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No. 29

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JPRS 82998

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USSR REPORT

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CONTENTS

UDC 575.24:582.263

MUTAGENIC EFFECT OF SODIUM AZIDE ON SCENEDESMUS ACUTUS

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 28 Oct 80; in revised form 13 Nov 81) pp 1803-1805

NIKOLOV, N. N. and KHUBAVENSKA, N. B., Scientific and Industrial Algology Laboratory, Bulgarian Academy of Sciences, Sofia

[Abstract] Tests were conducted on the mutagenic action of sodium azide on the unicellular alga Scenedesmus acutus. The mutagenicity ranged from 1.97-2.38% of examined colonies, and was independent of the solvent or duration of exposure. Compared with the nutagenicity rates obtained for N-nitrosoalkylurethanes (57.1%), N-nitrosoalkylcarbamides (34.67%), N-nitrosoalkylguanidines (12.31%), and N-nitrosoalkylamines (2.29%), sodium azide appears to be less potent as a mutagen than the N-nitroso compounds tested under identical conditions. This observation contradicts the generally-accepted view that sodium azide is a potent mutagen. References 8: 4 Russian, 4 Western.
[127A-12172]

UDC 577.3

BACTERIAL BIOLUMINESCENCE AND BIOLUMINESCENT ANALYSIS

Moscow BIOFIZIKA in Russian Vol 27, No 6, Nov-Dec 82
(manuscript received 22 May 82) pp 937-953

KRATASYUK, V. A. and GITEL'ZON, I. I., Institute of Biophysics, Siberian Branch of the USSR Academy of Sciences, Krasnoyarsk

[Abstract] Present methods used in bioluminescent analysis are reviewed. Three circumstances point to the promising nature of using bioluminescence in analytical work: 1) present methods for detecting radiation in the visible range enable high sensitivity, including at least the theoretical possibility of observing events at the molecular level; 2) these methods are highly specific because they are based on enzyme reactions; 3) bioluminescence occurs through the main metabolic pathways in the cell, enabling conjugation with luciferase in the substrates of enzyme reactions in order to determine most key metabolites and antimetabolites. The chemical bases of bacterial luminescence are described. A discussion of bacterial luminescence in analysis in vivo covers substrate analysis, the use of mutant luminescent bacteria, and analysis of bioluminescence inhibitors. Substrate analysis in bioluminescence reactions, analysis of enzymes and their substrates in conjugate systems, inhibitor analysis, and bioluminescence immune methods are included in a section on the analytical applications of the isolated bacterial luminescent system. The future of bioluminescence biochemistry and research and associated environmental protection are discussed. Present trends indicate that these methods will find applications in many fields of science, clinical medicine, agriculture and the biological industry thanks to their exceptional sensitivity and specificity. Figures 3; references 161: 13 Russian, 138 Western.
[124-9642]

HEAT CAPACITY OF DNA AT LOW TEMPERATURES AND VARIOUS HUMIDITIES

Moscow BIOFIZIKA in Russian Vol 27, No 6, Nov-Dec 82
(manuscript received 9 Jun 82) pp 987-994

MREVLISHVILI, G. M., ANDRONIKASHVILI, E. L., DZHAPARIDZE, G. Sh., SOKHADZE, V. M., TATISHVILI, D. A. and YEMEL'YANOV, K. A., Institute of Physics, Georgian SSR Academy of Sciences, Tbilisi

[Abstract] The equipment and methods used in a study of low temperature (2-400K) heat capacity in DNA are described and findings at various humidities are presented. Technical features of the cryostat and adiabatic envelope and the calorimetric ampoule are discussed extensively. Cooling equipment enabled temperatures of 2-4K to be maintained for two days without the need to add more liquid helium. Samples were held in evaluated calorimetric chamber in sealed, thermally insulated ampoules. An NM-10M computer was used to regulate and monitor the system. Purified salmon sperm NaDNA containing less than 1% protein was used in the study. Samples were in the form of non-oriented DNA strands maintained at various humidities and with various water contents. Across the temperature range 45-350K, DNA heat capacity remained close to linear at all humidities, indicating the possibility of using rigid "thin rods" as a model for the DNA molecule. Dynamic characteristics can be explained within the framework of the single-continuum model (Verkin et al.). Findings also indicate the need to take into account the interaction between separate chains since this affects the hydration centers in the molecule. At temperatures above 40K, "sliding" of the chains occurs, damping variations but not affecting the linear correlation between heat capacity and temperature. The findings enable conclusions to be drawn not only about the thermodynamic parameters of the DNA but also the properties of the solvent: interaction between the solvent (water) and the polynucleotide chains can alter polynucleotide conformation in double-stranded DNA. Figures 6; references 17: 12 Russian, 5 Western.
[124-9642]

DISTRIBUTION OF LARGE LIGANDS IN DNA MACROMOLECULES WITH VARIOUS HYDRATION CENTERS

Moscow BIOFIZIKA in Russian Vol 27, No 6, Nov-Dec 82
(manuscript received 29 Jun 81, after revision 25 Jan 82) pp 1000-1004

NOVOSELER, M. A., Institute of Experimental Biology, Yerevan

[Abstract] DNA complexes with large ligands were studied in an attempt to clarify the following questions: what kind of bonding constant exists between histones and DNA?; what is the pairing number for the DNA bases bonding with one ligand molecule?; is ligand bonding cooperative?; does the bonding affinity depend on the heterogeneity of the DNA?; Poly-l-lysine hydrobromide (molecular weights 52,000 and 20,000) and protamine sulfate were used as the ligands. Studies were done on calf thymus DNA, DNA T2 and T7

phages, and E. coli DNA. Complexes were prepared by direct mixing of the DNA with an aqueous solution plus subsequent addition of the ligands. Fusion was recorded at lambda = 259 and 340 nanometers using an SF-4 spectrophotometer. All ligands bonded strongly with the DNA and were distributed across the entire DNA molecule. Pairing is shown in a table; findings showed that ligand migration occurs at low ion strengths with the size of clusters varying linearly as calculated from hyperchromism as a function of DNA ligand saturation. Bonding does not depend directly on the hydration centers but rather on the ligand-lattice pair. Figures 3; references 13: 5 Russian, 8 Western.
[124-9642]

O-PHENANTHROLENE INHIBITION OF MITOCHONDRIAL RESPIRATION IN A PERMANENT MAGNETIC FIELD

Moscow BIOFIZIKA in Russian Vol 27, No 6, Nov-Dec 82
(manuscript received 14 May 81) pp 1057-1060

KOLESOVA, G. M., KAPITANOVA, N. G., RAYKHMAN, L. M. and KUZNETSOV, A. N., Scientific Research Institute for Biological Testing of Chemical Compounds, Kupavna, Moscow Oblast

[Abstract] Studies were conducted to clarify the possible effect of permanent magnetic fields on nonheme, iron-bearing mitochondrial proteins when acted upon by the iron chelating agent o-phenanthrolene, which damages the structure of nonheme proteins and leads to impairment of mitochondrial respiration. Respiration was measured polarographically in isolated murine liver mitochondria incubated for 20 minutes at 18°C in aqueous solutions of o-phenanthrolene at various strengths inside a 330-millitesla permanent magnetic field, and after removal from the magnetic field when substrate and ADP or substrates and dinitrophenol had been added. A glutamate-malate (NAD-dependent) mixture or succinate was used as substrate. Results from measurements showed no marked differences in mitochondrial respiration as a consequence of application of the magnetic field in the absence of o-phenanthrolene. When o-phenanthrolene was present a marked decrease in mitochondrial respiration was observed. It is concluded that in material not treated with o-phenanthrolene, either the magnetic field has no effect on the carriers or that the effect is temporary and disappears when they are removed from the field. These results are in disagreement with those obtained by Shishlo et al., but it should be noted that Shishlo's work was done at 0°C. Differences in mitochondrial sensitivity as a function of the substrate are discussed. Figures 1; references 11: 7 Russian, 4 Western.
[124-9642]

UDC 575.113:595.773.4

HEAT SHOCK IN DROSOPHILA AND REGULATION OF GENOME ACTIVITY

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 23 Sep 81; in revised form 10 Jun 82) pp 1749-1762

LOZOVSKAYA, Ye. R., LEVIN, A. V. and YEVGEN'YEV, M. B., Institute of Molecular Biology, USSR Academy of Sciences, Moscow

[Abstract] A literature review is presented of heat-shock-induced puffing of polytene chromosomes in Drosophila as a model for such a phenomenon in all eukaryotic cells. The essential features of this phenomenon, which can also be induced by some chemical agents, is that certain sites are depressed (while normally functional sites are repressed) and the RNAs synthesized as a result of the heat shock are translated into a small number of polypeptides (eight in the case of D. melanogaster). The heat-shock polypeptides enter the nucleus and bind to chromosomes and may thereby exert a protective action. Puffing is observed only in the case of heat-shocked organ or tissue explants, not with isolated nuclei, suggesting the need for a cytoplasmic factor(s) for the initiation of puffing. Evaluation of various mutants can be expected to provide a better understanding of the puffing mechanism and its con equences. For example, the 1(ts)403 lethal mutation in D. melanogaster causes the production of ten- to twenty-fold less heat-shock proteins and thereby affects recovery from heat shock. Figures 4; references: 54 (Western).
[127A-12172]

UDC 577.21:595.773.4

MOLECULAR AND GENETIC STUDIES ON THE cut LOCUS OF DROSOPHILA MELANOGASTER. PART 1. CLONING OF DNA FRAGMENT FROM THE 7B3 REGION OF X-CHROMOSOME

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 3 Mar 82) pp 1763-1771

CHURIKOV, N. A., ZELENTSOVA, Ye. S. and NAUMOVA, A. K., ANAN'YEV, Ye. V., BARSKIY, V. Ye., DOLGANOV, G. M. and GEORGIYEV, G. P., Institute of Molecular Biology, USSR Academy of Sciences [AS]; Institute of Molecular Genetics, USSR AS; Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR AS, Moscow

[Abstract] Conditions are described in which a transcribing 7 kb DNA fragment derived from the X-chromosome of Drosophila melanogaster, designated as H55, was cloned in plasmid pBR322. Furthermore, in situ hybridization studies with polytene chromosomes located that H55 fragment in the 7B3 region of the X-chromosome. The 7B3 region represents a thin band demonstrated, cytogenetically, to contain the cut mutations. Figures 6; references 27: 1 Russian, 1 Western.
[127A-12172]

UDC 577.21:595.773.4

MOLECULAR AND GENETIC STUDY OF THE cut LOCUS OF DROSOPHILA MELANOGASTER. PART 2. GENE H55 IS SPLIT, 3'-EXON IS REPETITIVE AND ITS SEQUENCE ("SUFFIX") IS PRESENT ON 3'-ENDS OF VARIOUS mRNAS

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 3 Mar 82) pp 1772-1783

NAUMOVA, A. K., CHURIKOV, N. A., ZELENTSOVA, Ye. S. and GOERGIYEV, G. P., Institute of Molecular Biology, USSR Academy of Sciences

[Abstract] Detailed studies conducted on the H55 DNA fragment from the 7B3 region of the Drosophila melanogaster X-chromosome showed that this fragment, which is approximately 7 kb long, is split. It contains a ca 2.9 kb exon which is separated by a ca 2.4 kb intron from a short repetitive 3'-end exon (ca 200-300 bp). These repetitive sequences (designated as "suffix"), of which 300-400 copies are present in the haploid Drosophila genome, are present at the 3'-ends of a variety of poly(A)$^+$mRNA molecules. Figures 7; references 28: 1 Russian, 27 Western.
[127A-12172]

UDC 575.24:576.852.182

CLONING DNA FRAGMENTS OF STREPTOMYCES COELICOLOR A3(2) PLASMID SCP2 IN ESCHERICHIA COLI

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 8 Jul 81; in revised form 22 Jan 82) pp 1811-1816

PIRUZYAN, E. S., VETOSHKIN, A. V., KOBETS, N. S. and SLADKOVA, I. A., Institute of Molecular Genetics, USSR Academy of Sciences; All-Union Scientific Research Institute of Genetics and Breeding of Industrial Microorganisms, Moscow

[Abstract] BamH1 fragments of Streptomyces coelicolor A3(2) plasmid SCP2 were cloned in Escherichia coli using the plasmid pBR322 as a vehicle. The successfully-cloned SCP2 fragments had molecular weight of 1.3, 2.7, and 5.6 Md; attempted cloning with a 10.9 Md DNA fragment was not successful. A number of hybrid plasmids were subsequently isolated, of which pPV37 was investigated in detail. pPV37 (8.7 Md) was identified as a hybrid consisting of pBR322 incorporating a 5.6 Md fragment of SCP2; a detailed restriction map is presented. Figures 3; references 21: 2 Russian, 19 Western. [127A-12172]

UDC 575.113:576.851.5

EXPRESSION OF ANTIBIOTIC RESISTANCE OF ENTEROBACTERIAL GENE UNDER THE CONTROL OF BACILLUS THURINGIENSIS REGULATORY SIGNALS IN GRAM POSITIVE AND NEGATIVE BACTERIA

Moscow GENETIKA in Russian Vol 18, No 11, Nov 82
(manuscript received 10 Jul 82) pp 1825-1834

SAKANYAN, V. A., TSOY, T. V., SEZONOV, G. V. and ALIKHANYAN, S. I., All-Union Scientific Research Institute of Genetics and Breeding of Industrial Microorganisms, Moscow

[Abstract] Investigations were conducted on the properties of recombinant plasmids pPBT9 and pPBT74, prepared by cloning promotor-active HindIII fragments of Bacillus thuringiensis in E. coli via plasmid pGA24 as a vehicle. The pPBT9 carries a 1.5kb fragment of B. thuringiensis DNA and pPBT74 a 0.75 kb fragment; both determine E. coli resistance to tetracyclin. The B. thuringiensis fragment of pPBT74 has one specific site for binding E. coli RNA polymerase, while the fragment in pPBT9 has 3 such sites. Bireplicon molecules replicating in E. coli and B. subtilis were constructed by joining pPBT9 and pPBT74 with pBD8 and pBD12 via EcoRI site; the resultant plasmids (pSTS98, pSTS912, pSTS748) promoted the expression of the enterobacterial tet gene in B. subtilis which is controlled by cloned B. thuringiensis DNA fragments. Most of the bireplicon plasmids were unstable

in B. subtilis, but stable in E. coli. One such molecule (pSTS228), wich possesses a natural promotor for the tet gene, did not impart tetracyclin resistance to transformed B. subtilis cell. Figures 4; references 25: 2 Russian, 23 Western.
[127A-12172]

UDC 576.858.9:576.851.48

SPECIFICITY OF Tn9 INSERTION INTO BACTERIOPHAGE GENOME $^{\lambda}$att 80 AS A FUNCTION OF ITS PREVIOUS LOCATION

Moscow GENETIKA in Russian Vol 18, No 8, Aug 82
(manuscript received 24 Jul 81, after completion 23 Oct 81) pp 1221-1230

ZAKHARENKO, V. I., SHATALIN, K. Yu. and SMIRNOV, G. B., Scientific Research Institute of Epidemiology and Microbiology imeni N. F. Gamaleya, USSR Academy of Medical Sciences, Moscow

[Abstract] The present work was undertaken to determine the role of DNA sequences of the donor site of Tn9 integration during its transposition from various locations of chromosome fragments into the bacteriophage $^{\lambda}$att 80 genome. It was shown that the donor site sequences can be responsible for the site selection in the insertion of transposon into the recipient genome. A transposition is a multiple stage enzymatic process accompanied by replication of the element being transposed. In the course of the present work the transposon integration sites were mapped by restriction and heteroduplex analyses. When transposed from chromosomal galT::IS1 gene Tn9 was inserted into the site with coordinates 44.5±2 kb. Transposition from the chromosomal att T9A site led to insertion at coordinates 31±0.7 kb or 33.3± ±0.5 kb and from att T9N site - to coordinates 26.5±5 kb from the left terminal. Two new specific recognition sites were identified for the endonuclease Hind III and it was established that the single strand loop of Tn9 was enlarged in the heteroduplex molecule. One could assume that the DNA sequences surrounding Tn9 in the donor replicon participate in the early stages of the selection: recognition of the transposon insertion fragment and possibly incision into the genome target filament. Figures 5; references 13: 3 Russian, 10 Western.
[136-7813]

UDC 575.24:576.851.48

ESCHERICHIA COLI K-12 MUTANTS WITH INCREASED RESISTANCE TO IONIZING RADIATION. PART 2: STUDY OF DNA DAMAGE AND REPAIR IN γ-IRRADIATED CELLS

Moscow GENETIKA in Russian Vol 18, No 8, Aug 82
(manuscript received 29 Jan 81) pp 1245-1254

BRESLER, S. Ye., VERBENKO, V. N. and KALININ, V. L., Leningrad Institute of Nuclear Physics imeni B. P. Konstantinov, USSR Academy of Sciences

[Abstract] One of the reasons for higher radioresistance of the mutants Gam^{r}E. coli K-12 may be their effectiveness in repairing lethal damage to DNA caused by ionizing radiation by other DNA inactivating agents. The present work was devoted to test this hypothesis by studying formation and repair of single strand (SB) and double strand (DB) breaks of DNA and degradation of DNA in γ-irradiated cells of wild type E. coli strain AB1157 and two of its mutants Gam^{r}445 - one of the least γ-resistant mutants, and Gam^{r}444 - one of the most resistant strains to γ-radiation (single and at least double mutations respectively). The work was performed by the centrifugation method in alkaline and neutral concentration gradients of sucrose. It was found that there were no differences between the three study-groups in respect to the initial yield of SB nor of the rate and extent of SB repair in postradiation incubation in the growth medium. The yield of DB in the Gam^{r}DNA was lower than in the parent DNA and it correlated with the relative radioresistance of the mutants. After exposure to γ or UV radiation, the DNA degradation in the Gam^r mutants was lower than in the wild type. On the basis of these experiments a conclusion was reached that increased radioresistance of Gam^r mutants may be due to two factors: lower formation of enzymic DB or enhanced ability to repair real DB. The first factor contributes to γ-resistance of both mutants, while the second is contributory only to the Gam^{r}444 mutant. Figures 6; references 23: 2 Russian, 21 Western (1 by Russian authors).
[136-7813]

