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REVIEW ARTICLE

DEPARTMENT OF TOXICOLOGY AND MILITARY PHARMACY – IMPORTANT PART OF THE FACULTY OF MILITARY HEALTH SCIENCES OF THE UNIVERSITY OF DEFENCE

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Summary

The Department of Toxicology and Military Pharmacy (DTMF) as a part of the Faculty of Military Health Sciences, University of Defense was founded in 1951. During more than sixty years of its existence, the Department has gained reputation of a highly qualified research centre focused on the effects of chemical warfare agents (CWA), development of antidotes including antidotal means for the Army, solving questions with medical protection against highly toxic agents and educational activities, both pre- and postgradual including international cooperation. Meetings and scientific conferences organized by the Department have been attended by recognized scientists. Its future activities are focused on further studies and development of medical countermeasures including means against effects of CWA preferably nerve agents. There is real and concrete contribution of the Department to the improvement of medical protection of armed forces against the effects of CWA.

Key words: Department of Toxicology and Military Pharmacy; history; nerve agents; research; antidotal means

INTRODUCTION

The history of the DTMF is as long as the history of the Military Medical Academy: the Department of Toxicology was founded more than sixty years ago as a part of the J. E. Purkyně Military Medical Academy (1951–1958), subsequently the Military Medical Research and Postgraduate Training Institute JEP (1958–1988) and then, once again, the Military Medical Academy (1988–2004). Since 2004, the Academy has been transformed into a part of the University of Defence as its 3rd Faculty of Military Health Sciences, including Department of Toxicology and on September 1, DTMF was established by integration of Department of Toxicology and selected parts of Centre of Advanced Studies and Department of Public Health.; COL Assoc. Prof. Pharm.Dr. Daniel Jun, PhD. has been appointed as the Head (2014).

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HISTORY

At the very beginning, the department was practically without any equipment and personnel. Its own

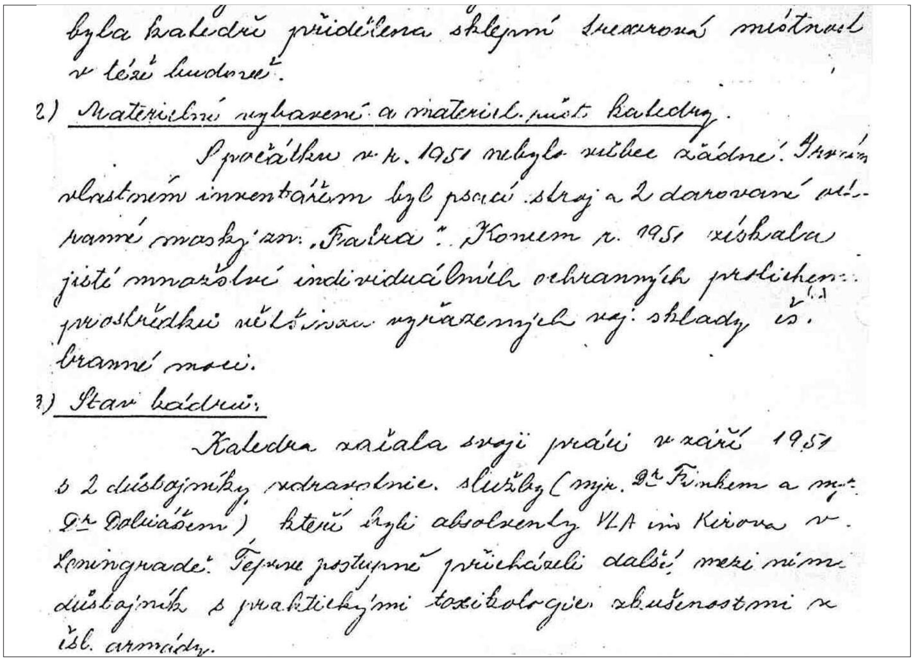

byla katedře přidělena sklepní suterénní místnost v téže budově.
2) Materiální vybavení a materiál. míst. katedry.
S počátku v r. 1951 nebylo vůbec žádné. Prvním vlastním inventářem byl psací stroj a 2 darované ochranné masky zn. „Fatra". Koncem r. 1951 získala jisté množství individuálních ochranných prostředků většinou vyřazených z voj. skladů čs. branné moci.
3) Stav kádrů.
Katedra začala svoji práci v září 1951 s 2 důstojníky zdravotnic. služby (mjr. Dr. Finkem a mjr. Dr. Doliašem) kteří byli absolventy VLA im Kirova v Leningradě. Teprve postupně přicházeli další, mezi nimi důstojník s praktickými toxikologic. zkušenostmi z čsl. armády.

