic acids as herbicides.

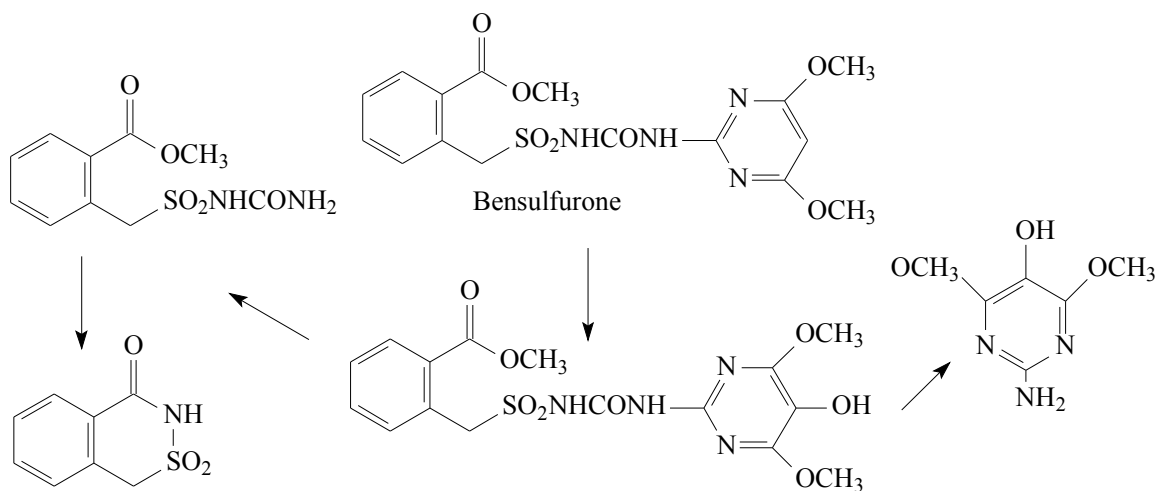
Carbamic acid undergoes the most complete metabolism only under the action of enzymes produced by soil microorganisms. The main reactions taking place here are hydrolysis and oxidation.

Metabolism of carbofuran, for example, can go in different directions according to the following scheme (R is a residue of glucose, glucuronic acid or sulfuric acid).



5. Derivatives of urea

The most widespread compound from this group is sulfonylurea. 15 its derivatives found their application in agriculture. These compounds are characterized by high selectivity and low consumption rates in weed control. Metabolism of bensulfurone goes the following way:



Decomposition of this substance starts from hydroxylation, followed by hydrolysis accompanied with removal of benzoyl group. Then arylurea is decomposed with production of anilin, which breaks up further in soil.

Derivatives of sulfonylurea are of great interest, for they are low toxic for mammals, birds and fishes. For the majority of them the consumption rate is low and is about 4-75 g/hectare.

CHEMICAL WARWARE

Lecture XVI. CHEMICAL WARFARE AGENTS AND THEIR BIOLOGICAL EFFECTS.

1. Historical overview of the development of chemical warfare agents.

The official date of foundation of nuclear-biological-chemical (NBC) defense troops is the 13th of November 1918. Nonetheless, military chemists were used already during the World War I. In summer 1916 a new position of an off-duty officer for gas defense was set in divisions. Special teams for chemical and meteorological observation, chemical attack reporting and military personnel training to use primitive individual means of protection: bulky dressing and (from August, 1915) charcoal gas mask of Zelinsky N.D.

From 1921 the term “gas defence” was substituted by “chemical defense”, starting from 50ies after nuclear weapons were passed into service it was called “defense from the weapons of mass destruction”. Now it is called “nuclear-biological-chemical defense” (NBC-defense).

The primary goals of chemical defense troops were chemical reconnaissance, smoke concealment of combat operations and key support facilities, handling of flame weapons.

Chemical defense troops withstood an acid test in Afghanistan, where flame and incendiary agents and aerosols were used with high efficacy. The experience collected in Afghanistan greatly contributed to the chemical defense tactics and organisation.

An impact to reformation of these troops were several large-scale disasters in chemical plants and nuclear facilities.

Large volume of difficult work was accomplished by chemical defense troops during recovery after the disaster on Chernobyl nuclear plant, happened on 26th of April 1986. 44% of the military forces deployed in the zone of disaster (30 thousands soldiers and officers) were chemical defense troops. The objectives accomplished by these troops were detection and estimation of radiation restricted areas, ongoing monitoring of the radiological situation; deactivation and dust suppression in the area around the atom power plant, human settlements, along the transport lines; support with radiation survey meters, the means of protection and decontaminating solutions.