UDC 547.963.3

CONSTRUCTION OF HYBRID PLASMIDS CONTAINING YEAST REPLICATOR

Moscow MOLEKULYARNAYA BIOLOGIYA in Russian Vol 16, No 5, Sep-Oct 82
(manuscript received 18 Nov 81) pp 948-954

LARIONOV, V. L. and SHUBOCHKINA, Ye. A., All-Union Scientific Research Institute of Highly Purified Preparations, Leningrad

[Abstract] Construction of a hybrid plasmid containing a yeast replicator was achieved with a system using a 3 mcm extrachromosomal rRNA gene derived from Saccharomyces cerevisiae 6-1G-P188, fragmented by EcoR1, and bacterial

plasmid pBR325 as a vehicle (which carries gene LEU2 coding for betaisopropylmalate dehydrogenase in the yeast). The resultant hybrid plasmids were tested for transforming efficiency on S. cerevisiae DC5 which carries a defective LEU2 gene. Highest transforming efficiency was shown by the hybrid plasmid Rcp21/11. Rcp21/11 carries a 2400 base pair EcoRi-B fragment of the 3 mcm extrachromosomal DNA which includes the 5S rRNA gene and two spacers which initiated and terminate transcription of the yeast ribosomal operon. Yeast cells containing the Rcp21/11 plasmid are genetically unstable; however, following prolonged cultivation on selective medium the LEU+ trait showed stabilization indicating integration of the constructed hybrid Rcp21/11 plasmid into the yeast chromosome. Figures 3; references 32: 4 Russian, 28 Western.
[189-12172]

UDC 547.963.32.04

USING SYNTHETIC OLIGONUCLEOTIDES IN SCREENING BACTERIAL CLONES FOR RECOMBINANT PLASMID DNA

Moscow BIOORGANICHESKAYA KHIMIYA in Russian Vol 8, No 8, Aug 82 (manuscript received 22 Feb 82) pp 1084-1093

YEFIMOV, V. A. and CHAKHMAKHCHEVA, O. G., Institute of Bioorganic Chemistry imeni M. M. Shemyakin, USSR Academy of Sciences, Moscow

[Abstract] Detailed procedures are described for the rapid screening of E. coli carrying recombinant plasmid DNA by in situ hybridization on nitrocellulose filters with a panel of 14 synthetic oligonucleotides varying in length (11-20 nucleotides). The results showed that oligonucleotide chains less than 13 nucleotides long are ineffective as molecular probes in this respect, while hexadecanucleotide chains are almost five times as efficient in hybridization as the tridecanucleotides. In addition, this system also showed 1.5- to 2-fold greater efficiency with oligonucleotides containing 50-60% GC composition than with 25-30% GC probes. Figures 3; references 14: 4 Russian, 10 Western.
[190-12172]

UDC 578.245:579.861.2

EFFECTS ON INTERFERON PREPARATIONS ON GROWTH OF PATHOGENIC MICROORGANISMS

Kiev DOKLADY AKADEMII NAUK UKRAINSKOY SSR, SERIYA B: GEOLOGICHESKIYE, KHIMICHESKIYE I BIOLOGICHESKIYE NAUKI in Russian No 11, Nov 82 (manuscript received 2 Aug 82) pp 83-85

SPIVAK, N. Ya., SMIRNOV, V. V., corresponding member, Ukrainian SSR Academy of Sciences, ZUYEVA, V. S., REZNIK, S. R. and MIT'KO, V. S., Institute of Microbiology and Virology, Ukrainian SSR Academy of Sciences

[Abstract] An investigation was made of the effects of murine type I virus-induced interferon on the growth of pathogenic bacteria (Staphylococcus aureus, Salmonella typhimurium, Sal. equiabortus, Sal. stanley, Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa, Erwinia carotovora). The vitro studies demonstrated that both native and heated preparations of the interferon inhibited the growth of all the bacteria tested with the exception of Pseudomonas. The inhibitory effects of heated interferon are of particular interest since such interferon does not exhibit antiviral properties. Figures 1; references 5: 4 Russian, 1 Western. [137-12172]

UDC 613.632.313.2

DIGESTIVE TRACT DISEASES IN WORKERS OF THE COKING BY-PRODUCT INDUSTRY

Alma-Ata ZDRAVOOKHRANENIYE KAZAKHSTANA in Russian No 10, Oct 82 pp 38-41

[Article by S. K. Amangel'din, G. V. Morozova and G. S. Amangel'dina, Karaganda Medical Institute]

[Text] Among the poorly-studied diseases of workers in the coking by-product industry are diseases of the organs of digestion. An extensive study, including a study on a person-by-person [?politsevaya] basis of material collected from 1964 to 1979 (22,081 patient's certificates and 8,426 workers' personal cards) for the Karaganda Coking By-Product Plant showed that these diseases accounted for from 5.9 to 14.4% of all the instances of diseases with a temporary loss of work capacity and from 4.8 to 7.7% of the days of work incapacity. From 1964 to 1973, they occupied second place with respect to incidence (after respiratory-organ diseases) and fourth place with respect to days; from 1974 to 1977, third and sixth, respectively; while from 1978 to 1979, fourth and sixth. On the average, from 1975 to 1979, these diseases comprised 5.03 instances and 48.23 days of work incapacity per 100 workers during a complete year. In the dynamics from 1964 to 1979, morbidity parameters with temporary work incapacity showed a distinct tendency toward decline for digestive-organ diseases: in 1964 the parameters of these diseases comprised 8.7 in instances and 64.4 in days; in 1975, 5.80 and 50.20, respectively; in 1979, 5.03 and 48.25.

In recent years (1975-1979) for a variety of digestive-organ diseases, both the number of instances and the number of days of work incapacity showed considerable fluctuations. In particular, per 100 coking laborers working the entire year, these parameters averaged 1.1 and 8.67, respectively, for gastritis and duodenitis, 0.99 and 24.60 for peptic ulcers of the stomach and duodenum, 0.93 and 1.56 for diseases of the oral cavity, salivary glands and jaws and 0.68 and 9.66 for diseases of the liver, gall bladder and pancreas. The remaining digestive-organ diseases were encountered (up to 0.56 instances) rather rarely and introduced no appreciable change in the structure and levels of morbidity.

As a whole in the coking by-product plant, digestive tract diseases were encountered more frequently in men than in women; the mean coefficient was,

accordingly, 1.161. However, disease duration was 1.76 times longer in women than in men. And women were on patient's certificate 1.64 times more frequently than men, only by reason of the liver and gall bladder. These differences in morbidity with respect to sex are explained not only by the anatomic and physiological characteristics of women but also by their working conditions. They perform work involving more frequent stays at the sites (tunnels, pump stations, etc.) most contaminated by chemical substances. Their liver and gall bladder are the most sensitive to various toxic substances.

With increase in the length of service and age of workers, an increase was noted in morbidity parameters. The greatest number of instances and of days with temporary loss of work capacity for the studied illnesses were found among workers with a length of service of 10 or more years. Their age was from 40 to 50 years ($t > 3.0$).

The season of the year exerted an appreciable ($t > 3.0$) influence on the level of morbidity. The highest morbidity parameters per 100 workers in instances (0.50 and 0.62) and in days (7.90 and 8.50) were noted in the summer and autumn, the lowest, in the spring (0.40 instances and 7.30 days) and winter (0.44 and 5.51). This indicates that, in addition to the disruption of the regimes of nutrition, the level of digestive tract diseases is also influenced by the characteristics of labor organization and the production environment developing at different times of the year in the studied plant. In particular, many of the workers take a holiday in the summer and autumn. A nonrational (nonrhythmic) work and rest routine is created; the volume of repair and auxiliary work performed in open areas under conditions of the impact on the body of a high air temperature (25-30° C) and inhalation increases; a large quantity of fluids is used (up to 3.0 kg), in which connection the functions of the gastrointestinal tract are disrupted.

In order to establish differences in morbidity in relation to the influence of separate or of a complex of harmful production factors, we conditionally divided all workers into eight groups taking into consideration the working conditions in shops and sectors. To the first group were assigned primarily workers exposed to coal and coke dust (coal-concentrating factories 1 and 2, coal-preparation and coke-sorting shop of coke shops); to the second, workers exposed to an unfavorable microclimate (coke and pitch-coke ovens); to the third, workers exposed to components of raw coke gas, such as ammonia, phenols, pyridine, sulfuric acid and carbon dioxide (chemical-catching shops without their benzene departments); to the fourth, workers exposed to aromatic hydrocarbons (shop of raw-benzene ratification and benzene departments of chemical-catching shops); to the fifth, workers exposed to aerosols of tar substances and coal pitch (tar-distilling shop and pitch-preparation departments of coke shop). The sixth group comprised worker-repairers (coking-equipment repair shop), the seventh, auxuliary shops (repair-mechanical workshops, warm-water supply shop) and the eighth, the engineering-technical workers.

An analysis of morbidity with respect to the cited occupational-production groups showed that its highest level in instances (3.37) and days (45.87) was in the workers of the second group. They were exposed in the summer to

a very high (up to 40°) air temperature and sharp (up to 70° C) temperature changes, intensive radiant energy (up to 6-8 cal/cm^2·min), harmful gases (carbon dioxide, oxides of nitrogen, etc.) and dust. Furthermore, most occupations in this group require considerable physical exertions.

The remaining occupational-production groups were arranged in the following sequence according to morbidity. Second place was occupied by the sixth group (3.46 instances and 43.9 days of temporary work incapacity); third place, by the first group (2.34 and 33.41, respectively); fourth place, by the third group (2.3 and 42.5); fifth place, by the fifth group (2.25 and 24.2); sixth place, by the seventh group (1.94 and 40.06); seventh place, by the eighth group (1.45 and 14.84); eighth place, by the fourth group (1.25 and 20.0). However, this rank distribution did not correspond to the characteristics of the working conditions. Therefore, the parameters of morbidity with temporary loss of work capacity were standardized with respect to age and sex. This standardization appreciably changed the morbidity parameters of the group ranks. In this case, the decline in the morbidity level according to groups had the following sequence: second, third, fifth, first, fourth, sixth, seventh and eighth. This indicates that in addition to sex and age, sanitary-hygienic factors of production also influence morbidity parameters. Thus, the greatest (2.8-3.7 instances and 24.8-47.8 days) level of morbidity with temporary work incapacity was that of workers in the principal (1-5) groups. Workers of auxiliary shops (group 6) and engineering-technical workers were ill less frequently ($t > 3.0$) than workers in the principal groups. The higher level of morbidity (2.1 instances and 21.9 days) in group 6 workers relative to group 8 (1.52 instances and 15.6 days) should be noted. This, apparently, is explained by the influence on the functions of the internal organs of a forced position of the body (work standing and half bent over) with the absence of organized nutrition (buffets and dining rooms) in these shops.

As a whole, the data presented indicate the important role of unfavorable factors and chemical substances in the spread and increase in the level of digestive-organ morbidity in coking workers. Nevertheless, one cannot fail to mention the significance of such factors as the production environment and the character of labor organization. Thus, the work of many occupations (chutemen, doormen, etc.) involves considerable physical exertions and a forced work posture (squatting, standing, etc.). There are occupations (machine operatives) in which there are no permanent work sites and rest sites. Labor in a number of shops (coking and chemical blocks) has stress components and is intensive due to labor intensification and the servicing of strongly heated (to 1,000° C) ovens and machines. No regulated work and rest routines have been organized for many principal occupations.

Of interest is the quality of the medical-sanitary service. Thus, the mean duration of one disease studied by us in 1975-1979 averaged 11.98 days. At the same time, the mean duration varied sharply for different digestive-organ diseases. In particular, the longer (30.6 days) periods of temporary work incapacity in workers with peptic ulcer of the stomach and duodenum are of interest. Frequently (in 12-18% of instances), an unwarranted, brief (three to five days) work incapacity is noted during diseases of the liver and gall bladder.

Thus, the data of morbidity with temporary work incapacity in coking workers with respect to digestive tract diseases indicate the need for the further intensification of the prophylactic and therapeutic-diagnostic work of the medical service at the Karaganda Coking By-Product Plant. Attention should be directed at sanitizing working conditions and improving the quality of the medical-sanitary service of the workers. At the same time, attention must be given to the execution of a complex of therapeutic-sanitary measures that can be performed without a break from work, that is to say, to the creation of prophylactic-sanitary and dietetic dining rooms, the organization of special diets for workers under harmful working conditions, the hygienic-physiological rationalization of work sites, intensification during the summer and autumn periods of the year of the sanitary supervision of the plant's food blocks and the correct drinking regime of workers in hot occupations and so on. The work and rest routine must be organized with consideration of the injuriousness, heaviness and intensity of work. The overall time required for rest and eating (T) should be computed by the formula:

$$T = Ch + Cit + Cij + 8.2\%$$

where Ch, Cit and Cij are the classes of labor heaviness, intensity and injuriousness and 8.2% is the generally-accepted percentage of the total work time devoted to lunch and personal needs.

Sanitation of the working conditions of workers must be realized with introduction of a complex of technological, technical and sanitary-technical measures.

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PROVISION OF HEALTH CARE IN RURAL AREAS OF KAZAKHSTAN

Alma-Ata ZDRAVOOKHRANENIYE KAZAKHSTANA in Russian No 10, Oct 82 pp 3-13

[Article by M. A. Gribanov, first deputy, Kazakh SSR Ministry of Health: "Tasks of the Republic's Health-Care Units and Institutions for the Improvement of the Medical-Sanitary Security of the Village Population"]

[Text] Thanks to the substantial socioeconomic measures carried out by the party and state, positive results in the health-care field have been attained in the condition of the health of the Soviet people.

The material-technical base of health-care institutions has received considerable development. In 1981 alone, 13 million rubles of capital investments were spent for the construction of hospitals and polyclinics in the rural area, hospitals for 920 beds and polyclinics for 2,700 visits per shift were commissioned and, in the first half of 1982, hospitals for 520 beds and polyclinics for 350 visits were completed. In recent years, 2,487 buildings were constructed and assigned to feldsher-midwife points, and in the past year 41 village pharmacies were moved to new buildings. This made it possible to increase the average capacity of hospitals to 35 beds, of central rayon hospitals centered in the city to 220 beds, of those centered in the village to 177 beds, and of oblast hospitals to 609 beds. In addition to this the conditions for patient maintenance and staff work were improved; diagnostic and treatment consulting rooms and milk kitchens were enlarged. The network of specialized consulting rooms in village rayon hospitals was expanded. By the start of this year, 501 medical outpatient clinics were organized and in operation. The emergency and medical first aid service received definite development, the number of medical positions and ambulances was increased, the volume of care was expanded and the number of calls reached more than 4.3 million. More than 125 million visits were made to all outpatient and polyclinic institutions during the past year.

The Kazakh SSR Ministry of Health attaches special importance to the further provision of our institutions with key medical personnel, to their professional growth and education. Today, 32.7 physicians and 102.0 middle medical workers are provided per 10,000 inhabitants.

In 1981 more than 4,500 physicians and 5,000 feldsher-midwives and nurses got advanced training.

More than 1,700 physicians and 7,000 middle medical workers are annually sent to village therapeutic-prophylactic institutions. Our resolute actions yielded positive changes: two physicians work in 32% of the uchastok hospitals and three and more work in 33%. For the moment, only 27.3% of the village medical outpatient clinics have two and more physicians.

The staffing of central rayon hospitals with physician-specialists has been improved. Medical care is provided in the 12 principal specialties in most rayons.

The organization of patient receiving in polyclinics has been improved, self- and preliminary registration has been introduced, modern methods for diagnosis and therapy are widely employed and information bureaus, pharmaceutical-information consulting rooms, pharmacy points and prophylaxis and rehabilitiative-therapy consulting rooms and departments have been organized. More than 2.5 million people annually undergo prophylactic medical examinations.

Advanced methods of medical care have become an integral part of daily work. Medical outpatient clinics, fluorographic and stomatological installations, clinical-diagnostic laboratories, woman's and children's consultations and, also, advanced, complex medical brigades continuously travel to uchastoks on the periphery.

Feldsher-midwife points have a large role in providing medical care to the village population. Most oblast health-care departments--with the assistance of local party and soviet organs and state and collective farms--have managed to improve the base, equipment and quality of prophylactic work, which has had a positive influence on the state of health of the population, especially that of the children.

The protection of mothers and children has become a law of socialist society. Pediatricians have increased both in the city and in the village. Their supply increased to 4.0, including an increase to 1.8 per 10,000 in the village. In Aktyubinsk, Guryev, Dzhezkazgan, Mangyshlak and Semipalatinsk oblasts, the supply reaches 4.6-4.8 pediatricians. This has yielded positive changes: indices of children's development and health have improved.

As is known, all oblast health-care departments have been assigned the annual task of subdividing the therapeutic and pediatric uchastoks. The mean numbers per single pediatric uchastok at the start of the current year was reduced to 840 children. It should be noted that Aktyubinsk, Turgay, Dzhezkazgan, Semipalatinsk and Tselinograd have performed, while Taldy-Kurgan, Kokchetav, East Dazakhstan, North Kazakhstan, Karaganda and other oblast health-care departments are close to performing the tasks of subdividing and reducing to the established norms the number of children per each uchastok.

As a result of persistent efforts, 922 milk kitchens are active at the present time, including 712 in the village. We note with satisfaction that the Taldy-Kurgan, Dzhezkazgan, Semipalatinsk and Tselinograd oblast

health-care departments have treated the organization of children's nutrition with thorough understanding and all seriousness. With the assistance of the local party-soviet units, work is actively underway here on the mechanization of milk kitchens, the organization of the commercial release of acidulated milk products for children and the introduction of new mixtures; shops have been opened in city milk plants for the release of children's products, which has already had an extremely positive effect on the state of children's health. As a result of the measures taken, child mortality in the republic declined in 1981.