Figure 1. A part of the chronicle of DTMF saying that DTMF at the very beginning was equipped with 2 protective masks and one typewriter.

material in 1951 was one typewriter and two protective masks (Fig. 1).

Research was not performed and all activities were focused on education only. The activities dealing with education continued resulting in elaboration of different textbooks of local and national importance [1]. However, at the end of the fifties, some instruments were obtained and research of CWA was beginning. Firstly, it was focused on asphyxiating agents and vesicants, later on on nerve agents. In the sixties and seventies, a new type of CWA was studied – psychotomimetic agents beginning with LSD-25 followed by anticholinergic hallucinogen BZ agent. The research finished by development of a new antidote against BZ – 7-methoxytacrine [2,3]; education including writing of new textbooks continued [4-6].

Research of the nerve agents was dedicated to antidotes – parasympatholytics and reactivators. After detailed studies, two anticholinergic drugs (atropine, benactyzine) and two reactivators of nerve agent inhibited acetylcholinesterase (trimedoxime, methoxime) were introduced into the Army for medical use. The most effective reactivator HI-6 was introduced into this antidotal spectrum, too. Simultaneously, prophylactics against nerve agents were studied and as a result of improvement of prophylaxis, new prophylactic antidote was developed containing pyridostigmine, benactyzine and trihexyphenidyle, having better prophylactic effectivity than pyridostigmine alone (it was/is used in some Armies till now).

PAST ACTIVITIES

Research of the department led to concrete results:

- Synthesis of tetrahydroaminoacridine derivatives (hundreds compounds), the best of which for clinical and antidotal use was 7-methoxytacrine (7-MEOTA). The development of tablets and injections was finished and the drug was tested on volunteers and introduced into the Armed Forces as a specific antidote against psychotomimetic agent BZ (Fig. 2).
- Synthesis of four medicaments for treating intoxication by nerve agents and four other compounds for testing neurotoxicity.
- Finalizing the development of aforementioned antidotes, such as CHONOL I and II, FOSAN (later on it was discarded), RENOL, PANPAL and 7-MEOTA.

Figure 2. Antidote against psychotomimetic agent BZ – 7-MEOTA.

- Cooperation in development of the GAI autoinjector and its introduction into the Armed Forces.
- Synthesis of the new reactivator HI-6; the method for its semi-operational production was elaborated, and 1.5 kg of HI-6 for the Czech Army (ANTIVA) was produced.
- A new decontaminant was introduced into the Armed Forces (IPB-80) and civil defence (DESPRACH).
- Analytical determination of nerve agents was improved.
- The method for delayed neurotoxicity testing was developed.
- New groups of nerve agents (GV) and highly toxic carbamates (T-1123) were characterized.
- The results were published in Czech and foreign journals.
- 6 textbooks were elaborated.
- 5 authorship certificates and 2 patents were granted.
- 11 movies were produced for education.

PRESENT ACTIVITIES

DTMF is a unique department both in the Czech Armed Forces and throughout the whole country. Its activities are focused on the following areas: executive activities such as diagnosis, therapy and prevention of effects of highly toxic compounds (including CWA), decontamination principles of persons, assessment of trends for the future in this field, educational activities in pre- and postgraduate systems, research, development and testing of new protective chemical equipment from the medical point of view including materials for the Armed Forces needs, consultation of environmental issues and accidents connected with the release of toxic chemicals. DTMF cooperates with national (State Office for Nuclear Safety) and international (Organisation for Prohibition of Chemical Weapons, OPCW) authorities for control of chemical weapons, and, in the field of research and education, with many civilian and military research institutes.