Taking into account the experience on liquidation of aftereffects of Chernobyl disaster and other emergencies, according to the resolution of the government about the structure of NBC troops, quick-reacting mobile chemical forces duly equipped to handle emergencies on extra-hazardous classifies objects of the Department of Defense of Russian Federation.

August, 1992 the chemical troops are renamed into nuclear-biological-chemical (NBC) defense troops. This new name encompasses the new tasks of these troops today. Besides their wartime tasks, these troops are also responsible for NBC defense of population during peacetime.

NBC defense troops are deployed near nuclear power plants, nuclear industry and large manufacturing outfits. They include forces for radiological, chemical and biological intelligence in case of emergency including technogenic catastrophes and elemental calamities. These troops have units for rescue operations, decontamination, deactivation, disinfections and engineering units. These troops being mobile and quick-reacting have special units in constant state of operational readiness. They can be quickly delivered to any place by transporter aircraft and as a rule are located near the aerodromes accepting transporter aircrafts.

2. Chemical weapons

Chemical weapons are **poisonous substances and agents used on the battle field**. The death-dealing effect of chemical weapons is owed to poisonous agents.

Chemical agents (CA) are the compounds, which if used can damage the unprotected manpower or decrease its operational capability. Owing to their death-dealing effect the chemical agents differ from other warfare agents: they can be conveyed with air into various buildings, tanks and other combat equipment and to damage the people located there; they are stable for certain sometimes quite long time in air, environment and buildings, conveyed by air over long distances and areas; they damage the unprotected people within their sphere of action; poisonous vapors can propagate in the direction of wind over long distances away from the actual places of chemical operations.

Chemical ammunition is classified according to the following criteria:

- persistence;
- evoked physiological action,
- ways and methods of delivery attack,
- tactical role,
- rapidity of the evoked action

a) Persistence

Depending upon how long after their dissemination the poisonous substances preserve their death-dealing effect they are tentatively classified as *persistent* and *unstable*:

The persistence of poisonous gases depends on their chemical and physical properties, methods of release, weather conditions and the relief.

Persistent poisonous substances preserve their harmful action from several hours to several days or even weeks. They evaporate slowly and hardly decompose under the influence of air and humidity.

Unstable poisonous substances preserve their action on open terrain only for several minutes, in the places congestion (forests, hollows, engineering constructions) for dozens of minutes and more.

b) Physiological effects

According to their action to the human organism the poisonous substances are classified in 5 groups:

1. Nerve agents
2. Blister agents and irritants
3. Systemic (blood) agents
4. Asphyxiants
5. Psychochemical agents

Nerve agents cause the damage of the central nervous system. According to the recommendation of US army command, these agents are efficient to cause damages in unprotected enemy personnel or for sudden attack on the personnel equipped gas masks. The latter implies that the personnel will not be able to secure the gas masks. The main goal of nerve agents use is the rapid and mass incapacitation of enemy personnel with maximal possible lethality.

Blister agents and irritants cause damage mainly through cutaneous covering, if used in the form of spray or aerosol then through respiratory organs.

Systemic (blood) agents act via respiratory organs causing the cessation of oxidation processes in human tissues.

Asphyxiants chiefly damage the lungs.

Psychochemical agents are relatively new in the inventory of CAs. They are able to incapacitate the enemy personnel only for a certain time. These CAs act on the central nervous system and interrupt the normal mental performance, causing the psychological disorders like transient loss of sight (amaurosis), deafness, sensation of fear and restriction of motor functions. The characteristic feature of these substances is that the lethal doses are 1000 times higher than those used to incapacitate the enemy.

According to the US data, psychochemical agents are used concomitantly with other lethal CAs in order to destroy the enemy morale and stamina.

Several representers of main CA classes are shown in the table 3.

c) Ways and methods of release.