In addition to the definite achievements, the condition of the medical-sanitary security of the village population in a number of oblasts and rayons lags behind the possibilities of modern medicine and the requirements of the village population. A number of central rayon hospitals are of low capacity, the medical outpatient care and emergency medical and first aid still develop at slow rates.

Although by comparison with 1975 the number of visits to physicians per single village resident increased somewhat (3.6 in 1975 and 5.3 in 1981), the health-care organs and institutions do not utilize the possibilities available in the country. In a number of village uchastok hospitals and medical outpatient clinics, patient receiving is conducted by middle medical workers, although physicians are available. We must help the village institutions correct this situation. But first of all, it is necessary to complete in the urban area the subdivision of the territorial therapeutic and pediatric uchastoks. Alma-Ata, Kokchetav, Guryev, and Chimkent oblast health-care departments should accelerate the performance of tasks for the completion of uchastok subdivision.

The average numbers of the population in individual regions in Guryev, Mangyshlak, Chimkent, Kokchetav, Kustanay, Karaganda, East Kazakhstan and other oblasts are still high. Even in Alma-Ata the population numbers exceed the established norm at most territorial therapeutic regions; the situation is no better in Tselinograd Oblast. Presently, the staffing of central rayon hospitals with physicians comprises 99.2%; the uchastok principle of service is being introduced extremely slowly to village rayon centers.

Experience is available in the republic in massive preventive dispensary treatment of the population in the city of Kentau in Chimkent Oblast and of the village population at Akmolinsk State Farm in Tselinograd Oblast. There have already been positive results. It is necessary to copy the experience of their work, to create one's own experimental bases--future schools of advanced experience in dispensary treatment.

A criterion of the effectiveness of preventive dispensary treatment is a decline in morbidity with temporary loss of work capacity and primary output for disablement, the restoration of work capacity and a decline in the mortality of the population.

Complex measures have been carried out in the republic for the preferential medical service of workers in industrial enterprises, transport, construction organization and agriculture and have played a positive role in the decline of worker morbidity with temporary work incapacity.

At the same time, the parameters of temporary work incapacity remain high in Karaganda, Guryev , Alma-Ata, East Kazakhstan, Dzhezkazgan, Pavlodar, Semipalatinsk, Chimkent and Uralsk oblasts in the agricultural and in a number of other branches of the national economy.

The primary output for disablement declined throughout the republic, especially in Pavlodar, Taldy-Kurgan, Tselinograd, Kustanay, Dzhambul, Alma-Ata, Aktyubinsk and Turgay oblasts.

However, worker and employee disablement increased in Guryev, East Kazakhstan, Dzhezkazgan, Karaganda, Uralsk and Chimkent oblasts. This is directly related to the organization of the appraisal of temporary work incapacity, under which individual physicians grossly violate the rules for issuing patient's certificates. This primarily concerns the therapeutic-prophylactic institutions.

The chief-physicians' deputies for the appraisal of temporary work incapacity and the chiefs of the departments of therapeutic-prophylactic institutions do not systematically analyze the quality of diagnoses and the therapeutic and appraisal work of physicians, do not monitor the issuance and extension of patient's certificates and frequently extend them without a personal examination of the patients.

Work proceeds continuously on fields and farms of the sovkhozes and kolkhozes. In order to assure the precise medical-sanitary service to agricultural workers, special attention was given to the work regime of health-care institutions. Additional measures must be taken to improve the work of therapeutic-prophylactic institutions in rural rayons to elevate the level of prophylactic and therapeutic-diagnostic work and to expand and elevate the quality of the prophylactic examinations and dispensary treatment of village inhabitants. A primary task is the need for organizational improvement of the work of emergency and first aid for the village population.

In addition to the activities of health-care organs, the assistance of party and soviet units is needed for the completion by 1985 of the organization of the emergency medical aid service in rural rayons. Whereas in oblast centers and large cities, the emergency medical aid hospitals have been considerably strengthened organizationally, staffed with physicians, well supplied with the necessary medical apparatus and transport, and have specialized brigades, in most rural rayons this service is still without the attention of health-care organizers. Almost everywhere the departments are staffed with only middle medical workers, who perform pre-physician aid, go out on house calls and are concerned with patient transport, the delivery of physicians and blood and, in a number of instances, management work. Therefore, the emergency medical aid of rural rayons is not held in respect and is losing the confidence of the population.

Little attention is given to improving the efficient work of the emergency medical aid service and equipping the line vehicles with radios. These deficiencies in the work of the emergency medical aid service elicit the justified reprimands of the population.

All oblast health departments must develop a plan of organization during the current five-year plan in all rural administrative rayons (where plans are lacking) for emergency and medical first aid hospitals and departments. The plan must provide for such measures as the assignment (or construction) of suitable buildings for the organization of these subdivisions; the determination of the actual requirement for medical and middle medical cadres in these institutions and plans for their preparation in problems in emergency and medical first aid; their staffing with physicians; the provision of hospitals (departments) with stretcher ambulances of enhanced cross-country ability, the appropriate medical equipment and means of communication; the equipping of all ambulances with tranceivers and the organization of their management by radio communications.

Substantial work in providing village residents with emergency aid is performed by the departments of emergency and planning and consultative aid in the oblast hospitals.

The relative importance of air and ground excursions for rendering planning and consultative medical aid to the rural population by specialists from the oblast hospitals has increased in Dzhambul, Kokcheta, Kustanay, Semipalatinsk and Taldy-Kurgan oblasts.

Meanwhile, few flights or trips are made to render planning and consultative aid to the rural population by specialists in Alma-Ata, Guryev, Mangyshlak, North Kazakhstan, Turgay and Tselinograd oblasts, where the departments organize only emergency medical aid and transport, to oblast therapeutic institutions, of the most difficult patients. The situation is no better in Aktyubinsk, East Kazakhstan, Dzhezkazgan, Kzyl-Orda and Pavlodar oblasts.

The attention of specialists and health-care organizers must be focused on the systematic planning aid to village physicians; city therapeutic-prophylactic institutions and the departments of medical and scientific-research institutes must be involved on a sponsorship basis, not to replace village medical workers but rather for the qualified aid of professors, docents and leading specialists and for the organization of quality patient examination and therapy.

Specialized medical aid to the rural population is primarily the responsibility of the oblast hospitals. These are usually large multi-specialty institutions, adequately supplied with medical equipment and apparatus and staffed with qualified cadres. Outpatient and polyclinical care is rendered in an average of 18 specialties, hospital care, in 12. At the same time, the low capacity of Turgay, Dzhezkazgan, East Kazakhstan, Taldy-Kurgan and Guryev oblast hospitals permits no increase in the volume of care.

The consultative care and organizational-methodological direction of several oblast hospitals is unsatisfactory. During excursions, the specialists do not

go thoroughly into the activity of the central rayon hospitals and do not provide concrete recommendations and instructions for the times of the elimination of demonstrated deficiencies; there is no control over execution.

Most chief physicians of the central rayon hospitals focus primary attention on the organization of the work of the rayon hospital itself, to the detriment of the direction of health care in the rayon; the role of chief-physicians' deputies in the medical serivce of the rayon population is disparaged, organizational-methodological work is weakened and the primary parameters of the work of therapeutic-prophylactic institutions are inadequately analyzed.

In recent years the oblast-heath care departments have taken measures for the development of village medical outpatient clinics as a first step in the outpatient care of the population. However, the material-technical base of the majority of village outpatient clinics, as does that of the uchastok hospitals, still remains unsatisfactory. The medical outpatient clinics of Aktyubinsk, Alma-Ata, Dzhambul, East Kazakhstan, Kzyl-Orda, Kokchetav,and Taldy-Kurgan oblasts are particularly poorly supplied with medical equipment and apparatus. Many errors are made in the diagnosis and therapy of patients, their superficial examination and ineffective therapy; this is the result of the inadequate level of the professional training of certain physicians and the low effectiveness of control over the work of the hospitals and medical outpatient clinics on the part of the chief physicians of central rayon hospitals and oblast specialists.

Many oblast health departments are persistently concerned with the improvement of our outposts of rural health care--the feldsher-midwife points. Their physical base, staffing with cadres, equipment and qualitative work parameters have improved. More than 16 million visits are recorded annually in these institutions; they carry out an extensive prophylactic work. Our primary link merits universal attention and concern. However, this is not observed everywhere. Not one building was constructed in 1981 in Alma-Ata, Guryev and Mangyshlak oblasts; the feldsher-midwife points in Guryev, Chimkent, Dzhambul, Dzhezkazgan, Semipalatinsk, Uralsk and other oblasts are poorly supplied with refrigerators, furniture and equipment.

In Dzhezkazgan, Kokchetav, Mangyshlak and Pavlodar oblasts virtually no attention is given to raising the qualifications of middle medical workers.

Inattention, the absence of aid and lack of control on the part of central rayon hospitals in Guryev, Pavlodar, Taldy-Kurgan and Uralsk oblast health-care departments have led to the neglect of certain feldsher-midwife points.

It is impossible to deal with the work of the primary medical subdivisions in general; each feldsher-midwife point individually requires fixed attention and constant monitoring and aid. It remains to increase the role and importance of those points in the medical-sanitary security of the population, especially during the spring-summer and autumn field work. With this purpose, their work must first be concentrated on rendering medical care and performing

prophylactic measures directly at field camps, repair shops and dairy-product farms, on carrying out prophylactic measures and public-health service for pregnant women and children, on the early detection and hospitalization of ill children and on the sanitary-hygienic education of the population.

Because of the specific conditions of agricultural production, especially sheep raising, a portion of the population lives in remote localities. Therefore, we attach special importance to these contingents. It is no accident that the Kazakhstan Communist Party Central Committee and the Kazakh SSR Council of Ministers constantly give attention to the further improvement of the cultural-social service of agricultural workers involved in distant-pasture animal raising. In 1981, alone therapeutic-professional institutions serving the herder population received 316 physicians, including 28 stomatologists, 776 middle medical workers and 93 ambulances. All village uchastok hospitals and medical outpatient clinics serving the herder population have physicians. The inclusion of the herder population in prophylactic examinations increased in the republic as a whole from 85.8% in 1980 to 89% in 1981.

At the same time, for the herders of Chimkent, Mangyshlak and Dzhezkazgan oblasts, 50-67% of the population presently undergoes medical examinations. The health care of the herder population is inadequate in Dzhezkazgan, Mangyshlak and Chimkent oblasts. The quality of the professional examinations and preventive dispensary treatment of the herder population is low, there is no monitoring of the treatment of diagnosed patients, morbidity is not analyzed and, consequently, the appropriate prophylactic measures are not taken.

Certain improvements have been achieved with tuberculosis, but the overall results are still inadequate. The inclusion of the population in prophylactic examinations for tuberculosis in the republic as a whole increases annually; however, a portion of the republic's rural population is not examined.

Our psychiatric and narcological institutions have worked productively. In 1981, narcological dispensaries were newly opened in Ust'-Kamenogorsk and Petropavlovsk, narcological departments have been additionally organized at enterprises, children's departments have been opened at certain psychiatric hospitals and psychoneurological and narcological consulting rooms have been enlarged. The measures taken have made it possible to improve the ability to diagnose mental and narcological diseases. The physician-psychiatrist specialty has become prestigious and the numbers of such specialtists have increased, but today's task is to staff all central rayon hospitals with psychiatrists, to diagnose in good time the borderline state and to transfer psychiatrists' receiving to polyclinics so that they might work hand in hand with therapists, neuropathologists and other specialists.

One of the most massive is stomatological care of the population. Much has been done in the country. Children's stomatological polyclinics and stomatological and dental-prosthetic consulting rooms have been opened. Large material and personnel resources are, however, only a necessary condition and prerequisite for the service's successful activity. However, the

oblast health-care organs have not given the requisite attention to the development of a network of stomatological and dental-prosthetic consulting rooms in the village district. Aktyubinsk, Kokchetav, Kustanay, Pavlodar and Tselinograd oblasts poorly supply the village population with physicians of the stomatological specialty.

The effectiveness of the utilization of the available means and cadres is not increasing, and stomatological polyclinics make few excursions to rural rayons. Therefore, the volume of prophylactic work in Aktyubinsk, Karaganda and Uralsk oblasts has declined. In many rayons, stomatological care is rendered in circuit and frequently amounts only to the removal of teeth, even those liable to treatment. Modern filling materials--silver amalgam, fillings of which last six to eight times longer than those of cement--are little used. Frequently, poorly prepared teeth are filled, which results in the rapid loss of the fillings. Prophylactic work is done nominally.

In the interests of the complete satisfaction of the village population in stomatological care, it is incumbent upon the oblast health-care departments and the Republican Stomatological Polyclinic to introduce into the work of all stomatological polyclinics and consulting rooms modern methods of dental treatment, effective methods of anesthetization, the maximum utilization of silver amalgam for tooth filling and new prosthetic methods.

Special attention must be given during the current five-year plan to the development of a network of stomatological institutions in village regions, to increase significantly the provision of the village population with stomatological care and to increase its quality. This requires the additional organization of a series of stomatological departments and consulting rooms within rural hospitals, polyclinics and outpatient clinics and, within the rayon centers of large rayons, stomatological polyclinics; their provision with modern means of medical technology and the introduction of effective methods and means of prophylaxis, therapy and prosthesis; the work of the leading stomatological consulting rooms and dental-prosthetic laboratories must be further improved. It must be taken as a rule that the brigades of the oblast and city stomatological polyclinics must make systematic, year-round excursions to village regional hospitals and medical outpatient clinics for the massive oral hygiene of adults and children.

In the past year the supply of physician-pediatricians and obstetricians-gynecologists has increased both in the cities and in the village.

The supply of pediatric beds has increased.

At the same time, great alarm is provoked by the delayed subdivision of pediatric uchastoks. Whereas the task of subdividing uchastoks has been accomplished by the Aktyubinsk, Turgay and Dzhezkazgan oblast health-care departments and the Taldy-Kurgan, Kokchetav, East Kazakhstan, North Kazakhstan and Karaganda oblast health-care departments are close to completion, the situation in Alma-Ata, Uralsk, Chimkent, Kustanay and Mangyshlak oblasts is more complex. The subdivision of uchastoks must be completed by the end of 1982.

We have carried out specific work on the organization of children's nurseries. Milk kitchens, including those in the village, were enlarged, But the buildings in which they are located in some places are crowded and poorly constructed, which affects the capacities of the kitchens.

Because of this, in certain rural rayons in Aktyubinsk, Guryev, Mangyshlak, Kzyl-Orda and Turgay oblasts the milk kitchens, not having the conditions for work and the adherence to the technological process in the preparation of milk mixtures, were converted to whole-milk distribution posts. In Aktyubinsk, Dzhezgazkan, Guryev, Kzyl-Orda, Mangyshlak and Turgay oblasts a number of milk kitchens stand idle due to the absence of milk. It is fully understandable that such occurrences elicit justified complaints from the population.

In checking the statements and complaints reaching health-care units, it was established that factors giving rise to complaints and statements have not been eliminated; this causes the repeated recourse of the citizens to higher organizations. A prejudiced, superficial checking always discredits any commision, including also the health-care units.

In connection with the vigorous development of agricultural production, an acute need has arisen for a strengthening of state sanitary supervision in rural locales, especially supervision of the adherence to hygienic norms in the planning and building of villages, water supply, the use of poisonous chemicals and the prophylaxis of occupational, gastrointestinal and other diseases. Much has already been done, and there have increased the level and effectiveness of the state snaitary supervision of environmental protection and control of the work of agricultural and communal objects, of enterprises of the food industry, trade and public nutrition and in children's pre-schools and youth institutions.

At the same time, oblast health-care departments and chief physicians in therapeutic institutions and sanitary epidemic stations are not taking active measures for appreciably improving the work of therapeutic-prophylactic institutions, which must be corrected.

An increased level of infectious morbidity has been noted in the republic for many nosologic forms. At the same time, in Aktyubinsk Oblast, the existing model infectious department in the oblast hospital is not utilized according to its mandate. Six rayons in Aktyubinsk, three in Tselinograd and two rayons each in Semipalatinsk and Uralsk oblasts and others lack beds for infectious disease care.

The spottiness and irregularity of intestinal infections and viral hepatites in various oblasts under identical economic parameters testifies to the varying levels of our work. The Ministry's Sanitary Epidemiological Main Administration, the republic's sanitary-epidemiological stations and their institutions jointly with the oblast health-care departments must concentrate the activity of sanitary-epidemiological station workers on the strengthening of control of food objects, animal-husbandry objects and water supply, of transport and the use of poisonous chemicals. Measures should be taken

towards the organization of toxicological and other inter-rayon laboratories on the basis of the large rayon sanitary epidemiological stations, having supplied them with advanced sanitary epidemiological laboratories. It is necessary to intensify work on the prophylaxis of infectious diseases among the village population.

The quality and sophistication of the medical care of the population in large degree depend upon the level of knowledge and experience of the supervisors of health-care institutions. The position of supervisor, whatever post he may occupy, requires that one's own actions and behavior reflect a high measure of conscientiousness and responsibility, that one be accessible, sensitive and attentive to people and always and in everything exemplify the strict adherence to our laws and communist morality.

Basically, the posts of health-care institution supervisors are occupied by qualified health-care organizers. However, sometimes random people, who in the level of their knowledge and moral qualities are incapable of heading collectives, end up in supervisor posts.

The staff personnel of the Fogelevskaya Uchastok Hospital, Chimkent Oblast, turned to the republic's Ministry of Health with a request to examine the compentency of chief physician Comrade A. S. Syyuntayev for the position occupied. Upon checking, serious deficiencies were uncovered in the chief physician's work. The uchastok hospital in the past was a school of advanced experience, while in recent years many parameters of its work worsened. Signals of the unsatisfactory work of Comrade A. S. Syyuntayev had reached Chimkent Oblast Health-Care Department even earlier; however, no measures were taken. And only after the intervention of the Ministry of Health was the chief physician of the uchastok hospital released from the occupied position.