After the velvet revolution in 1989, the Department was moved into a new phase of its history. Cooperation with NATO countries was increased as well as inclusion of the DTMF into international research. These activities were summarized in some publications [7,8].

To fulfil the tasks of the Department, it is divided into two groups – Biochemical Group and Group for Experimental Therapy. The first group uses a biochemical and analytical laboratory, laboratory for organic synthesis, and decontamination laboratory. The list of laboratories allotted to the second group is as follows: toxicological, pharmacological,

neurobehavioral and genotoxicological laboratory. The department laboratories contain standard equipment such as spectrophotometers, fluorimeters, microscopes, centrifuges etc.; however, in addition, DTMF has developed a unique inhalation chamber for studies of inhalation toxicity of nerve agents in rodents, and some analytical instruments including GC-MS, HPLC and others are included. If necessary, neurobehavioral research is carried out by means of some instruments and techniques enabling the researchers to test various nervous functions of experimental animals in more than 40 parameters with the help of Functional Observational Battery. Certain special methods (COMET assay, etc.) are applied for genotoxicity testing. The developed structure and equipment facilitates characterization of the analyzed agents according to different aspects ranging from the information about the agent through its physicochemical and biological features up to the practical output.

EDUCATION ACTIVITIES

Education consists of pregradual study of military students of medicine and pharmacy as well as students of bachelors programs. It contains lectures, practical seminars and training not only for military students but also for military medical officers and other soldiers connected to CBRN protection (chemical part). Postgradual study is organized in the accredited doctoral programmes, with „toxicology“ on a high professional level. The Department fulfils also other activities such as lectures for the rescue system and other civilian and military institutions. DTMF guarantees specialized preparation of all members of Army missions abroad before starting their mission including medical doctors, nurses, and non medical personnel, organizes exercises of different programs (from students to highly specialized experts) and education is also realized for NATO members and civilian organisations.

According to the achieved results and literature survey, new textbooks dealing with different aspects of military toxicology were elaborated [9-13].

RESEARCH ACTIVITIES

The results of research are not only presented as the contributions in specialized scientific literature but also as antidotal means introduced into the Army:

- The newest prophylactic antidote containing HI-6 was introduced into the Czech Army; because of impossibility to be administered orally, a transdermal way of administration (patch impregnated with HI-6) was used (TRANSANT). TRANSANT was introduced into the Armed Forces as a prophylactic antidote of a new generation. When both prophylactics (PANPAL and TRANSANT) are administered simul-

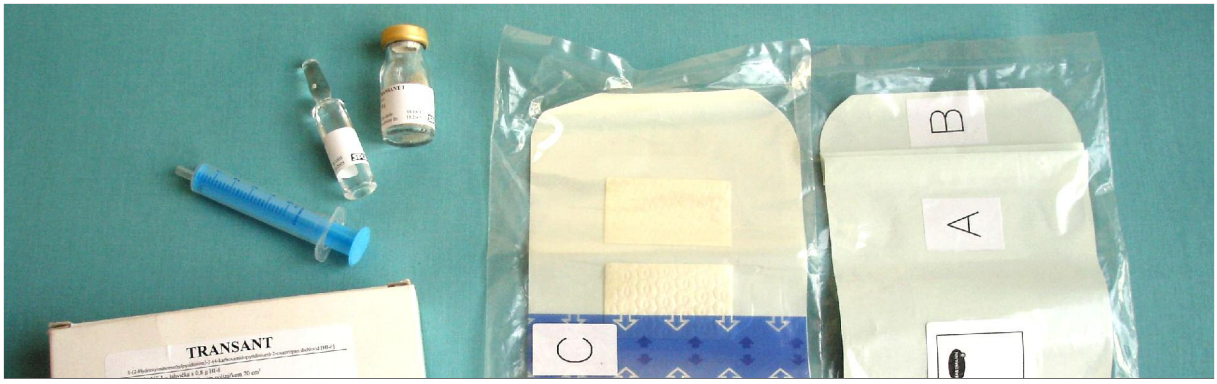


Figure 3. Prophylactic antidotes PANPAL and TRANSANT.