Military professionals consider the wartime use of CAs to accomplish the following tasks:

- antipersonnel CAs leading to the complete elimination of enemy personnel, mainly nerve agents;
- antipersonnel suppressive CAs in order to force the enemy to take security measures for chemical protection and therefore to hinder the maneuver, decrease the combat fire rate and fire accuracy; this task is fulfilled with the use of blistering and nerve agents;
- enemy interdiction and attrition in order to hinder its combat operations for long time and to cause personnel losses; this task is best fulfilled by the use of persistent CAs;
- area contamination in order to force the enemy to extricate from positions;

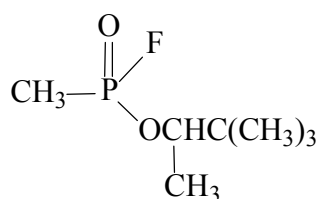
To accomplish these tasks the following weapons can be used:

- Rockets
- Aviation
- Artillery
- Chemical mines

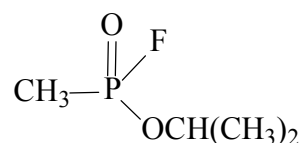
The damage of enemy personnel is caused by mass attack with chemical agents, especially with multi-barrel rocket launchers.

d) Properties of main classes of CAs.

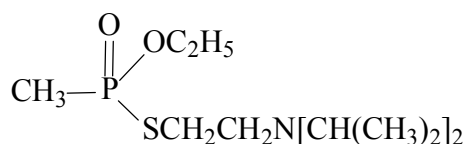
Today the following agents are used as CAs:



sarin



soman



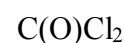
V-gas



mustard gas



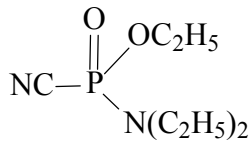
hydrogen cyanide



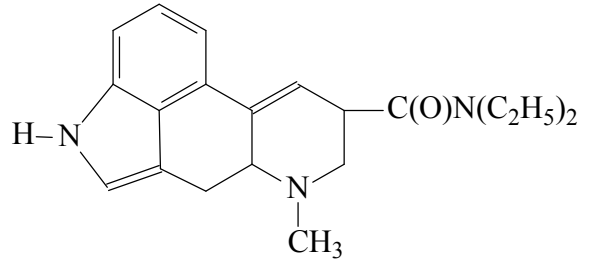
phosgene

HCN
cyanogen chloride

$\text{CCl}_3\text{OC(O)Cl}$
diphosgene



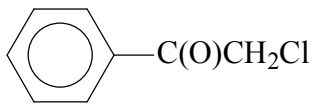
tabun



LSD

$\text{CCl}_3\text{OC(O)Cl}$
diphosgene

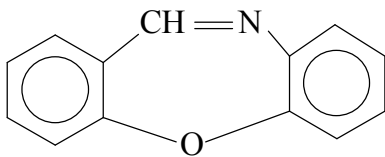
ClCN
chlorocyan



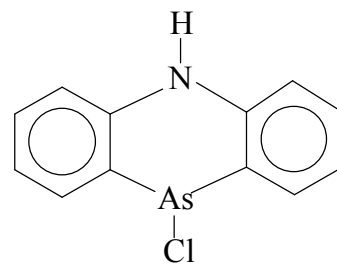
chloroacetophenon



chloropicrin



dibenzoxazepin



adamsit

$(\text{C}_6\text{H}_5)_2\text{AsCl}$
diphenylchlorarsine

$(\text{C}_6\text{H}_5)_2\text{AsCN}$
diphenylcyanoarsine

Table 3. Main classes of chemical warfare agents.

Toxic agents				
Nerve agents	Blister agents and irritants	Systemic (blood) agents	Asphyxiants	Psychochemical agents
GB (sarin) GD (somane) V-gases Tabun Phosphorylthiocholines	HD (mustard agent) Lewisite Trichloroethylamine Diphenylchloroarsin Diphenylcyanarsin DM (Adamsite) Ortho-Chlorobenzal-malonodinitryl Chloropicrin Chloroacetophenon	Prussic acid Cyanogen chloride (CK) Diphenylcyanarsin Dibenzoxazepin	CG (phosgene) DP (diphosgene) HD (mustard agent) Trichloroethylamine Lewisite Chloropicrin Chloroacetophenon Ortho-Chlorobenzal-malonodinitryl	Lysergic acid diethylamide (LSD) 3-quinuclidinyl benzilate (QNB) also known as BZ

Sarin is a colorless or yellowish fluid with almost no odour, that hinders its detection basing upon external characteristics. It belongs to the group of nerve agents. Sarin is primarily used to contaminate the air with vapors and fog, e.i. as an unstable CA. However, sometimes it can be used as liquid gas to contaminate the terrain and war equipment located on it, in this case sarin can persist there for several hours in summer and for several days in winter.