The main administrations, the Ministry of Health administrations and departments and the oblast health-care departments must assure an increase in the level of supervision of health care in rural rayons and control of the realization of measures for the development and improvement of the medical care of the village of measures for the development and improvement of the medical care of the village population. For these purposes, a council for the medical-sanitary security of the village population must be created in the near future. Similar councils should be created under the oblast health-care departments. Systematic organization-methodological and consultative aid must be supplied to supervisors of health-care organs and institutions and physician-specialists in rural rayons by medical and scientific research institutes and republic and oblast hospitals.

In the interests of generalizing the best experience, encouraging advanced collectives and developing socialist competition, republican competitions for the best work organization must be conducted annually with the active participation of labor unions. Apparently, the time has come for the Social Hygiene and Health-Care Organization Department of the Marginal Pathology Scientific Research Institute and the appropriate departments in medical institutes and the Advanced Training of Physicians Institute to study

carefully and generalize the experience of the supervision of rural health care in the rayon link and to publish methodological recommendations in the necessary quantity for use by the chief physicians of central rayon hospitals in their work. Unfortunately, there are for the moment no good methodological studies on the organization of medical first aid in the central rayon hospitals of rural rayons, in village medical outpatient clinics and the attached (therapeutic and pediatric) uchastoks, on the organization of advanced types of medical care in village rayons and on the work of interrayon specialized departments.

Unquestionably, this is laborious work, but it is now most urgent; it follows from the Food Program, ratified by the May (1982) Plenum of the CPSU Central Committee. It must be hoped that the Science Council of the Ministry jointly with the scientific research institutes will consider the pressing tasks of health care and in the near future will begin resolving this task.

In realizing measures for the strengthening of health-care supervision in village rayons, the roles should be elevated of the chief physicians of central rayon hospitals and of their deputies, especially the deputy for the medical service of the rayon population. His role has somehow been disparaged. The organizational-methodological departments of the central rayon hospitals are not universally staffed with physician-methodologists and in a number of central rayon hospitals these posts are occupied by inactive persons holding more than one office. The organizational-methodological departments of oblast hospitals and oblast health-care departments are exercising poor control over their work. Quality work in any therapeutic-prophylactic institution depends upon the level of diagnosis and therapy and the supply of medical equipment. In spite of the large sums spent on the acquisition of medical equipment, the health-care units in local areas do not give the requisite attention to supplying the therapeutic institutions of rural rayons with medical equipment and apparatus. This, in 1981, out of the republic's fund, 27% of the thermometers, 34% of the stomatological installations, 32% of the anesthesia-respiratory apparatus, 32% of the tonometers, etc., were sent to rural institutions. As a result of simple inattentiveness, certain feldsher-midwife points lack tonometers, scales for weighing newborns and height meters, while the demands of the republic for such apparatus are fully met.

The supervisors of central rayon hospitals have made many complaints against the workers of the Kazmedtekhnika system on account of poor maintenance service and the primitive repair of valuable medical equipment, especially of the X-ray type.

Advanced fluorometry installations frequently break down and are not repaired in good time. Thus, installations were long inoperative in the Kurchumskiy and Glubokovskiy rayons of the East Kazakhstan Oblast. The Main Administration of Kazmedtekhnika required 10 months to repair the X-ray equipment at Tselinograd oncological preventive dispensary.

Electroroentgenographic apparatus was for a long time inoperative due to technical reasons and the low qualifications of the engineering-technical

personnel in Dzhezkazgan, Tselinograd, Kzyl-Orda and Kokchetav oblasts. There is virtually no maintenance service of any kind for the apparatus in village uchastok hospitals and medical outpatient clinics. Here the Kazmedtekhnika Main Administration and its oblast administrations are presented a vast field of activity.

Considerable attention is given to the improvement of the supply of the republic's population with drugs and also to the control of the rational distribution and utilization of the available drug resources. However, the letters of the population testify to serious deficiencies in medicine supply.

In a number of the republic's therapeutic-prophylactic institutions, the requisite contact for the distribution and storage of drugs has not yet been established; as a result drug stocks in hospital departments considerably exceed the established norms.

In spite of the significant development of informational work in the republic, pharmaceutical-information consulting rooms were opened with great difficulties in Karaganda, Turgay, Mangyshlak, Taldy-Kurgan, Aktyubinsk, Dzhezkazgan and Kzyl-Orda oblasts.

The main pharmaceutical and the oblast pharmaceutical administrations should expand the network of pharmacies and pharmacy points and take measures for the wide circular delivery of medicines and increase the number of trucks and vans for drug transport and sale directly at field stations, farms and herder pastures. In the distribution of drug resources, priority is given to the supply of agricultural workers with medicines and pharmaceutical dressing materials.

The Food Program is not only a radical turning point in the rise of agriculture and its associated branches. In its character and scale it is called upon to provide for the progress of the entire national economy, the further prosperity of our Motherland. Health-care workers are called upon to make an important contribution to the Food Program. The improvement of prophylaxis and the elevation of the effectiveness of all links in the medical-sanitary security of workers in agricultural production will promote a strengthening of their health and, in the final analysis, a preservation of labor resources.

The health-care units and all the republic's medical workers will apply their efforts, knowledge and experience for the realization of the tasks advanced by the May (1982) Plenum of the CPSU Central Committee for the improvement and further development of rural health care.

9942
CSO: 1840/173

DEVELOPMENT OF SANATORIA IN SIBERIA

Moscow TRUD in Russian 30 Oct 82 p 2

[Article by USSR Academy of Medical Sciences Academician Yu. Borodin, chairman of the presidium of the Siberian Deparment, USSR Academy of Medical Sciences: "Resources of Siberian Sanatoria. Problems in the Organization of Sanatorium-Health Resort Therapy and Rest", Novosibirsk]

[Text] The economy of Siberia and the Far East has grown vigorously in recent years. This process has been accompanied by the arrival of a population from other zones of the nation. Under such conditions, guaranteeing the protection and consolidation of the health of Siberians is not the most simple of problems.

Where is it preferable for Siberians to rest and undergo treatment? This question is complex, and there is no single answer. It is important to proceed from modern concepts of the cost of human adaptation to new climatogeographic conditions and of alteration in biological rhythms upon rapid change in time zones.

Health-resort specialists long ago determined that treatment and rest yield the greatest returns under familiar conditons of weather and climate. A change in conditions, for example moving from north to south, is an additional load on the body and, in patients, requires a rather prolonged adaptation. This lasts an average of 12 days in northerners arriving in the Crimea and 9 days in inhabitants of the central belt. The justly famous Soviet climatologist G. M. Danishevskiy stressed: "In the practice of sanatorium-health resort selection it must be taken as a rule that the sending of ill northerners to southern Black Sea resorts is contraindicated during the hot summer months--July and August." With certain reservations, this can refer also to residents of the more southern regions of Siberia

As shown by the research of scientists at the Physiology Institute of the Siberian Department, USSR Academy of Medical Sciences, the rapid change in time zones during flights from east to west or from west to east causes prolonged disturbances in human biological rhythms. The restoration of bodily functions after their unbalancing, or desynchronization, requires a certain amount of time.

From the foregoing it is clear that it is no accident that we have devoted so much attention to comparing the effectiveness of patient treatment at Siberian and southern health resorts. The research of associates at the Institute of Clinical and Experimental Medicine of the Siberian Department, USSR Academy of Medical Sciences, has shown that the most pronounced therapeutic effect, for example, in peptic ulcers of the stomach and duodenum and in hypertension, is observed at resorts located in the zone of the patients' permanent residence.

It must be stressed that many Siberian sanatoria, while sometimes inferior to their southern "sisters" in the level of service, frequently surpass them with respect to treatment factors. For example, the Belokurikha Health Resort in Altai Kray possesses unique radon waters. Their activity is approximately seven-fold higher than in Tskhaltubo.

Of course, the economics of treatment must also be considered. The Siberian sanatoria again have a distinct advantage here. According to the data of the Tomsk Scientific Research Health-Resort Science and Physical Therapy Institute of the USSR Ministry of Health, the total expenditures of Siberians are threefold lower during treatment at their own home than in the south. At the same time, a trip to local sanatoria and back costs an average of 21 rubles, while a trip to southern resorts costs 135.

Thus, the utilization of the natural therapeutic factors in Siberia is not only a medical but also a most important socioeconomic task. A further study of local health-resort resources and the scientific foundation of sanatorium construction in various regions are required. The workers of a number of the nation's scientific centers have located promising mineral-water reserves in Western and Eastern Siberia, along the Baikal-Amur Railroad and in the Far East. Vast deposits of therapeutic sapropelic muds and petroleum have been discovered. There was first published the "Klimaticheskiy atlas Zapadnoy Sibiri dlya meditsinskikh tseley" [Climatic Atlas of Western Siberia for Medical Purposes], prepared by the Tomsk Scientific Research Health-Resort Science and Physical Therapy Institute. These investigations demonstrated the prospects for constructing a network of sanatoria not only in the southern regions of Siberia and the Far East but also in other regions.

In speaking of the advantages of rest and treatment for Siberians at, so to speak, their own home, we do not reject the nation's other climatogeographic zones. Our region is still clearly deficient in sanatoria for the treatment of pulmonary diseases, metabolic disorders and others. There are specialized sanatoria of such profiles in other regions and they must be utilized. True, in doing this it is important to consider all treatment indications and the seasons of the year.

The scientists of the Siberian Department, USSR Academy of Medical Sciences, are developing recommendations for the organized rest of the people for the protection and consolidation of the population's health. Organized rest assists in eliminating fatigue and forestalling illness. Children are given special attention. No less important is the health of adolescents and youth.

There are virtually no specialized health resorts for them. What is the solution? One can offer special trips to the usual sanatoria during the holidays. The experience of a number of santoria-dispensaries of industrial enterprises offers convincing evidence of these trips' effectiveness.

Today the Siberians' demand for sanatorium-health resort treatment is not fully satisfied. One of the reasons, on our opinion, is the weak material-construction base.

Mentio is especially needed of Siberian sanatorium projects that neglect the local conditions. For example, a new sanatorium has been constructed for mothers with children at the Belokurikha Health Resort. The Soyuzkurortproyekt Institute has created a veritable palace: vast glazed passages, a light-filled dining room of glass and aluminum...but who needs this beauty if in the winter the patients must sit here in a coat and felt boots? A similar story is repeated regarding the sanatorium Ozero Karachi.

Health-resort resources are a national treasure. But how do matters stand with their conservation in Siberia? We cannot but be alarmed by the situation that has developed at the sanatoria Ozero Shira and Ozero Karachi. The therapeutic lakes have been polluted by sewage and household wastes. The construction of purification facilities, in particular at the Ozero Shira Health Resort, has been delayed.

The list of such sanatoria can be extended by including the threatened therapeutic springs and lakes of Tuva, Buryatia and Transbaikalia. Only joint efforts of local party and soviet units and health-resort councils can provide for effective conservation of health-resort resources.

In our days we attach special importance to the improvement of sanatorium-health resort treatment and rest for agricultural workers. This will be a marked contribution to the realization of the Food Program. An important reserve here is the accelerated construction of sanatoria-dispensaries shared between collective and state farms.

Of interest from this point of view is the experience of Novosibirsk residents. The Dovolenskiy and Krasnozerskiy prophylactic sanatoria were constructed for agricultural workers in this oblast. It would be useful to make one of them a base for studying the problems of organizing the rest of the village population.

Scientists of the Siberian Department, USSR Academy of Medical Sciences, and the Novosibirsk Medical Institute might help in the development of such an institution.

It is worth while to consider also the creation of a new department on questions in health-resort science at the Advanced Training of Physicians Faculty of the Novosibirsk Medical Institute. This department would be involved in creating new treatment methods (including preparations from sapropelic muds), the training of cadres in the field of health-resort science and physical therapy and many other problems.

Scientists of the Siberian Department, USSR Academy of Medical Sciences, have expanded the research front in the field of medical climatology and health-resort science. These directions relate to the program "Health of Man in Siberia". A special scientific program "Health-resort Science in Siberia and the Far East" is now under development. The medical scientists of our vast region are doing everything incumbent upon them to utilize more effectively the region's health-resort resources for strengthening the health of the Soviet people.

9942
CSO: 1840/132

BRIEFS

CARDIOGRAMS BY RADIO--More than 30,000 cardiograms from transport and fishing vessels, from geological expeditions and remote taiga hospitals have been received by radio and interpreted by associates of the Consultative-Cardiological Center of the Maritime Kray Clinical Hospital. As the chief of the center, L. Glybin reported, the Volna-1M telemetric system has become a reliable aid for Far Eastern physicians. It is effective in the early diagnosis and observation of the dynamics of cardiovascular diseases whose symptoms can be judged from an electrocardiogram. [By A. Pushkar'] [Text] [Moscow IZVESTIYA in Russian 17 Jan 83 p 3] 9942

ERA OF 'BIOCHIPS'?--The electronics industry is at the threshold of a new era. This will be the era of "biochips"--devices no bigger than large molecules. The creation is envisioned of "biochips" that are capable of reproducing themselves and, also "biochips" comparable in the complexity of performable functions to the work of the brain. Such a "biochip" introduced into the spine of a patient afflicted with paralysis will receive electrical signals and transform them into commands for the control of the paralyzed limbs. And an artificial nervous system can be created from several of these "biochips" to replace, for example, injured regions of the brain. A "biochip" is under development that is capable of detecting the smallest changes in the concentration of calcium ions in the muscles of the actively working heart and determining on this basis disruptions in the rhythm of cardiac activity. [Text] [Moscow KOMSOMOL'SKAYA PRAVDA in Russian 28 Nov 82 p 4] 9942

PHYSICIANS HOLD CONFERENCE--A conference of Russian physicians was recently held in Voronezh. Its participants discussed in detail how to carry out the resolution of the CPSU Central Committee and USSR Council of Ministers "Additional Measures for the Improvement of Health Care of the Population". The speaker--First Deputy of the RSFSR Ministry of Health N. Trubilin--and the participants presented facts and figures characterizing a constant concern for the health of the people which is a national treasure. The work of emergency care and polyclinics is being improved, greater attention is given to disease prophylaxis and the prevention of job-related accidents; mobile medical care has been diversified. All subdivisions have a steadily increasing supply of the latest equipment developed by scientists, designers and physicians. Good medical service saves tens of thousands of hours of work time. Of interest were the reports on the search for new forms of service to miners, fisherman and shepherds. However, unutilized resources and serious

deficiencies were a definite theme here. And indeed, it is not alarming that capital investments are not fully utilized and medical institutions are very slowly constructed, for example, in Saratov, Gorkiy and Kursk oblasts? At the same time, in Kaluga and Orlovsk oblasts, Altay Kray and Bashkiria small uchastok hospitals are prematurely and unjustifiably closed. As a result, the residents are forced to travel for help for tens and sometimes hundreds of kilometers. It is also difficult to explain the practice, where, in Krasnoyarsk Kray, for example, about 80 feldsher-midwife points have been abolished. It is also impossible to remain silent about the fact that a fifth of the republic's pharmacies have been transfered to carelessly prepared buildings. Justified complaints were addressed to the RSFSR Ministry of Agriculture. There, they at times display regionalism and for years have neglected the expansion of the network of medical institutions. Certain ministries and departments arbitrarily reduce the level of partial participation in the construction of medical institutions. The conference vigorously discussed such distressing phenomena as callousness, negligence and violation of the physician's oath. It is wholly natural that there was sharp argument concerning the work routine of medical institutions. Why, in spite of the orders of the Ministry, nearly a third of the polyclinics, hospitals and dispensaries still do not work on Saturdays, while as many finish work at 5 pm. Many local soviets are resigned to this and do not take note of the violation of executive discipline. Now, the recommendations generalized by the proposals must be followed by practical efforts for strengthening the health of the population and prolonging the active, creative life of the Soviet people. [By V. Komov] [Text] [Moscow IZVESTIYA in Russian 19 Jan 83 p 2] 9942

CSO: 1840/181

BRIEFS

AIR AMBULANCES IN AZERBAIJAN--A telephone rang at the dispatcher center of the air ambulance service in Baku. A distant caller said that an urgent operation was needed for a patient in the Lenkoran District, and that the local surgeon required practical assistance from a specialist in the capital. The call was acknowledged and the center's staff started their usual routine. They found the name of the necessary specialist and his substitute, checked their home an and work addresses and telephones. All this information was given to an ambulance driver who found the surgeon and drove him to the airport which had already been alerted to prepare a plane or helicopter for flight. Over 1,600 such flights are performed each year. There are very few people on the Republic air ambulance service center's staff--the head, dispatchers and technical specialists. And all the 42- physicians of the air ambulance service work according to a special schedule at different medical centers in Baku. They are the best in their own fields in the Republic. The patient doesn't pay anything for the air ambulance's services, although each flight-hour, depending on the class of aircraft, costs the state from 95 to 535 rubles. Altogether, the state spends over 500,000 rubles a year for the up-keep of the air ambulance service in Azerbaijan. [By Kyamil Shakhvaliyev] [Text] [Moscow MOSCOW NEWS in English 23-30 Jan 83 p 8]

CSO: 1852/6

UDC 362.121:658.387

REDUCING THE ANNUAL LOSS OF WORKING DAYS BY PHYSICIANS AT AMBULATORY AND POLYCLINIC ESTABLISHMENTS

Moscow SOVETSKOYE ZDRAVOOKHRANENIYE in Russian No 8, Aug 82
(manuscript received 25 Jan 82) pp 15-220

KANEP, V. V., LIPOVETSKAYA, L. L. and DIL'DAROV, I. Ye.