Figure 4. Three chambered Autoinjector MULTIPEN HAD.

taneously, the achieved prophylaxis is potentiated and represents the best prophylactic protection against nerve agents worldwide (Fig. 3).

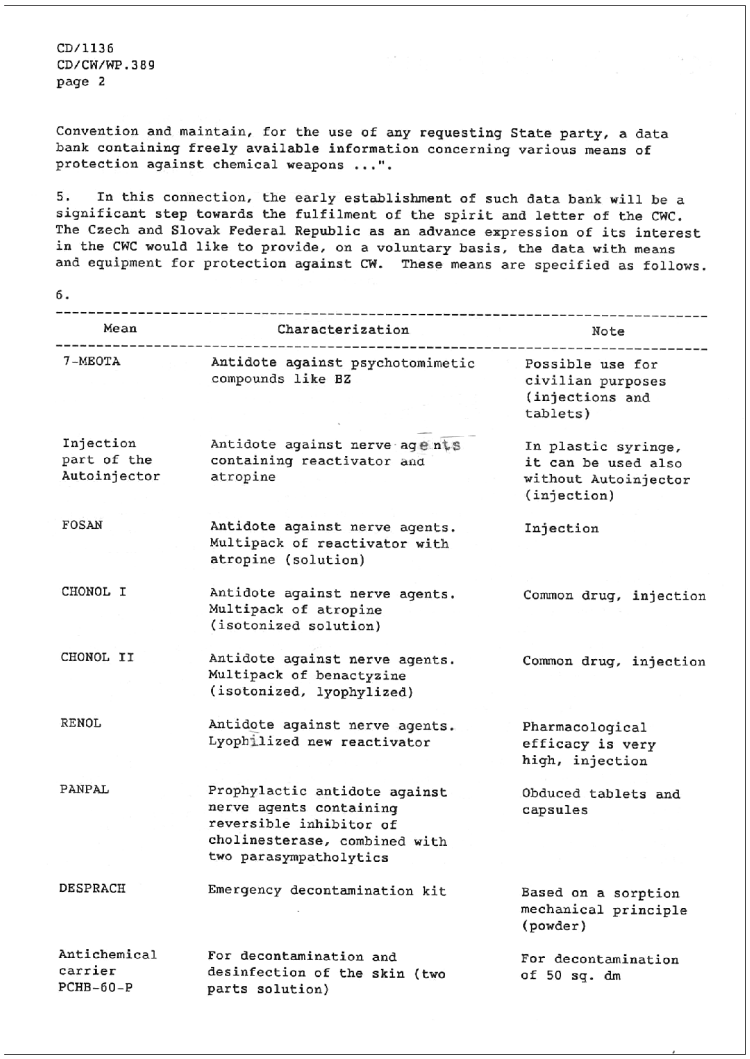
- For diagnostic purposes, a prototype kit for determining blood acetylcholinesterase activity and its reactivation was developed and used for measuring in various exercises.
- In connection with the so-called "Gulf Syndrome", the research program was focused on effects of low-level concentrations of sarin and soman during an inhalation exposure. It was demonstrated that sublethal doses (without clinical symptoms) can cause different effects (neurobehavioral, biochemical) emerging weeks or months after the exposure.
- A new prophylactic approach was studied in cooperation with the USA. It is based on administration of purified butyrylcholinesterase acting as "scavenger" and binding a nerve agent before it reaches target organs. These results are very prospective and, at present, the experiments are in progress. A similar problem using other enzymes (phosphotriesterases, phoshorylphosphatases) is being solved in cooperation with the CRSSA, France; the attention has been paid to pseudocatalytic scavengers, too.
- Synthesis of new reactivators, aimed at obtaining more effective reactivators, is another direction of the contemporary research.
- DTMF participates in the development of a new three chambered wet-dry autoinjector containing atropine, HI-6 and diazepam (MULTIPEN HED) (Fig. 4)
- The complex kit for medical treatment of intoxication with CWA – M-9 special aid (role 1-3) was also developed.
- Publications in Czech or foreign Journals (books); use of some results to obtain different academic degrees (Professor, Associate Professor, PhD).