Sarin causes damage via respiratory organs, skin, gastrointestinal tract; it acts via skin as liquid case or vapor, causing no local damage. The degree of contamination with sarin depends on its air concentration and the exposure time.

Symptoms of sarin damages are hypersalivation, hyperhidrosis (profuse sweating), vomiting, dizziness, loss of consciousness, convulsive attacks, paralysis and ultimately death.

Soman is a colorless and odorless liquid, belonging to the class of nerve agents. In many aspects its properties are similar to those of sarin. The persistence is higher than that of sarin, but the toxicity for humans is about 10 times higher.

V-gases are low-volatile liquids with very high boiling point and several times more persistent than sarin. Like sarin and soman they also belong to nerve agents. V-gases are from 100 to 1000 times more toxic than other nerve agents. They are characterized by high efficacy when acting via cutaneous covering, especially in the liquid gas form: skin contact with several droplets usually leads to lethal effect.

Mustard gas (yperite) is a dark-brown oily liquid with a characteristic smell mimicking the smell of garlic or mustard. It belongs to blistering agents. Mustard slowly evaporates from contaminated areas, its persistence on terrain is from 7 to 14 days in summer and up to a month in winter. Mustard possess multiple effects on human organism: in liquid gas and vapor form it causes damage of skin and eyes, in vapour form it harms to the respiratory tract and lungs, by ingestion together with water and food through gastrointestinal tract it penetrates to inner organs. The effect of mustard reveals with some delay, called “delayed action period”.

By skin contact the droplets of mustard rapidly sink in without painful sensation. Those exposed usually suffer no immediate symptoms. Within 4 to 24 hours the exposure develops into small vesicles which tend to merge into deep, itching or burning blisters wherever the mustard contacted the skin. The blister fluid is initially thin and clear or slightly straw-colored; later it turns yellowish and tends to coagulate. The blistering is accompanied with high discomfort and fever. The eyes (if exposed) become sore and the eyelids swollen, possibly leading to conjunctivitis and blindness. After 2-3 days the blisters burst and bare the sores which needs weeks to heal. If the sores are contaminated they become purulent and need much more time (up to 6 months) to heal.

Eyes are usually damaged with mustard vapors even if its concentration in air is extremely low and the exposure was as short as 10 minutes. The delayed action effect lasts from 2 to 6 hours, then the symptoms of damage manifest: “sandpaper” in the eyes, photophobia, lachrymation. The damage symptoms can persist for 10-15 days and then recover. The mustard gas damage of gastrointestinal tract on intake of the food and water contaminated with mustard gas. In severe cases after the delayed action period (30-60 minutes) manifest the signs of damage: pain in the pit of stomach, nausea, vomiting followed by general fatigue, headache, hyporeflexia and evil-smelling nasal and oral discharges. The further development of the damage leads to paralysis, fatigue and cachexy. The death occurs on the 3rd-12th day due to break-down and cachexy.

Hydrogen cyanide is a colorless liquid with characteristic smell mimicking the smell of bitter almond, in lower concentrations the smell is hardly distinguishable. The hydrogen cyanide is a highly volatile substance and acts only in the vapor form. It belongs to the systemic CAs. Characteristic signs of cyanide damage are metallic flavour, sore throat, dizziness, weakness, nausea. They are followed by severe breathlessness, pulse deceleration,

the damaged person loses the consciousness with following convulsive attack. The convulsions last for a short period of time followed by total muscle relaxation and loss of sensitivity, sharp drop of temperature, respiratory depression until the complete respiratory arrest. The heart action can last for 3-7 minutes after the complete respiratory arrest.

Phosgene is a colorless highly volatile liquid with a smell of rotten hay or rotten apples. It causes damage in its vapor form and belongs to the suffocative CAs (asphyxiants). Phosgene has the delayed action period of about 4 to 6 hours, the duration depends upon phosgene air concentration, exposure time, health status of the damaged person and temperature. If inhaled the sweetish off-flavour is tasted, followed with cough, dizziness and general weakness. As soon as the person leaves the contaminated area the signs of intoxication rapidly recover, marking the so-called symptom-free interval. But 4-6 hours later the CA casualties state suddenly aggravates. The rapidly developing lip, nose and cheek cyanosis; general fatigue; headache; hurried respiration, severe breathlessness, troublesome cough with liquid frothing pinky sputum indicate the developing pulmonary edema. The intoxication of phosgene culminates on the second-third day. In case of favorable clinical outcome the casualty gradually recovers, in severe cases the intoxication ends lethally.