[Abstract] A statistical evaluation was carried out at the title units in Riga to determine the primary causes of lost working days by their physicians. The results showed that in the 1967-1971 period such losses amounted to 4175 days per 100 medical positions, equalling almost 14% of the total physicine work time. Most of the time lost from work (82%) was due to vacations, illness in the family, maternity leave, service in military registration and enlistment committees, post-graduate education, etc. Based on improved time-planning and work scheduling, by 1979 time lost from work for such causes was cut by 1681 days per 100 positions, which represented a decrease of 36.2% over 1967. References 5 (Russian). [136-12172]

UDC 61:658.386.3(470.45)

CURRENT STATUS AND PLANNED IMPROVEMENTS IN POSTGRADUATE MEDICAL EDUCATION IN THE VOLGOGRAD OBLAST

Moscow SOVETSKOYE ZDRAVOOKHRANENIYE in Russian No 8, Aug 82
(manuscript received 1 Feb 82) pp 50-54

SHCHUCHKIN, V. V. and ZHUKOV, V. A., Volograd Oblast Health Department; TsOLIUV [Central Order of Lenin Institute for the Advanced Training of Physicians] Moscow

[Abstract] Evaluation of postgraduate medical training in the Volgograd Oblast showed that until 1976 no studies had been conducted to determine the need for such a program. However, available data do indicate that anesthesiologists, pathoanatomists, and forensic experts showed the highest

incidence of such training (12.7-22.1%), while physicians specializing in emergency medicine and functional diagnosis were entirely left out of postgraduate education in the 1972-1976 period. Consequently, appropriate measures were taken to provide, and encourage participation in, postgraduate medical training in the Oblast which involved an annual analysis of available programs and participants, centralization of administration of the various regional programs, and improvements in the programs. As a result, the number of physicians availing themselves of such opportunities for professional education can be expected to increase. Figures 2; references 1 (Russian, footnote).
[136-12172]

UDC 575.591

KAMCHATKA KORYAKS. GEOGRAPHICAL STRUCTURE. EFFECTIVE DIMENSIONS AND GENE MIGRATION IN POPULATION

Moscow GENETIKA in Russian Vol 18, No 8, Aug 82
(manuscript received 8 Apr 80 after completion 14 Jul 81) pp 1363-1370

SHEREMETYEVA, V. A. and GORSHKOV, V. A., Chair of Anthropology, Moscow State University imeni M. V. Lomonosov

[Abstract] A study of genetic characteristics of the Koryak people found that average frequencies of genes based on examined blood group loci were within the ranges characteristic of the population of Northern Asia. To analyse the degree of genetic differentiation and the causative factors one needs to study geographical structure of the population, its effective size N_e and gene migration m_e among the component micropopulations. Such a study was performed using questionnaires, genealogic and demographic data obtained during expeditions to the Koryak settlements on the Kamchatka peninsula and on the shores of the Okhotsk Sea. Average age of Koryaks was determined to be 27.3 years. In spite of the changes in population structure and smaller settlements, the population of Koryaks changed little during the past century. The ratio of the effective population volume to the total population N_e/N_t was found to be 29%. This is a stable value in various micropopulations. Because N_e is directly related to reproductivity of a population through generations, it also reflects to a large degree chances for genetic differentiation. Such a differentiation could be countered by gene migration. Two models of gene migration were considered in this study: the "island" and the "stepping stone" models. The "island" model gave the intensity of gene migration $\overline{m}_e = 0.0218 \pm 0.091$ and the "stepping stone" model gave the value $\overline{m}_e = 0.0260 \pm 0.0014$. References 14: 8 Russian, 6 Western.
[136-7813]

UDC: 577.391:576.3

INVESTIGATION OF CHANGES IN CELL MEMBRANES OF CHINESE HAMSTER FIBROBLASTS USING FLUORESCENT PROBE AFTER EXPOSURE TO LASER AND X-RADIATION

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 10 Dec 80) pp 155-159

[Article by A. K. Abdvakhitova, I. M. Parkhomenko and T. N. Sokolova, Biology Faculty of Moscow State University imeni M. V. Lomonosov]

[Text] A study was made of interaction between a fluorescent probe--1-anilinonaphthalene-8-sulfonate--and Chinese hamster cells exposed to a helium-neon laser in stimulating doses. A decrease in fluorescence was demonstrated in the probe bound with irradiated cells; the binding constant (K_b) decreased 1.7-1.8 fold while quantum yield decreased to 1/2-1/3. The quantum yield decreased to 1/2-1/3 and K_b increased 1.5-1.7 fold after x-irradiation in a dosage of 8 Gy.

We previously demonstrated [6] that exposure of Chinese hamster cells to helium-neon laser light at intensity of 8 mW and energy of 60-550 mJ/cm^2 leads to an increase in survival rate of cells, as assessed by the method in [2]. This increase reached 130-140%, as compared to the control. A stimulating effect was also obtained with exposure to monochromatic light from a mercury lamp at a wavelength of λ = 630 nm [6] and low doses of x-radiation. In the last two cases, an effect was observed only with irradiation of unattached cells, and it was concluded that the effect was related to change in their adhesive properties. By exposing cells to laser radiation, we were able to study survival of only unattached cells. The hypothesis had been expounded that, in this case too, the stimulating effect is related to conformational changes in the external surface of cells, and data were obtained to the effect that there is an increase in number of cells attached to glass [slides?] with exposure to lasers. For this reason, we tried to demonstrate, using a fluorescent probe, changes in the surface of unattached cells exposed to laser light, on which the biological effect of stimulation is observed, as well as changes in the surface of cells attached to the glass, which do not present the stimulation effect. In addition, we studied the changes in cell surfaces under the effect of x-radiation in a dosage of 8 Gy, as well as the combination of x-rays and lasers. There are data in the literature about the use of fluorescent probes for investigation of postradiation structural changes in various membranes--liposomes [8], purified erythrocyte membranes [5] and cell nuclei [10].

Material and Methods

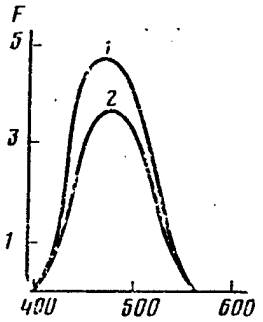
The object of our study consisted of Chinese hamster *Blldii* FAF-28, clone 431 cells cultivated in vitro. We irradiated cells that were not attached to glass and the formed monolayer of cells attached to glass in the case of laser radiation, and only unattached (suspension) cells in the case of x- and combined radiation. The cells were removed from glass mechanically, with a spatula, after they formed a monolayer. Cell concentration in different experiments constituted $1 \cdot 10^5$-$3 \cdot 10^6$ cells/mℓ, but it was the same in control and irradiated specimens in each experiment.

Laser irradiation. Cells were exposed to helium-neon laser light at a wavelength of λ = 633 nm for 25-30 s. Intensity of radiation was 8 mW, i.e., energy constituted 200-240 mJ and energy density 70-85 mJ/cm^2. X- and laser radiation was delivered from an RUM-11 x-ray unit (15 mA, 180 kV, 1 mm Al and 0.5 mm Cu filters, dose rate 1 Gy/min) in a dosage of 8 Gy. Combined radiation was used in two variants: laser radiation in a stimulating dosage preceding x-radiation and, on the contrary, x-radiation before lasers.

Measurement of ANS fluorescence. We used 1-anilinonaphthalene-8-sulfonate (ANS) with a negative charge as a fluorescent probe. Intensity of ANS fluorescence (F) was measured with an SPIL spectrophotometer. Wavelength of exciting light was λ_{exc} = 380 nm and maximum fluorescence spectrum was λ_{max} = 470 nm. We added to 1.9 mℓ cell suspension 0.01 mℓ 10^{-4} M ANS. The titration curve forms a plateau with ANS in a concentration of 3.5-5 μM, depending on concentration of cells. It is known that up to 75% of ANS fluorescence is due to its binding with the plasma membrane of cells [7]. We previously demonstrated that ANS in the above concentration does not penetrate well into cells. We determined the constant for ANS binding with cells, K_b, which characterizes the degree of affinity of the probe for the cell membrane [7], from the titration curve for the cell suspension with ANS solution in dual reciprocal [or inverse] coordinates $1/F = f(1/C_{ANS})$. In addition, we plotted the titration curve for a solution of ANS in concentrations of 3.5-5.0 μM with concentrated cell suspension, and after 7-10 additions the cell concentration constituted 10^5-$3 \cdot 10^6$ cells/mℓ. The curves of ANS titration with the cell suspension were used to plot lines in dual reciprocal coordinates $1/F = f - (1/C_{cell})$ by the least squares method, after which we counted the sites of ANS binding with cells--N. The relative quantum yield of fluorescence of cell-bound ANS was determined in the following manner. The original cell suspension was diluted 1.33-, 2- and 4-fold. ANS was added in concentrations of 3.5-5 μM, incubated for 10 min at room temperature, we recorded fluorescence spectra from 400 to 550 nm, and plotted graphs in the coordinates of $1/F_{470\ nm}/1/C_{cell}$. The intersection of the line and y-axis yields maximum fluorescence of ANS with a concentration of cells tending to infinity. The value of F_0 can serve as a gauge of quantum yield of fluorescence [5]. We assessed the shift of fluorescence maximum according to the ratio, F_{440}/F_{500} [7].

Results and Discussion

The Figure illustrates the ANS fluorescence spectra in a suspension of control cells and unattached cells exposed to a stimulating dose of radiation. We see that F of ANS diminished appreciably after exposure to lasers. Such a decline of F could be related to slowing of ANS binding with cells after they are



Fluorescence spectra for ANS bound with nonirradiated (1) and laser-irradiated (2) (in stimulating dosage) unattached cells
X-axis, wavelength, nm
Y-axis, intensity of fluorescence, relative units

irradiated, to a change in parameters of ANS binding with irradiated cells or decrease in quantum yield of fluorescence of ANS bound with irradiated cells. The influence of the first factor is unlikely, since we know that ANS inserts itself rapidly in the membrane--up to 5 μM ANS in 1 ms [7]. Nevertheless we plotted curves describing the kinetics of ANS binding in a concentration of 5 μM with irradiated and nonirradiated curves over a period of 0.5-16 min. We failed to observe slowing of the binding reaction of ANS with cells after exposure to lasers. X-radiation, as well as both combinations of radiation, led to a decrease in F of ANS by the same magnitude as in the case of laser irradiation. No slowing of ANS binding was observed after irradiation.

Determination of the number of binding sites and ANS binding constants (Table 1) revealed that there was no appreciable change in number of binding sites before and after laser radiation, and if it did decrease, it did so negligibly, by 1.2 times, and could hardly play a deciding role in lowering the intensity of fluorescence of laser-irradiated unattached cells. When unattached cells were exposed to a laser beam in a stimulating dosage, there was a 1.7-1.8-fold decrease in K_b, i.e., the affinity of the probe for the membrane also diminished to the same extent, and this is apparently one of the causes of decrease in F. The table indicates that the quantum yield of fluorescence of ANS bound with irradiated cells decreased to 1/2-1/3. Thus, the decrease in F of ANS bound with unattached cells exposed to a stimulating dose of laser light is determined the most by decrease in quantum yield of probe fluorescence, as well as decrease in constant for probe binding with cells.

Table 1. Parameters of binding and quantum yield of ANS fluorescence in control unattached cells and those exposed to laser radiation in stimulating dose

PARAMETER	CONTROL	RADIATION	RADIATION/ CONTROL
NUMBER OF BINDING SITES OF ANS WITH CELLS N, μM	3,18 2,35	2,68 1,89	0,84 0,80
QUANTUM YIELD, F_0	1 1 1	0,50 0,61 0,34	0,50 0,61 0,34
BINDING CONSTANT K_B FOR ANS WITH CELLS, μM^{-1}	0,46 0,77	0,27 0,43	0,59 0,56

Examination of cells attached to glass involved determination of cell fluorescence immediately after irradiation, 1 and 2 days after irradiation. F of control and irradiated cells showed virtually no change, both immediately after exposure and 1 and 2 days after irradiation. As can be seen in Table 2, exposure of cells attached to glass to lasers did not alter the number of sites

of ANS binding with cells or quantum yield of ANS fluorescence, and altered K_b insignificantly. These changes were observed immediately after irradiation and leveled off within 1 day after exposure. Perhaps, the appreciably milder degree of observed changes is related to the fact that only the part of the cell surface on the boundary of the medium is involved in the process of change in this surface, whereas another part, which is firmly attached to glass, does not participate in it.

Table 2. Parameters of binding and quantum yield of ANS fluorescence in control cells attached to glass and those exposed to stimulating dose of laser radiation

PARAMETER	RIGHT AFTER IRRADIATION/ CONTROL	AFTER 1 DAY/ CONTROL	AFTER 2 DAYS/ CONTROL
N NUMBER OF BINDING SITES OF ANS WITH CELLS, μM	$\frac{0,62}{0,61}=1,02$	$\frac{0,50}{0,49}=1,02$	$\frac{0,43}{0,39}=1,10$
QUANTUM ANS FLUORESCENCE YIELD, F_0	$\frac{143}{125}=1,14$	$\frac{500}{500}=1$	$\frac{250}{250}=1$
BINDING CONSTANT K_B FOR ANS WITH CELLS, μM^{-1}	$\frac{3,49}{2,96}=1,18$	$\frac{0,75}{0,73}=1,03$	$\frac{1,84}{1,89}=0,97$

Table 3. Parameters of binding and quantum yield of ANS fluorescence in control unattached cells, those exposed to radiation in a dosage of 8 Gy (R), x- and laser radiation (R+L), laser and x-radiation (L+R)

PARAMETER	R/CONTROL	R+L/CONTROL	L+R/CONTROL
NUMBER OF ANS-CELL BINDING SITES N, μM	1	1	1
QUANTUM YIELD OF ANS FLUORESCENCE, F_0*	0,46	0,35	0,37
ANS-CELL BINDING CONSTANT K_B, μM^{-1}	$\frac{0,36}{0,25}=1,44$	$\frac{0,25}{0,24}=1,04$	$\frac{0,21}{0,24}=0,88$
	$\frac{0,42}{0,25}=1,68$	$\frac{0,27}{0,25}=1,08$	$\frac{0,24}{0,25}=0,96$

*Quantum yield of intact cell fluorescence is taken as 1.

It was previously shown [6, 11] that the deleterious effect of ionizing radiation can be modified by a stimulating dose of laser radiation. This effect is observed only when cells are exposed to lasers after ionizing radiation. It was interesting to observe the change in cell surface under these conditions. It was established that x-radiation and combined exposure of unattached cells lowers F of ANS. In all three cases, there were no changes in number of ANS binding sites with cells, as compared to the control; but in all three variants of irradiation there was a decrease to 1/2-1/3 in quantum yield of ANS fluorescence (Table 3). Exposure of unattached cells to x-radiation in a dose of 8 Gy elicited a 1.5-1.7-fold increase in K_b, i.e., increased affinity of the probe for the cell membrane. In the case of combined irradiation, in both orders--

x-rays before lasers and lasers before x-rays--the value of K_b reverts to the control level.

The decrease in quantum yield after x-irradiation could be due to formation of peroxidation products which extinguish fluorescence [7], penetration of water molecules deep into the membrane, which is also a fluorescence extinguisher [7, 10], conformational or biochemical (for example, oxidation of protein SH groups) changes in membrane proteins or lipids [5]. An increase in polarity of the microenvironment of the probe and/or decrease in microviscosity of the medium could result from biochemical and conformational changes in proteins or lipids. However, an increase in polarity should be associated with a shift of fluorescence maximum to the long-wave region. Since such a shift was not observed, either in our experiments with use of x-rays and lasers or under the effect of damaging doses of x-radiation on erythrocyte membranes [5], the decrease in microviscosity, change of the membrane to a more fluid state, apparently makes the main contribution to the decrease in quantum yield. We cannot rule out the possibility that exposure of cells to laser radiation, like x-radiation, causes changes in the membrane that are conformational in nature, which are manifested by decrease in membrane microviscosity, as indicated by the decreased quantum yield of ANS fluorescence.

The changes in K_b in different directions with lasers and x-rays could be related to changes in ion permeability of the cell membrane. There are indications that there is increased loss of endogenous calcium ions in mitochondria of irradiated plants, mitochondria of the rat liver, as well as elimination of potassium into the surrounding solution after x-irradiation. The incubation medium did not contain Ca^{2+} and K^{+} ions [9]. The release of ions, particularly bivalent calcium, which has a high affinity for phosphate to whose local field ANS reacts first of all, could lead to decrease in negative charge of the cell membrane and, accordingly, increase in affinity to it of ANS and rise in K_b. There are also data in [3] in favor of this assumption, which indicate a decrease in electrophoretic mobility of erythrocytes with increase in dosage of x-radiation, due to decrease in membrane surface charge. It is important to mention that mouse melanoma cells, in which there was restoration of surface charge, also presented restoration of their colony-forming capacity [4].

We have demonstrated that there is inhibition of Ca^{2+} exit from cells after exposure to lasers, and this could cause a decrease in K_b. For the time being, it is difficult to explain why K_b returns to the control level with both orders of combined radiation, whereas the protective effect is observed only when x-rays precede lasers. Perhaps, the changes in the cell membrane caused by laser radiation do not have time to be manifested "in depth" in the interval (15-30 min) between exposure to lasers and x-rays.

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INVESTIGATION OF RADIOPROTECTIVE EFFECT OF CYSTEAMINE ON MODEL OF HEAT-INDUCED PROPHAGE LAMBDA

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 25 May 81) pp 176-182

[Article by S. Ye. Bresler, V. L. Kalinin and I. N. Suslova, Leningrad Institute of Nuclear Physics imeni B. P. Konstantinov, USSR Academy of Sciences, Gatchina]

[Text] Studies were made of lethal and mutagenic effects of ^{60}Co γ-quanta on prophage λc1857 in lysogenic cells of Escherichia coli AB1886 uvrA6 and AB2463 recA13 irradiated in the absence or presence of cysteamine (0.05 M). With heat induction immediately after γ-radiation, cysteamine sensitizes prophage to the lethal effect of γ-quanta (DMF [dose modification factor] ≈1.5). In the presence of cysteamine, the frequency of γ-induced *c*-mutations is much higher in prophage than in the absence of cysteamine, in lysogen AB1886, but not lysogen AB2463. With induction of prophage after postradiation incubation in broth, neither survival nor incidence of γ-induced mutations depend on presence of cysteamine at the time of irradiation or on the product of the recA$^+$ gene.