INTERNATIONAL COOPERATION

In the field of developing prophylactic and therapeutical antidotes against nerve agents and organophosphorus insecticides, the Department has started or continued cooperation with some research institutes (Medicinal Science Division, Korea Research Institute of Chemical Technology, Taejon – Korea, Institute for Medical Research and Occupational Health, Zagreb – Croatia, Department of Pharmacology and Therapeutics, Faculty of Medicine and Health Science, United Arab Emirates University, Al Ain – United Arab Emirates, Institute of Pharmacology and Toxicology of Federal Armed Forces Medical Academy Munich – Germany, TNO Prins Maurits Laboratory in Rijswijk – the Netherlands, Department of Toxicology of NBC Research Centre of Military Medical Academy in Sofia – Bulgaria, Centre de Recherches du Service de Sante des Armees /CRSSA/ Grenoble – France). The cooperation is mostly characterized as the exchange of scientific personnel, information, common projects, but in many cases, it has the form of testing the antidotes prepared by the Department in the research institutes abroad. Within the framework of the program aimed at identifying mechanisms of chemoprevention in the initial phases of mutagenesis and carcinogenesis, the DTMF has also continued the cooperation with the Institute of Nutrition Research in Oslo (Norway) and the Institute of Preventive and Clinical Medicine in Bratislava (Slovak Republic).

The Department was active in cooperating with the Organization for Prohibition of Chemical Weapons (The Hague). This activity was shown at the Conference on Disarmament (CD) in the past when CWC was formulated. After 1989, four documents were presented. It would be of interest that it was for the first time in the CD negotiation history that antidotes against CWA were openly published (Fig. 5)

DTMF personnel are also members of ediorial boards of various journals such as The ASA Review, Acta Medica, Archives of Industrial Hygiene and Toxicology, Journal of Enzyme Inhibition and Medicinal Chemistry, members of Scientific Advisory Board on the Applied and Sciences Analysis (USA), Journal of Medical Chemical Biological and Radiological Defense etc. The Department of Toxicology was awarded (by the NATO Scientific Committee) three



CD/1136
CD/CW/WP.389
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Convention and maintain, for the use of any requesting State party, a data bank containing freely available information concerning various means of protection against chemical weapons ...".

5. In this connection, the early establishment of such data bank will be a significant step towards the fulfilment of the spirit and letter of the CWC. The Czech and Slovak Federal Republic as an advance expression of its interest in the CWC would like to provide, on a voluntary basis, the data with means and equipment for protection against CW. These means are specified as follows.

6.

Mean	Characterization	Note
7-MEOTA	Antidote against psychotomimetic compounds like BZ	Possible use for civilian purposes (injections and tablets)
Injection part of the Autoinjector	Antidote against nerve agents containing reactivator and atropine	In plastic syringe, it can be used also without Autoinjector (injection)
FOSAN	Antidote against nerve agents. Multipack of reactivator with atropine (solution)	Injection
CHONOL I	Antidote against nerve agents. Multipack of atropine (isotonized solution)	Common drug, injection
CHONOL II	Antidote against nerve agents. Multipack of benactyzine (isotonized, lyophylized)	Common drug, injection
RENOL	Antidote against nerve agents. Lyophilized new reactivator	Pharmacological efficacy is very high, injection
PANPAL	Prophylactic antidote against nerve agents containing reversible inhibitor of cholinesterase, combined with two parasympatholytics	Obduced tablets and capsules
DESPRACH	Emergency decontamination kit	Based on a sorption mechanical principle (powder)
Antichemical carrier PCHB-60-P	For decontamination and desinfection of the skin (two parts solution)	For decontamination of 50 sq. dm

Figure 5. The copy of the second page of the Czechoslovak contribution to the Conference on Disarmament dated 27 February 1992 [Protection against Chemical Weapons (Data bank of available basic means), CD/1136, CD/CW/WP.389], showing for the first time at the CD different antichemical means.