Lysergic acid diethylamide (LSD) is a previously described psychedelic drug, belonging to the group of psychochemical agents. On contact it leads to rapid (within 3 minutes) development of slight nausea and pupil dilatation, followed by visual and acoustic hallucinations lasting for several hours.

3. Ways and methods of population protection.

Anti-gas protection is an action plan aimed at prevention or abatement of CA effects on humans. On the objects of national economy these actions are guided by Chief of Staff for Civil Defense. The actions are practically carried out by special troops of Civil Defense.

a) Objectives of the anti-gas defense

1. Timely detection of the gas contamination and population warning.
2. Population protection, protection of animals, foodstuff, potable water, material and cultural values.
3. Recovery of gas contamination.

b) Modes of anti-gas protection.

1. Use of the individual protective equipment (IPE), cessation of all activities and sheltering of population in special protective shelters.
2. Use of individual protective equipment and continuation of the work.
3. Evacuation of the population from the zone of gas contamination..

c) Chemical weapon disposal: technical approach to the problems of health care, operating safety and environmental protection.

The main technology used to dispose the chemical weapons is incineration. Thereby about 4 tones of wastes are produced for every tone of disposed weapons.

Unfortunately, Russia does not have enough amount of facilities for chemical weapons disposal due to extremely high costs of the program for disposal of chemical weapons, in 1995 the total costs were about 24 billions rubles (about 4 billions USD).

d) Destruction by incineration.

The most effective way to dispose the chemical weapons used in all countries is incineration meeting all the requirements of modern environmental science, elaborated and

constantly developed during the last 25 years. This method is well-suited for disposing of chemical weapons in any form: weapons taken out of their containers and for whole round incineration, including those with non-defused detonating fuze, as well as of the contaminated packaging material.

Big installations for incineration were built as the objects of the first order to dispose the chemical weapons required immediate disposal. These objects constitute about 45% of the total chemical weapons stock.

Surely there are public movements pleading for even safer ways of chemical weapons disposal, but not because the modern methods do not meet the environmental requirements. The modern incinerators the emission status is about one tenth of the admissible concentration limit for restricted compounds. Under the pressure of public the US Army was obligated to look and research for alternative technologies. Under the influence of this general public 2 US states storing the chemical weapons in the most safe form (containers with 1 tone capacity) and whose disarmament plan allows to procrastinate the disposal for at least 5 years more approved the strategy of chemical disarmament using alternative technologies. During this 5 years these alternative technologies should be developed up to the level of production standard and thoroughly tested.

The alternative technologies meant here are the chemical neutralization with subsequent biological decomposition of the resultants (this method is applicable only for rather limited number of CAs) for some CAs and use of other currently not approved technology for the others. Two technologies first must be tested for efficacy.

e) Alternative methods of CA disposal.

Despite the relatively high efficacy of incineration there is an on-going research on alternative methods of CA disposal. These are in the first order various technologies for neutralization of chemical agents in containers and bulk storage containers.

In actual truth the process of neutralization technically is not an universal process and requires a big amount of chemicals, there are still problems with disposal of chlorine, sulfur etc, the problems of the ultimate disposal of resultants.

RECOMMENDED READING

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Madsen U. (2002), Textbook of Drug Design and Discovery, CRC, ISBN 0-415-28288-8

Gareth Thomas, Fundamentals of Medicinal Chemistry

Gareth Thomas, Medicinal Chemistry: An Introduction

Thomas Nogrady, Medicinal Chemistry: A Molecular and Biochemical Approach

K. C. Nicolaou, Classics in Total Synthesis: Targets, Strategies, Methods

Richard C. Larock, Comprehensive Organic Transformations: A Guide to Functional Group Preparations

E. J. Corey, The Logic of Chemical Synthesis

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Graham L. Patrick, An Introduction to Medicinal Chemistry

Thomas L Lemke, Review of Organic Functional Groups: Introduction to Medicinal Organic Chemistry

David A Williams, Foye's Principles of Medicinal Chemistry

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<http://www.pesticides.org/dpindex.html> **Marion Moses, MD**, Designer Poisons: How to Protect Your Health and Home From Toxic Pesticides.

<http://en.wikipedia.org/wiki/Pesticide>

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