One can use heat-inducible prophage λc1857 ind$^-$ to study damage and repair of DNA in γ-irradiated Escherichia coli cells [1], since the DNA of this prophage is an element of the cell chromosome in lysogenic cells and is not excised under the effect of radiation due to ind$^-$ mutation. The prophage can be induced by raising temperature to 43°C at any time: either immediately after irradiation or after prolonged postradiation incubation. Survival of prophage, as determined by the capacity of thermoinduced cells to form negative phage colonies (NC), depends on development of lethal damage in prophage DNA and subsequent repair in independently replicating phage DNA in the former case and in the cell chromosome in the latter. Prophage λc1857 makes it possible to observe not only lethal, but mutation damage to DNA [2]. It is the most convenient to study *c*-mutations that lead to formation of transparent NC at 32°C, the temperature at which parent phage forms cloudy NC.

In this study, we used heat-induced prophage λc1857 to investigate the distinctions of processes of repair and radiation mutagenesis in E. coli cells exposed to γ-radiation in the absence or presence of cysteamine, which is a radioprotective agent that effectively protects bacterial cells against the lethal effect of ionizing radiation.

Material and Methods

We used the following lysogenic strains of E. coli K12: AB1886 uvrA6 (λc1857) deficient in system of excision repair of UV [ultraviolet] damage and AB2463 recA13 (λc1857) deficient in RecA protein and mutagenic system of SOS repair of DNA.

Lysogenic cultures were cultivated at 32°C in aminopeptide broth to the middle of the exponential phase; cells were precipitated by centrifugation and resuspended in the initial volume of phosphage buffer M9 with or without cysteamine HCl (0.05 M). The suspension was incubated at 32°C for 15 min, then exposed at 0°C to ^{60}Co γ-quanta from a "Issledovatel'" [Researcher] unit (dose rate 110 Gy/min). Irradiated specimens were diluted 2-fold in aminopeptide and divided into two batches, one of which was submitted to heat induction (43°C, 15 min) immediately after irradiation ("instant induction"), and the other was incubated at 32°C with slight mixing for 90 min, then induced with heat ("delayed induction"). The infection centers were inoculated on nutrient aminopeptide agar by the standard two-layer method, using an overnight broth culture of wild type strain AB1157 as indicator, and incubated at 32°C. Phage titer (N) was calculated after 18 h, while the number of c-mutants (N_m) forming clear NC at 32°C was counted after 48 h. When counting N_m, the suspension of heat-induced lysogens was diluted before inoculation, so that there would be 3000-5000 NC per Petri dish. We used the method described in [3] to determine the capacity of γ-irradiated cells to maintain growth of nonirradiated phage λ ("efficiency" [productivity, output]).

In a control experiment, we determined the amount of free phage in lysogenic cultures before and after irradiation, treating aliquots of noninduced culture with chloroform, removing killed cells by centrifugation and inoculating the supernatant on a subculture of strain AB1157. The number of free phages in all samples, including those irradiated in the presence of cysteamine, did not exceed 1% of the titer of heat-induced infectious centers. We used the method described in [2] for statistical processing of results of independent experiments (10 for lysogen AB1886 and 5 for lysogen AB2463).

To test the effect of cysteamine on survival of γ-irradiated lysogenic AB1886 cells, aliquots of irradiated culture that were not submitted to heat treatment were inoculated on aminopeptide agar, incubated at 32°C and we counted the colonies after 18 h. In the study of induction of direct Lac$^-$ mutations in the cell chromosome that lead to loss of capacity to ferment lactose, we used the wild type prototrophic strain W3110 of E. coli, which was inoculated on lactose tetrazolium agar (1.5 g beef extract, 3 g yeast extract, 6 g peptone, 10 g lactose, 50 mg 2,3,5-triphenyltetrazolium chloride and 18 g agar per liter water). On this medium, colonies of Lac$^-$ mutants are stained dark red, while colonies of the parent strain remain white.

Results

Cysteamine was effective in protecting lysogenic cells of strain AB1886 (λc1857) against the lethal effect of γ-radiation: the dose modification factor (DMF) on the level of LD_{10} constitutes 3.5 (Figure 1a, curves 5 and 6). However, in the case of instant induction of prophage λc1857, in these cells, presence of cysteamine during γ-irradiation not only failed to protect prophage against inactivation, but sensitized it with DMF ≈1.5 (Figure 1a, curves 1 and 2).

Death of prophage in γ-irradiated cells was unrelated to decreased efficiency of cells, since even with exposure to γ-radiation without cysteamine, efficiency diminished by less than a factor of 10^1, with delivery of radiation in a dosage of 4 kGy, with which prophage survival decreased by a factor of 10^3 (Figure 1a, curves 1 and 7). Moreover, with irradiation in the presence of cysteamine, in the case of instant induction prophage perishes, at lower doses, than bacterial cells that contain it.

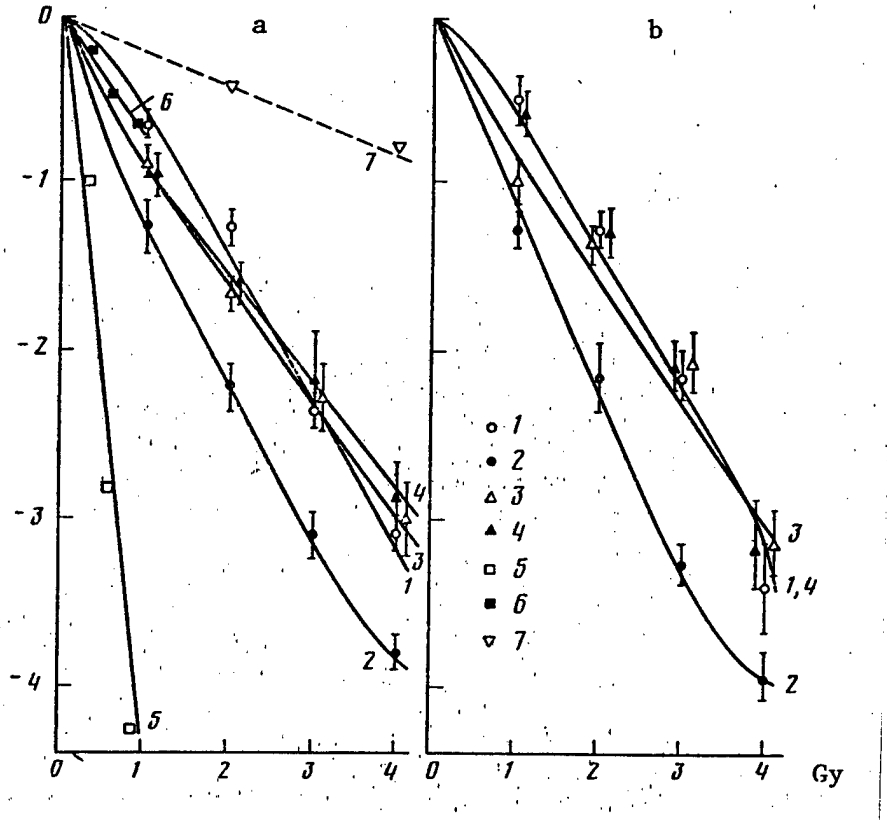

Figure 1. Lethal effect of γ-quanta on prophage λ and E. coli cells. X-axis, dosage of γ-quanta, kGy; y-axis, logarithm of survival

a) strain AB1886 uvrA6(λc1857)
b) strain AB2463 recA13(λc1857)
1,2) prophage survival with instant induction
3,4) prophage survival with delayed induction
5,6) survival of E. coli AB1886 uvrA6(λc1857) cells
7) E. coli cell capacity to maintain reproduction of phage λ
1,3,5,7) irradiation without cysteamine
2,4,6) irradiation in the presence of 0.05 M cysteamine

Postradiation incubation of cells exposed to γ-radiation in nutrient broth did not increase survival of prophage after irradiation without cysteamine, and was associated with perceptible increase in survival after irradiation in the

presence of the protective agent (Figure 1a, curves 3 and 4). In the case of delayed induction the dose-survival curves for prophage exposed to radiation with and without cysteamine virtually coincided. Presence of cysteamine increased appreciably the incidence of γ-induced mutations with instant induction of prophage λc1857 in AB1886 cells (Figure 2a, curves 1 and 2). Postradiation incubation of irradiated lysogenic cells did not alter the dose curve for yield of *c*-mutants in the case of irradiation without cysteamine, and elicited a reliable reduction of N_m/N in prophage irradiated in the presence of the protector (Figure 2a, curves 3 and 4). As in the case of survival rate, curves $N_m/N = f(D)$ were very similar to one another with delayed induction of prophage after irradiation in the absence and presence of cysteamine. A coincidence of $N_m/N = f(D)$ curves with irradiation in the absence and presence of cysteamine was also observed for induction of direct Lac^- mutations in the bacterial chromosome (Figure 3). The form (presence of plateau with high doses) of the $N_m/N = f(D)$ curves for bacterial Lac^- mutations resemble the corresponding curves for *c*-mutations in prophage with delayed induction.

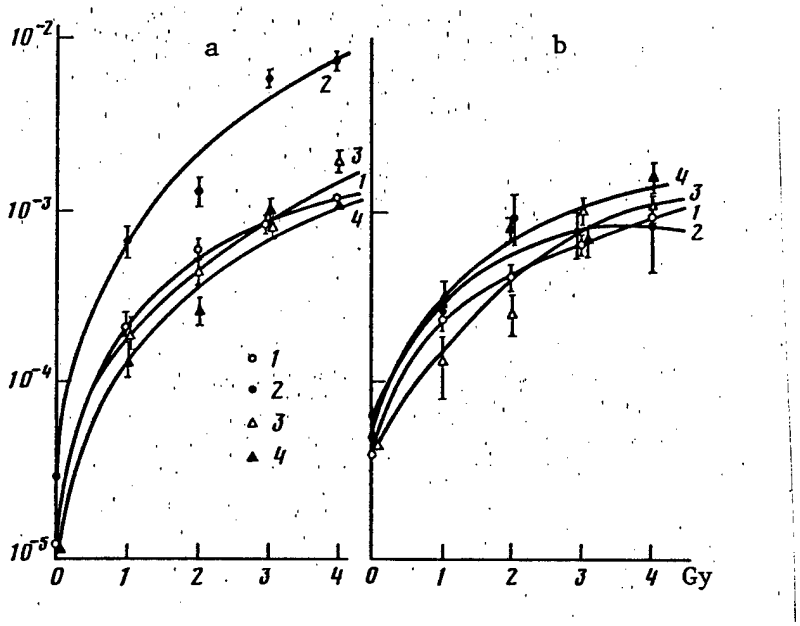

Figure 2. Mutagenic effect of γ-quanta on prophage λ. X-axis, dose of γ-quanta, kGy; y-axis, relative incidence of *c*-mutants (N_m/N)

a) strain AB1886 uvrA6(λc1857)
b) strain AB2463 recA13(λc1857)
1,2) induction immediately after irradiation
3,4) induction 90 min after irradiation
1,3) irradiation without cysteamine
2,4) irradiation in the presence of 0.05 M cysteamine

The curves of dose as a function of survival and mutagenesis with instant and delayed induction of prophage λc1857 in γ-irradiated E. coli wild type cells (strain AB1157) did not differ from the illustrated curves for strain AB1886

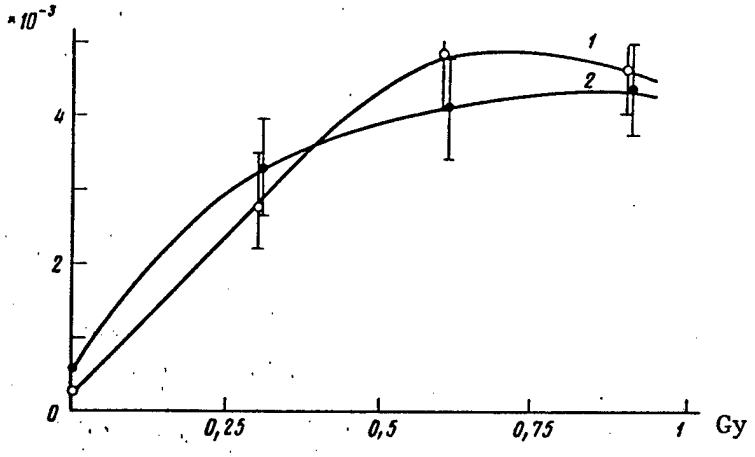

Figure 3. Induction of Lac⁻ mutations with exposure of E. coli cells to γ-radiation. X-axis, dosage of γ-quanta, kGy; y-axis, relative incidence of Lac⁻ mutants

1) irradiation in the absence of cysteamine
2) irradiation in the presence of cysteamine

(data not shown). Survival of γ-irradiated prophage in AB2463 recA13 cells (Figure 1b) also coincided with survival in AB1886 cells. Incidence of γ-induced *c*-mutations as a function of dose with instant and delayed induction of prophage after irradiation in the absence of cysteamine, as well as with delayed induction after irradiation in the presence of cysteamine, was the same for strains AB1886 and AB2463 (Figure 2a and 2b). It is only with instant induction of prophage after irradiation in the presence of cysteamine that the yield of *c*-mutants was much lower for prophage in AB2463 cells than AB1886 cells, and it virtually failed to differ from the yield of mutants with irradiation in the absence of cysteamine.

Discussion

When exposed to γ-radiation in the absence of protective agent, prophage λcl857 in E. coli AB1886 uvrA6 cells that are not deficient for repair of most γ-induced injuries is inactivated with smaller doses than extracellular phage λ irradiated in 4% nutrient broth [4]. In the former case the median lethal dose is about 1.2 kGy (Figure 1a) and in the latter, 2.7 kGy [4]. Intensified death of prophage is unrelated to impaired efficiency of bacterial cells (see also [1]). The coincidence of curves of dosage as a function of prophage survival with instant and delayed induction suggests that correction of γ-induced lethal damage proceeds with equal efficiency in DNA of phage that reproduces vegetatively and in the cell chromosome. Gamma-induced premutation injuries were also fixed with equal efficiency in inherited mutations. Neither prophage survival nor fixation of premutation damage after γ-irradiation in the absence of cysteamine is related to the product of bacterial gene $recA^+$ in the case of both instant and delayed induction. This warrants the assumption that the recA-dependent system of SOS repair is not involved in fixation of mutations in prophage exposed to γ-radiation in the absence of cysteamine. Probably, mutations are formed in this case by a replicative, rather than repair, mechanism.

N_m/N as a function of survival (but not dosage) was about the same for prophage irradiated without protector as for phage irradiated in an extracellular state in nutrient broth [4]. Moreover, the $N_m/N = f(D)$ curves were very similar for induction of direct mutations in prophage DNA and the host cell chromosome proper in the case of low doses (up to 1 kGy). Consequently, as in the case of ultraviolet irradiation [2], γ-induced mutagenesis reflects well in prophage with delayed induction the formation of direct mutations in the cell chromosome.

Let us now refer to the effect of cysteamine on behavior of γ-irradiated prophage. There are two opinions in the literature concerning the mechanism of radioprotective action of cysteamine and other protective agents on bacterial cells exposed to γ-radiation. According to one of them, protective agents emerge in the role of interceptors of free radicals eliciting cell death [5]. The alternative hypothesis is that protectors chemically modify DNA damage caused by radiation, eliciting physical restitution [6] or creating conditions for more efficient DNA repair [7]. The radiosensitizing effect of cysteamine, which we discovered with instant induction of prophage, is absolutely inconsistent with the first of these hypotheses: interception of inactivating free radicals could only elicit a dose-modifying protective effect. At first glance, our data also contradict the second hypothesis. However, they only seem to be contradictory, and can be readily attributed to the differences in replication of the bacterial chromosome and DNA of phage that multiplies vegetatively.

According to the hypothesis of radioprotective action of protective agents that was developed in our laboratory, the protective effect of cysteamine is based on inhibition of incision γ-endonucleases [7]. In the case of irradiation without protective agent, many single-stranded breaks occur in DNA, both as the direct result of radiochemical processes and under the influence of repair γ-endonucleases, which cause incision of DNA next to damaged bases. Each of the single-stranded breaks is a potential site for initiation of exonuclease degradation of DNA, which could lead to appearance of enzyme-induced repair of double-stranded breaks as a result of overlapping of an extensive exonuclease break in one of the DNA strands with a single-stranded break in the complementary strand [7, 8]. Unrepaired double-stranded DNA breaks, including those of enzymatic origin, are the main cause of death of wild type cells exposed to γ-radiation [9, 10]. Irradiation of cells in the presence of protector reduces the initial yield of single-stranded breaks and exonuclease degradation of DNA [7], and ultimately suppresses formation of enzymatic double-stranded breaks.

Hence, it becomes clear why cysteamine, which effectively protects lysogenic cells proper, does not protect prophage with delayed induction exposed to γ-radiation from destruction. Most likely, this is related to the dissimilar probability of double-stranded DNA breaks (including those induced by repair enzymes) in chromosomes of phage and the bacterial cell, which differ from one another in molecular weight by almost 100 times: while the first double-stranded break appears with exposure to radiation in a dosage of 5.3 kGy in the DNA of superinfective phage λ irradiated with 4 MeV electrons [11], the dosage of γ-radiation is 25 Gy for development of the first double-stranded break in a bacterial chromosome [9]. In the former case, this is reliably higher than the median lethal dose LD_{37} and in the latter, it is lower. Consequently, because of the limited size of the genome of phage λ, double stranded DNA breaks induced by enzymes are not the principal cause of prophage death

when exposed to γ-radiation, and elimination of these breaks should not affect prophage survival in the case of delayed induction.