Linkage Grants dedicated to solving the task of treating nerve agent poisoning in cooperation with Military Medical Academy in Munich (Germany), TNO Prins Maurits Laboratory in Rijswijk (The Netherlands) and Military Medical Academy in Sofia (Bulgaria). According to the Institute for Scientific Information (WoS), the research results of the Department were published in more than thousand publications and are frequently cited. The Faculty of Military Health Sciences (formerly as the Military Medical Academy) and DTMF were organizers of the m-CB MTS in Hradec Kralove (1997) as the first (and up to now the last) East European country able to organize such a meeting. This ability was confirmed in 2005 when the Faculty was the organizer of the TG-004 NATO Meeting held in Hradec Kralove in May 2005. In cooperation with civilian organizations, the Department held the 6th Czech and Slovak Toxicological Conference in Hradec Kralove (3-5 September 2001) including the International Symposium on CWA with interesting presentations given by internationally renowned experts (USA, The Netherlands, Russia, France, Sweden, Germany and others). The years of the 21st century were also successful for the DTMF personnel – they were nominated as chairs or invited speakers to different conferences and scientific meetings throughout the world. The members of DTMF published the book „Vojenská toxikologie /Military Toxicology/“ [11], they were authors of 7 chapters (of 72) in the book edited by professor Gupta

„Handbook of Toxicology of Chemical Warfare Agents“ (1147 pages) published in 2009 (Elsevier-Academic Press) [14], reedited in 2015, and the authors of the book „Central and Peripheral Nervous System: Effects of Highly Toxic Organophosphates and their Antidotes“ released in 2009 (Research Signpost, Kerala; J. Bajgar, Editor) [15] (Fig. 6). Elsevier also published (2012) the book of J. Bajgar „Nerve Agents Poisoning and its Treatment in Schematic Figures and Tables“ [16]. The book elaborated in cooperation with Slovak collegues was a common publication on chemical and biological weapons [17].

Figure 6. Some authors of the book *Central and peripheral nervous system: effects of highly toxic organophosphates and their antidotes (15)*. From left to right, first line, LTC Prof. Dipl. Eng. J. Cabal, CSc., Assoc. Prof. J. Bajgar, MD, ScD., Prof. J. Kassa, MD, CSc. (former heads of the Department), second line Mgr. O. Soukup, PhD., Prof. Dipl. Eng. K. Kuca, PhD. (former Vice-dean of the Faculty) and COL Assoc. Prof. PharmDr. D. Jun, PhD. (present head of the Department).

AWARDS

Some workers of the Department were granted by different awards:

Prof. Fusek was granted the title "doctor honoris causa" at the WAM Lodz, Lodz, Poland (1999). 2nd Prize in the Czech Competition of Medical post-graduate students 2004 (Kuča), the Prize of the Rector of University of Defence 2004 (Kassa) and 2007 (Bajgar), the Prize of the Dean of the Faculty of Military Health Sciences (2006 – Kuča and 2008 – Musilek)), the 1st Prize of the Society for Clinical and Experimental Pharmacology and Toxicology of the Czech Medical Society 2005 (Bajgar), 2007 (Štětina) and 2010 (Musilek). Two important awards were granted in 2007: K. Kuča was awarded the Prize of the Lord Mayor of Hradec Kralove, Otakar Divišek, for contributing to scientific activities of young students. The Lord Mayor medal for scientific work was given to O. Soukup in 2012. J. Bajgar received the Society of Toxicology/IUTOX Astra Zeneca Award at the 46th SOT Meeting in Charlotte, NC, USA in March 2007 which was granted to senior toxicologists. Different fellowships were gained from OPCW, ASA, and International Neurochemical Society.

A new generation of medical students develops this tradition, as exemplified by the fact that Libor Vašina won the 1st Prize at the International Medical Students Competition in Liptovsky Mikulaš, Slovak Republic, in 2007. Kamil Musilek was awarded Sanofi-Aventis First Prize – Prix de pharmacie by the French Embassy in the Czech Republic (2008). K. Musilek was also awarded by the Ministry of education, youth and sport in 2008; his work is dedicated to the synthesis of new cholinesterase reactivators and their evaluation against organophosphate poisoning in vitro. V. Šepsová obtained the Prize of the University Rector for the best student work („Student´s Head 2010") in the academic year 2009/2010. In 2014, Mgr. E. Nepovímová was awarded the MUDr. Jan Bureš Prize afforded by the Alzheimer foundation.

PERSONAL STAFF

It is impossible to enumerate all persons working or contributing to described results:

they were at the very beginning, Z. Fink, V. Dobiáš, later on V. Hrdina, V. Vondráček, M. Krejcar, J. Tulach, R. Urban, F. Ornst, all as active officers (COL rank). Civilian specialists also contributed as follows J. Vachek, J. Bielavský, J. Patočka, J. Herink, M. Koupilová, I. Elsnerová. New officers were present in the 70th and 80th: J. Bajgar, J. Fusek; J. Matoušek, J. Kassa, J. Cabal, O. Krs. From the Academy of Sciences, R. Štětina arrived.

New collegues, K. Kuča and D. Jun, began their work at the DTMF at the end of 20th century. Young officers J. Žďárova Karasová, V. Šepsová, as well as K. Musilek, L. Bartošová, G. Kunešová, O Soukup and M. Hrabinová were engaged.

Laboratory assistants are important workers dealing with highly sophisticated activities either using complicated instruments or precise handling of experimental animals: they were following:

V. Tříletá, E. Seidlová, V. Marelová, L. Benýšková, M. Zechovská, M. Gregorová, J. Bajgarová, Z. Klinská, V. Komanec, I. Ježková, E. Lískovská, J. Petrová, R. Táborská, R. Věříšová, E. Vodáková, O. Ochrymovič and secretaries A. Vagnerová, H. Roobová and E. Komárková.

Laboratory assistents still working at the department are J. Uhlířová, V. Škrancová, and E. Reslová.

FUTURE DIRECTIONS

Directions for further research and new trends in the field of toxicology studied at the Department were formulated in several articles [e.g. 18-23]; these papers are of interest of various scientists as it is documented by number of citations – e.g. up to now, they were cited 350 times [22], 221 times [21] or 130 times [23].

- to cover the entire spectrum of nerve agents, expecially tabun intoxication, new reactivators or combinations of two reactivators are studied to achieve better antidotal efficacy;
- to treat longer effect of soman poisoning, new anticonvulsants are searched including their optimal timing;
- to improve prophylaxis, new scavengers, especially of catalytic and pseudocatalytic nature, and new reversible inhibitors are studied;
- mechanism of mustard including early diagnostic markers is one of the main directions for further studies;

Some aspects of future research were discussed in various publications (18-20).

CONCLUSIONS

DTMF is an important and non-replaceable part of the University of Defence. It is a base for education and research, for testing new means from medical aspects, consulting questions connected to the effects of CWA including medical protection. The achieved results are of both theoretical and practical importance allowing improving medical protection against CWA in the Czech Army.

ACKNOWLEDGEMENT

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-Bajgar, J., Fusek, J., Kassa, J., Kuca, K., Jun, D.: Chapter 64. „Pharmacological prophylaxis against nerve agent poisoning: experimental studies and practical implications“ (pp. 877-886),
-Bajgar, J., Fusek, J., Kassa, J., Kuca, K., Jun, D.: Chapter 3. „Global impact of chemical warfare agents used before and after 1945“ (pp. 17-24),
-Bajgar, J., Kassa, J., Fusek, J., Kuca, K., Jun, D.: Chapter 24. „Other toxic chemicals as potential chemical warfare agents“ (pp. 331-338),
-Kassa, J., Bajgar, J., Kuca, K., Jun, D.: Chapter 33. Behavioral toxicity of nerve agents (pp. 481-492);
-Jun, D., Bajgar, J., Kuca, K., Kassa, J.: Chapter 58. Monitoring of blood cholinesterase activity in workers exposed to nerve agents (pp. 877-885).
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