However, the prophage chromosome contains many damaged DNA bases after irradiation in the presence of protective agent. It can be assumed that, at least some of them, like the ultraviolet-induced pyrimidine dimers, are irreparable injuries that block DNA replication. In the relatively slowly replicating bacterial chromosome, these modified bases are gradually repaired without error, by means of excision repair, without production of "enzymatic" double-stranded DNA breaks, and they do not affect cell viability. Such injuries play a different role in the case of rapidly replicating phage DNA. With instant induction of prophage after exposure to γ-radiation in the presence of cysteamine, rapid replication of DNA with irreparable damage leads to formation of lethal postreplication gaps, which are probably corrected less efficiently than single-stranded breaks, which prevail after γ-irradiation in the absence of the protective agent. This is what leads to cysteamine sensitization of prophage death in the case of instant induction after γ-irradiation. Evidently, the postreplicative gaps are eliminated with the participation of inducible, recA-dependent system of SOS repair, which tends to make mistakes, which leads to drastic increase in incidence of γ-induced mutations in prophage in $recA^+$ cells, but not in $recA^-$ cells. Postponement of heat induction of prophage in cells irradiated in the presence of cysteamine is instrumental in flawless excision repair of γ-damaged bases and restores both lethal and mutation effects to "normal" levels, as observed after irradiation in the absence of cysteamine. Since repair of lethal and premutation damage was demonstrated in ultraviolet-induced injuries to $uvrA^-$ cells that are deficient in excision repair, it is not ultraviolet-endonuclease, but some other enzymes that are involved.

We previously demonstrated that cysteamine protects extracellular phage against the lethal effect of γ-radiation in nutrient broth, and the DMF depended on the repair genotype of the host cell [4]. We attributed this effect to change in nature of DNA injuries with exposure to γ-radiation in the presence of protective agent, i.e., in essence to the same factors that elicit radiosensitization in the case of exposure of prophage to γ-radiation. To explain this contradiction, we must assume that the chemistry of modified bases formed after γ-irradiation in the presence of cysteamine in free phage DNA is not the same as in bacterial cell DNA. This could be related to the different environment of DNA in free phage and bacterial chromosome. Nor can we rule out the possibility that the differences are attributable to the set-up of experiments: in the case of instant induction of prophage, its development is initiated several minutes after termination of irradiation, whereas in the experiments with extracellular phage [4] cells were infected at least several hours after irradiation. Preliminary experiments revealed that when extracellular phage irradiated in the presence of cysteamine is stored, both survival and frequency of mutations in it change gradually. In any case, prophage is a more adequate model for investigation of the protective effect of cysteamine on bacterial cells than extracellular phage.

In conclusion, let us note one more contradiction. In our experiments, cysteamine did not affect the yield of direct γ-induced mutations either in prophage with delayed induction or the chromosome of bacteria proper, although it had been previously demonstrated that there is reliable decrease in yield

of reverse $argF_{am} \rightarrow Arg^+$ mutations in E. coli B in the case of γ-irradiation in the presence of cysteamine [12]. It can be assumed that this is related to differences in nature of premutation damage responsible for induction of direct mutations in structural genes and suppressor mutations in tRNA loci.

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COMPARATIVE EVALUATION OF EFFICACY OF RADIOPROTECTIVE AGENTS ACCORDING TO CRITERIA OF BONE MARROW AND GASTROINTESTINAL TRACT PROTECTION

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 3 Sep 80) pp 183-186

[Article by N. N. Pyatovskaya and I. Ye. Brumberg, Military Medical Academy imeni S. M. Kirov, Leningrad]

[Text] In experiments on mice, it was demonstrated that the radioprotective agent, 4-aminobenzo-2,1,3-thiadiazol, unlike cystamine, protects hemopoietic tissue against ionizing radiation and has no radioprotective effect on the gastrointestinal tract. The effect of this agent is manifested in bone marrow on the level of stem cells and does not affect cells in the proliferative and maturing pool.

By virtue of differences in their physicochemical properties, distinctions referable to distribution in the body, as well as depending on mode of administration, radioprotective agents protect to dissimilar degrees the bone marrow and gastrointestinal tract (GIT) [1-4].

Our objective here was to make a comparative study of efficacy of radioprotective agents according to the criterion of protection of bone marrow and GIT with different routes of administration of the agents. We compared agents containing in their structure an atom of sulfur, but differing in chemical structure: 4-aminobenzo-2,1,3-thiadiazol (ABT) and cystamine [5, 6]. It is known that cystamine is a highly effective radioprotector, which protects the organism against both bone marrow and intestinal death [2]. Its radioprotective effect on bone marrow has been studied quite comprehensively [7-9]. We repeated some of the studies in order to be able to compare, in one experiment, the efficacy of cystamine and ABT, an agent that has been relatively little-studied.

Material and Methods

Experiments were conducted on male mongrel and BALB/c mice (18-20 g). The animals were exposed to ^{60}Co γ-rays (dose rate 0.5 Gy/min). Cystamine dihydrochloride and ABT were given intraperitoneally in doses of 225 and 50 mg/kg, respectively, and by mouth in doses of 400 and 75 mg/kg. The study of radioprotective action of these agents on bone marrow was pursued with exposure of

mice to radiation in a dosage of 7.5 Gy. The severity of the bone marrow syndrome was assessed according to animal survival between the 7th and 30th days, quantity of myelokaryocytes in the femur and cells with chromosome aberrations (ana-telophase analysis 24 h after irradiation). We also counted colony-forming units (CFUc) in exogenous cloning of bone marrow cells in recipients exposed to 7 Gy radiation [10].

To study protection of the GIT, the mice were exposed to radiation in a dosage of 10 Gy. We assessed radiation damage using criteria that were analogous to those used to examine bone marrow, with the exception of determination of CFUc. We assessed the condition of the GIT according to survival of animals for 6 days after irradiation, i.e., during the period of "intestinal" form of death [2, 11, 12]; we also counted cells in the mucosa of the small intestine on the 3d day [3], during the period of maximum decline in number of cells. Aberrant mitoses were recorded at the ana-telophase on squashed preparations of duodenal mucosa [13]. Analysis of chromosome aberrations was made 24 h after irradiation.

Results and Discussion

Mouse survival between the 7th and 30th days constituted a mean of 81% in the case of using cystamine and 57% with ABT (Table 1). The quantity of myelokaryocytes was greater than in the control at all tested times in mice given cystamine (Table 2). The radioprotective effect of ABT was not manifested on the 3d day, and was noted only in the recovery period--10th and 15th days. In contrast to cystamine, the number of aberrant mitoses in bone marrow did not diminish under the effect of ABT (Table 3). The two agents were characterized by approximately the same radioprotective effect only with regard to CFU (Table 4). According to all of the criteria used, we virtually failed to observe dependence of degree of protection on route of administration of the agent, and it is only in the case of intake of ABT by mouth that the quantity of myelokaryocytes was somewhat smaller on the 15th day than when this agent was given intraperitoneally.

Table 1. Effect of cystamine and ABT on mouse survival (%) after exposure to radiation in doses of 7.5 and 10 Gy

RADIATION DOSE, GY	OBSERV. PERIOD, DAYS	AGENT	ROUTE OF ADMINISTRATION	M±m
7,5	7—30	CONTROL	--	8±6(25)*
		CYSTAMINE	INTRAPERITONEAL	75±7(38)
			PER OS	87±6(39)
		ABT	INTRAPERITONEAL	55±9(29)
			PER OS	59±9(29)
10	1—6	CONTROL	--	13±5(52)
		CYSTAMINE	INTRAPERITONEAL	76±8(33)
			PER OS	76±7(41)
		ABT	INTRAPERITONEAL	8±4(40)
			PER OS	17±6(36)

*Number of animals indicated in parentheses.

Table 2. Effect of cystamine and ABT on quantity of nuclear cells (millions)* in femoral bone marrow of mice exposed to 7.5 Gy radiation (M±m)

AGENT	ROUTE OF ADMINISTRATION	POSTRADIATION TIME, DAYS		
		3	10	15
CONTROL	--	2,1±0,15 (25)	1,9±0,52 (21)	4,3±0,40 (10)
CYSTAMINE	INTRAPERITONEAL	3,5±0,56** (12)	5,7±0,82** (12)	9,2±1,1** (8)
	PER OS	3,3±0,55** (12)	4,6±0,84** (14)	8,3±1,4** (7)
ABT	INTRAPERITONEAL	2,4±0,17 (13)	3,9±0,35** (12)	9,0±1,2** (12)
	PER OS	2,7±0,21 (11)	3,8±0,51** (11)	5,8±0,7 (10)

*Normal amount of nuclear cells 18.2±1.7.
**Here and elsewhere, $P<0.05$, as compared to control

Table 3. Quantity of aberrant mitoses (%) in bone marrow and duodenal crypts of mice 24 h after irradiation in doses of 7.5 and 10 Gy, and with preventive administration of cystamine and ABT

OBJECT STUDIED AND RADIATION DOSAGE	AGENT	ROUTE OF ADMINISTRATION	M±m
BONE MARROW, 7.5 Gy	CONTROL	--	83±1,7(12)
	CYSTAMINE	INTRAPERITONEAL	69+2,9** (13)
		PER OS	73+2,7** (12)
	ABT	INTRAPERITONEAL	82±2,0 (10)
DUODENUM, 10 Gy	CONTROL	--	75±1,6 (13)
	CYSTAMINE	INTRAPERITONEAL	50±1,0** (5)
		PER OS	60±2,5** (5)
	ABT	INTRAPERITONEAL	75±3,0 (6)
		PER OS	78±4,0 (6)

Studies of radioprotective effect of the protectors on the GIT revealed even greater differences between cystamine and ABT. Thus, while the former protected 76% of the mice against intestinal death (Table 1), prevented a drop in enterocyte quantity (Table 5) and increase in aberrant mitoses in crypts of the duodenum (Table 3), ABT did not attenuate damage to the GIT with respect to any of the listed parameters (Tables 1, 3 and 5). The opinion has been voiced in the literature that there can be greater protection of intestinal epithelial cells with oral intake of radioprotective agents than with parenteral administration due to the direct contact of the agent with enterocytes [14].

However, this was not observed in our experiments, even with the use of such a highly sensitive criterion as count of aberrant mitoses (Table 3).

Table 4. Quantity of CFU in spleen of recipient mice 8 days after giving them bone marrow from donor mice protected with cystamine or ABT

AGENT	ROUTE OF ADMINISTRATION	$M \pm m$
CONTROL	--	2,3±0,3 (18)
CYSTAMINE	INTRAPERITONEAL	15,0±1,9** (15)
	PER OS	12,0±2,3** (17)
ABT	INTRAPERITONEAL	10,0±2,6** (13)
	PER OS	8,0±1,6** (14)

Table 5. Quantity of epithelial cells (millions)* in small intestinal mucosa on 3d day after exposing mice to radiation in dosage of 10 Gy and preventive administration of cystamine and ABT

AGENT	ROUTE OF ADMINISTRATION	$M \pm m$
CONTROL	--	100±11,2 (17)
CYSTAMINE	INTRAPERITONEAL	235±17,0** (10)
	PER OS	220±10,0** (14)
ABT	INTRAPERITONEAL	80±9,5 (12)
	PER OS	115±14,5 (9)

*Normal epithelial cell count is 475±18.

Thus, our comparison of radioprotective efficacy of cystamine and ABT revealed both common and different patterns in manifestation of radioprotective activity of these two radioprotective agents. For example, ABT differs from cystamine in that its use does not affect cells in the proliferative and maturing pool. This was confirmed by absence of a positive effect in the test for aberrant mitoses and quantity of nuclear cells during the period of maximum depletion of hemopoietic tissue. At the same time, both ABT and cystamine had a protective effect on bone marrow stem cells, which probably explains the increase in number of myelokaryocytes in the recovery period, as compared to control levels. Evidently, the radioprotective effect of ABT only on stem cells of bone marrow yields only 57% survival of mice during the period of death chiefly due to the bone marrow syndrome. At the same time, cystamine, which also has a protective effect on the cells in the proliferative and maturing compartment of bone marrow, protects 81% of the animals against death. The fact that ABT does not have a protective effect on the intestine is another cause of its lesser efficacy.

Thus, when investigating the radioprotective effects of agents and determining whether they are promising, it is important to make a combined study of the

protective effect of agents on different radiosensitive systems, in particular, bone marrow and the GIT. This is all the more necessary since, as shown in [4] and confirmed by this study, when there is no protection of the GIT by an agent, it is not always possible to predict the outcome of radiation sickness due to development of the bone marrow syndrome, using hematological parameters.

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EFFECT OF SOME PHARMACOLOGICALLY ACTIVE SUBSTANCES ON CYSTAMINE TRANSFORMATION IN MOUSE TISSUES

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 9 Sep 80) pp 246-249

[Article by L. G. Tarnopol'skaya]

[Text] It is known that sulfur-containing radioprotective agents, in particular, cystamine, are subject to rather rapid transformation in the body [1, 2], and intensity of metabolism of the agent increases as its dosage decreases [3]. This circumstance is largely the reason for administering the protective compound in doses that are close to the maximum tolerated level in order to create and maintain a high level of the active form, with respect to radioprotection, of this agent in tissues by the time of exposure to radiation. However, it is very probable that accumulation of the required amount of cystamine for protection could also be obtained with smaller than optimum radioprotective doses, if there is slower conversion of the radioprotective agent. Since cystamine metabolism is closely related to oxidative processes in tissues, it could have been assumed that its combined use with pharmacologically active agents capable of altering the level of metabolic processes in the organism would lead to a change in rate of breakdown of the sulfur-containing radioprotector.

We have studied here the effect of vasodilating agents, mexamine and ethyrone [thiourea derivative], as well as gutimine [guanylthiourea], which is an antihypoxia agent, on intensity of conversion of cystamine in white mouse tissues when small doses of this radioprotective agent are given.

Material and Methods

We used 66 white male mice weighing 18-20 g in our experiments. Sulfur-labeled cystamine (specific activity SA 1.11 GBq/g) was given to animals intraperitoneally in different combinations with mexamine, ethyrone or gutimine in the following doses: 10 mg/kg cystamine, 8 mg/kg mexamine, 2 mg/kg ethyrone and 80 mg/kg gutimine. Thirty min later, the animals were decapitated; their liver and spleen were excised. Batches of tissues were homogenized under refrigeration in a double volume of 10% trichloroacetic acid. The obtained homogenates were centrifuged at 3000 r/min for 15 min, after which the sediment was discarded, while the protein-free tissue extracts (TCA extracts) were treated with N-ethylmaleimide [4] and used for chromatographic analysis.

Effect of mexamine, ethyrone and gutimine on relative levels of products of cystamine conversion in white mouse liver and spleen; percent of SA of tissue extract

AGENT	DOSAGE MG/KG	NUMBER OF MICE	LIVER						SPLEEN					
			MEA		HYPOTAURINE		TAURINE		MEA		HYPOTAURINE		TAURINE	
			M±m	P	M±m	P	M±m	P	M±m	P	M±m	P	M±m	P
CYSTAMINE	10	10	—	—	26±1,7	—	68±2,1	—	11±2,5	—	68±2,9	—	8±1,3	—
CYSTAMINE + MEXAMINE	10 8	7	7±0,7	<0,05	38±2,6	<0,05	42±4,2	<0,05	29±5,3	<0,05	53±5,6	<0,05	4,2±1,5	>0,05
CYSTAMINE + ETHYRONE	10 2	7	3±0,9	>0,05	19±1,9	<0,05	70±4,1	>0,05	4±2,7	<0,05	72±1,5	>0,05	10±2,1	>0,05
CYSTAMINE + GUTIMINE	10 80	16	11±1,8	<0,05	65±2,8	<0,05	12±0,9	<0,05	20±3,6	<0,05	72±4,8	>0,05	3,5±0,8	>0,05
CYSTAMINE + MEXAMINE + ETHYRONE	10 8 2	15	13±1,3	<0,05	47±2,8	<0,05	28±2,5	<0,05	30±4,1	<0,05	47±2,9	<0,05	1,4±0,9	<0,05
CYSTAMINE + MEXAMINE + GUTIMINE	10 8 80	11	14±1,3	<0,05	52±5,0	<0,05	6±1,1	<0,05	50±4,7	<0,05	35±3,0	<0,05	—	<0,05

Cystamine and products of its conversion--β-mercaptoethylamine (MEA), hypotaurine and taurine--were separated by the method of thin-layer chromatography on cellulose. Powdered cellulose was prepared from chromatographic paper (type F, No 15, GDR) by the method in [5]. TCU-extracts were applied to chromatographic film using automatic 0.002-0.003-mℓ automatic pipettes. TCU-marker solutions were applied to the same points. Separation was done in a system of solvents: isopropanol--formic acid--water, taken in a ratio of 10:4:1 (for 2.5 h). After this, the chromatograms were dried at room temperature and developed in 0.4% ninhydrin solution in acetone. Spots corresponding to cystamine, the complex of MEA and ethylmaleimide, hypotaurine and taurine were removed and eluated in 0.005% copper sulfate solution in 76% ethyl alcohol [6]. The eluates were applied on a target and counted on a "Protok" radiometric unit. The results were expressed as percentage of SA of the original TCU-extract.

Results and Discussion

To study the effect of the tested compounds on intensity of conversion of cystamine in tissues of white mice, the radioprotective agent was given to animals in a dosage of 10 mg/kg. We selected as object of investigation the spleen, which is a highly radiosensitive organ, as well as the liver, which participates the most actively in metabolism of sulfur-containing radioprotective agents.

First it was necessary to estimate the amount of unchanged radioprotector in mouse tissues after administration in a dosage of 10 mg/kg. Chromatographic analysis of protein-free tissue extracts recovered 30 min after giving the mice cystamine revealed that there was no nonoxidized form of the protector in the liver, whereas in the spleen it was represented by a very small amount of MEA (no more than 10% of total radioactive sulfur-containing compounds in the tissue extract). The process of cystamine digestine is the most intensive in the liver. Most of the radioactive label in this tissue is referable to the end metabolite--taurine (about 70%). In the spleen there is prevalence of the intermediate conversion product--hypotaurine (68%), whereas only 8% of the SA of tissue extract is referable to taurine.

Since mexamine and ethyrone are capable of altering hemodynamics and, as a result, induce hypoxia, it could have been assumed that these compounds would have an inhibitory effect on intensity of cystamine conversion. Gutimine should have an analogous effect; as we know, it is capable of interfering in mitochondrial metabolic and cell respiration processes, depressing nonphosphorylating oxidation reactions [7, 8].

Investigation of relative amount of cystamine metabolites when different combinations of this radioprotective agent with mexamine, ethyrone or gutimine were given revealed that these compounds have different effects on the process of cystamine transformation. As can be seen in the Table, when cystamine was given together with mexamine or gutimine, metabolism of cystamine was much slower. This was manifested in the liver primarily by a decrease in amount of taurine. While relative taurine content in this tissue constituted 70% after giving cystamine, addition of mexamine or gutimine led to a decline of taurine content to 40 and 12%, respectively. In the spleen of mice given cystamine together with mexamine or gutimine, the MEA level was higher (3 and 2 times higher, respectively). At the same time, ethyrone had virtually no inhibitory

effect on cystamine metabolism. Moreover, in this case, MEA level in the spleen was even lower, which should be interpreted as evidence of some intensification of conversion of the sulfur-containing protective agent.

In all probability, the different effects of mexamine and ethyrone on cystamine metabolism are related to the specifics of their pharmacological action. Mexamine elicits a complex functional circulatory disorder associated with decrease in volumetric blood flow rate in a number of tissues (including the spleen) and drop of oxygen tension [9, 10]. At the same time, the hemodynamic disturbance elicited by ethyrone is not associated with such phenomena [11]. In addition, this agent activates carbohydrate metabolism [12] and, perhaps, as a result stimulates somewhat the process of cystamine conversion.

The change in cystamine metabolism becomes even more distinct if this radioprotective agent is given in combination with two products. And, while in the case of giving mice cystamine together with mexamine and ethyrone we can refer only to some intensification of the inhibitory effect, with use of cystamine together with mexamine and gutimine, this effect becomes significant. This is indicated by the decline of the end metabolite level--taurine--in the liver (to almost 1/10th) and, what is the most important, increase to 50% in MEA content of the spleen.

Thus, our findings are indicative of the possibility of slowing cystamine conversion by combined administration with agents that alter oxidative processes in cells and tissues. The inhibitory effect of complexes (mexamine + ethyrone) or (mexamine + gutimine) on intensity of cystamine metabolism leads to accumulation in radiosensitive tissues of the form of this sulfur-containing radioprotector that is active in this effect when given in doses that are considerably smaller than the optimum radioprotective dosage. Consequently, our results can be interpreted as the prerequisite for developing radioprotective formulas based on cystamine and including substances that are capable of interfering in pharmacokinetics of the sulfur-containing component.

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PROTECTIVE EFFECT OF HYPOXIC GAS MIXTURE ON COMBINED EXPOSURE TO RADIATION AND PHYSICAL LOAD

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 18 Nov 80) pp 250-252

[Article by A. I. Britun, R. B. Strelkov, N. G. Kucherenko and O. I. Kurochkina, Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk]

[Text] It was previously shown that breathing a hypoxic gas mixture containing 10% oxygen and 90% nitrogen (HGM-10) enhances radioresistance of different animal species [1-12].

We investigated here the radioprotective effect of HGM-10 in the presence of a physical load. Studies in this direction expand our knowledge about the oxygen effect and enable us to broaden use of HGM-10 for practical purposes.

Material and Methods

Experiments were conducted on 296 mongrel male mice weighing 20.0±3.0 g, 124 male CBA mice weighing 20.0±2.0 g, 70 male BALB/c mice weighing 20.0±1.0 g, 280 Wistar rats weighing 200.0±20.0 (140 males and 140 females), as well as 74 male guinea pigs weighing 310.0±30.0 g. The swimming test [13] was used as a physical load, without additional weights on the animals. The animals were exposed to radiation delivered by a GUB-20000 γ-unit with circular arrangement of radiation sources (^{60}Co). Absorbed dose rate in water constituted 0.005 Gy/s; absorbed dose constituted 5, 6.5, 7.5 and 8.5 Gy for the mice, 7, 8.5 and 10 Gy for the rats and 4 Gy for the guinea pigs. Control and experimental animals were irradiated in special containers 8.0 and 12 dm^3 in size, divided into two halves by an airtight partition, which were filled with water of 28-30°C temperature. One half of the container communicated with the atmospheric environment, whereas HGM-10 was delivered into the other half under a polyethylene hood 3-5 min before and continuously during irradiation, at the rate of 6-10 ℓ/min. Control and protected animals were irradiated in the same field.

There were some distinctions to the technique of irradiating the BALB/c mice. The first group of animals was exposed to a dosage of 6.5 Gy during the swimming test under normal atmospheric conditions. The second group of mice, also in water but not swimming, which stood on a special platform, i.e., which did not exercise, was irradiated in the same field with the first group. The third

group was irradiated during swimming test in an HGM-10 atmosphere; the fourth group of mice was protected with HGM-10 and the animals of this group were kept on a platform in water, and they did not swim; the fifth group was the intact control.

For 30 days after irradiation of mice, rats and guinea pigs, we recorded survival of unprotected and HGM-10-protected animals; the results were submitted to statistical processing, we calculated the dose reduction factor (DRF) in series with a sufficient range of doses. We checked the animals' clinical condition daily and recorded times of death.

Results and Discussion

According to the data listed in Table 1, HGM-10 protected, with statistical reliability, both mongrel and purebred mice during the physical load exposed to radiation in doses of 6.5-7.5 Gy. In the case of irradiation of CBA mice in a dosage of 6.5 Gy, the differences in survival rate were on the borderline of reliability, which is due to the small sample (10 animals per group). DRF was 1.25. It should be stressed that the swimming test we used, even without adding weights to the animals' body, led to a state corresponding to average and severe fatigue: after the test, we observed adynamia and decline of defense reflexes for 1 min in mice, as well as in rats and guinea pigs.

Table 1. Animal survival after irradiation, during physical exercise, without and with HGM-10 protection

RADIATION DOSE, Gy	WITHOUT PROTECTION		WITH HGM-10		PROBABILITY INTEGRAL T
	NUMBER OF ANIMALS	30-DAY POST-RADIATION SURVIVAL %	NUMBER OF ANIMALS	30-DAY POST-RADIATION SURVIVAL %	
MONGREL MICE					
5,0	20	70,0±10,3	20	90,0±6,7	1,63
6,5	40	32,5±7,4	40	55,0±7,9	2,10
7,5	40	2,5±2,5	40	37,5±7,6	4,30
8,5	39	0,0±2,4	37	10,8±5,1	1,91
CBA MICE					
6,5	10	30,0±14,7	10	70,0±14,7	1,92
7,5	20	0,0±4,3	20	50,0±11,2	4,17
8,5	22	0,0±4,0	22	18,2±8,2	2,00
WISTAR RATS					
7,0	40	65,0±7,6	40	90,0±4,8	2,80
8,5	40	37,5±7,7	40	75,0±6,8	3,60
10,0	40	0,0±2,3	40	32,5±7,4	4,19
GUINEA PIGS					
4,0	25	32,0±9,3	29	68,9±8,8	2,90

Note: There were 20 mongrel mice, 20 CBA mice, 40 Wistar rats and 20 guinea pigs in the intact control; no deaths were observed during the experiment.

Table 2. Survival of BALB/c mice exposed to radiation in dose of 6.5 Gy at relative rest and during swimming test without and with HGM-10 protection

EXPERIMENTAL CONDITIONS	WITHOUT PROTECTION		WITH HGM-10		PROBABILITY INTEGRAL T
	NUMBER OF ANIMALS, GROUP	30-DAY POSTRAD. SURVIVAL %	NUMBER OF ANIMALS, GROUP	30-DAY POSTRAD. SURVIVAL %	
IRRADIATION IN WATER WITH PHYSICAL LOAD	15 (I)	13,3±8,8	15 (III)	33,3±3,9	2,10
IRRADIATION IN WATER WITHOUT PHYSICAL LOAD	15 (II)	6,7±6,5	15 (IV)	33,3±3,9	2,97
INTACT CONTROL	10	ALL MICE SURVIVED TO 30TH EXPERIMENTAL DAY.			

Statistical processing of the data revealed that HGM-10 also had a reliable protective effect on rats submitted to swimming test during irradiation (DRF 1.25-1.3). In experiments with the swimming test conducted on guinea pigs, the animals received one dose of radiation, 4.0 Gy, which is close to $LD_{75/30}$. The results of this series of tests revealed that HGM-10 reliably enhanced radioresistance of guinea pigs (probability integral T = 2.9).

The physical load factor did not have an appreciable effect on survival of either unprotected mice or degree of radioprotective efficacy of HGM-10 in the case of BALB/c mice exposed to radiation during swimming test and in a state of relative rest (Table 2). The data obtained in this series of experiments conform to the results of previous studies of the radioprotective effect of HGM-10 on rats and guinea pigs exposed to radiation without the physical load [2, 4], which warrants the conclusion that there are no differences in radioprotective efficacy of a hypoxic gas mixture when irradiating animals in a state of relative rest or while performing exercise.

Thus, we demonstrated on three species of animals--mice, rats and guinea pigs--in a state of increased activity during irradiation that the physical load did not diminish the radioprotective effect of moderate hypoxia, which develops when breathing with HGM-10.

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ROLE OF ENDOGENOUS SUBSTANCES IN ENHANCING RADIORESISTANCE BACKGROUND REPORT 16: INVESTIGATION OF EFFECTS OF SOME AET DERIVATIVES ON ENDOGENOUS RADIORESISTANCE BACKGROUND

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 27 Nov 80) pp 252-255

[Article by Ye. N. Goncharenko, S. V. Stoyev, S. V. Antonova and Ye. E. Grayevskaya, Moscow State University imeni M. V. Lomonosov, Biology Faculty]

[Text] Data were published in 1974 concerning the radioprotective effect of adeturon [S-2-aminoethyl isothiuronium adenosine triphosphate], a product synthesized with use of two compounds, ATP and AET [aminoethylisothiuronium [1]. Somewhat later, two more products were developed in the same laboratory, and they were also based on AET: 2-amino-4-iminothiazoline (DAT) and bromoethylisothiourea (BET) [2, 3]. Adeturon and DAT demonstrated good radioprotective properties in mammals, and this served as grounds for intensive investigation of the mechanism of their action [4]. We describe here a study of these radioprotective agents from the standpoint of endogenous radioresistance background [5].

Material and Methods

Experiments were conducted on male white mice. We determined the DRF [dose reduction factor] of the agents using an RUM-11 source of radiation (dose rate $2.15 \cdot 10^{-4}$ A/kg, 1.0 mm Al + 0.5 mm Cu filters). We used previously described methods [6-8] to measure the different components of radioresistance background. In selecting tissues to be examined, we took into consideration both their radiosensitivity and participation in metabolism of the tested amines. AET, ATP and a mechanical mixture thereof in doses corresponding to constituents of adeturon served as controls for adeturon (Table 1).

Results and Discussion

The results of our experiments confirmed data concerning the rather high radioprotective efficacy of adeturon and DAT [1, 2]. Table 1 shows that the constituents of adeturon and their mechanical mixture in the indicated doses did not have such a high radioprotective efficacy. BET was found to be less effective. Such a difference in radioprotective efficacy of agents that were similar in chemical structure enabled us to conduct a comparative study in order to determine the role of the endogenous background in forming radioresistance modified by the new products. Since the endogenous radioresistance

background is viewed as the result of overall change in many endogenous components (radioprotective and radiosensitizing agents) [5], consideration of as many components of the background as possible is a mandatory condition for correct evaluation of endogenous background in expression of the agents' radioprotective capacity.

Table 1. Radioprotective efficacy of agents in mice*

AGENT	DOSE MG/KG	$LD_{50/30}$, Gy	DRF
CONTROL (0.4 ML H_2O)	—	4,07±0,07	1,0
ADETURON·$2H_2O$	300	5,90±0,15	1,45
AET, HYDROBROMIDE	127	4,70±0,12	1,15
ATP, DISODIUM SALT	282	4,40±0,15	1,10
AET + ATP	127+282	5,30±0,10	1,30
DAT, HYDROCHLORIDE	600	6,80±0,23	1,67
BET, HYDROBROMIDE	190	4,60±0,15	1,13

*Agents were given 15 min before irradiation.

Table 2. Lipid hydroperoxide content in mouse tissue after giving them radioprotective agents, %

AGENT	SPLEEN	SMALL INTESTINE	LIVER
ADETURON	68±2	81±4	49±3
	$P<0,001$	$P<0,001$	$P<0,001$
ATP	107±6	105±6	111±4
AET	57±3,5	66±4	84±4
	$P<0,001$	$P<0,001$	$P<0,001$
AET+ATP MIXTURE	77±5	63±6	95±4
	$P<0,001$	$P<0,001$	55±3
DAT	70±3	71±3,5	
	$P<0,001$	$P<0,001$	$P<0,001$
BET	90±3,5	—	101±5
	$P<0,05$		

Table 2 lists data on levels of endogenous radiosensitizing agents (hydroperoxides of higher unsaturated fatty acids), while Tables 3 and 4 list data on serotonin and histamine content, which characterize to a significant extent the pool of endogenous radioprotectors. As we see, the maximum decrease in hydroperoxide content occurred with administration of adeturon and DAT: overall level thereof (in examined tissues) dropped to almost one-half. There was also more significant change in radioprotective components of the endogenous background (serotonin and histamine) than with administration of other agents: overall content thereof in tested tissues increased by 150-230% after giving adeturon and DAT, respectively; less marked changes (only by 40-70%) were demonstrable with administration of BET, ATP and AET, which had mild radioprotective activity under our experimental conditions. The low efficacy of AET in this case is attributable to its small dosage, which was equivalent to the one used for adeturon synthesis (127 mg/kg),

which constitutes half the optimum protective dosage. The lower radioprotective efficacy of the mixture of ATP and AET, as compared to adeturon, and corresponding insignificant changes in levels of constituents of radioresistance background favor the conception that radioprotective efficacy of adeturon is determined by the product of synthesis of constituents, rather than simple summation of radioprotective efficacy of these elements.

Table 3. Serotonin content of mouse tissues after giving radioprotective agents

AGENT	SPLEEN		SMALL INTESTINE	
	μG/G	%	μG/G	%
ADETURON	5,2±0,3	128±8 $P<0,05$	3,7±0,3	132±10,7 $P<0,05$
ATP	4,2±0,4	102±10	2,6±0,3	91±12
AET	4,9±0,4	119±10	3,0±0,1	110±3
AET+ATP MIXTURE	4,1±0,3	100±9	2,8±0,1	100±2
DAT	6,0±0,6	147±15 $P<0,05$	5,3±0,6	189±21 $P<0,01$
BET	4,0±0,4	98±10	3,5±0,4	127±13
CONTROL	4,0±0,3	100±9	2,7±0,2	100±9

Table 4. Histamine content of mouse tissues after giving radioprotective agents

AGENT	SPLEEN		SMALL INTESTINE		STOMACH	
	μG/G	%	μG/G	%	μG/G	%
ADETURON	30,4±2,6	109±9	31,2±3,1	153±15 $P<0,05$	44,2±1,8	125±5 $P<0,01$
ATP	26,6±2,5	97±9	22,2±2,5	108±12	37,7±3,5	107±10
AET	28,1±1,1	100±4	22,8±2,1	112±10 $P<0,05$	39,1±4,0	111±11 $P<0,02$
ATP+AET MIXTURE	29,8±2,7	106±10	28,1±2,7	138±13 $P<0,05$	33,5±4,3	95±12
DAT	40,4±1,5	144±5 $P<0,01$	27,6±1,4	135±7 $P<0,01$	41,8±2,2	118±6 $P<0,01$
BET	38,3±1,6	137±6	22,8±1,8	112±9	36,0±2,8	102±8
CONTROL	27,9±1,5	100±5	20,4±1,4	100±7	35,3±3,3	100±9

Our data indicate that the radioprotective activity of new radioprotective agents (adeturon and DAT), like many other radioprotectors, is causatively related to specificity of change in levels of constituents of the endogenous background: decrease in lipid radiosensitizers in animal tissues and increase in overall endogenous radioprotectors, in particular, serotonin and histamine.

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INVESTIGATION OF GENERAL ADAPTABILITY OF OFFSPRING OF IRRADIATED ANIMALS. REPORT 3: MOUSE RESISTANCE TO RADIATION, HYPOXIA, ENDOTOXIN AND PHYSICAL EXERCISE

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 14 Apr 80) pp 261-264

[Article by I. Ye. Vorobtsova and K. L. Gol'zberg, Central Scientific Research Institute of Roentgenology and Radiology, USSR Ministry of Health, Leningrad]

[Text] Analysis of the literature dealing with distinctive features of offspring of biological objects [1] indicates that the information on this score is contradictory and insufficient. At the same time, the importance of such studies is obvious, since evaluation of genetic sequelae of ionizing radiation can be considered full enough only if it is based not only on data concerning the speed of the mutation process, as determined by appearance of major genetic abnormalities in generations of an irradiated population, but the results of studying the offspring of irradiated organisms with reference to the most diverse quantitative criteria characterizing general fitness of these specimens (life expectance, resistance to deleterious agents, etc.).

No differences were found in [2, 3] between $F_1$0--offspring of irradiated mice--and F_1K--offspring of nonirradiated mice--with regard to resistance to single exposure to radiation. At the same time, Spalding, who did not detect differences between analogous groups of mice in resistance to acute radiation, demonstrated lower radioresistance of $F_1$0 to delivery of divided doses and chronic ionizing radiation [4, 5]. Evaluation of sensitivity of $F_1$0 mice to infection revealed that animal mortality due to paratyphoid fever, bacteremia and bacterial contamination of organs was higher in the $F_1$0 group than F_1K [6]. We do not know of any information concerning physical endurance of offspring of irradiated animals or their resistance to hypoxia.

Material and Methods

We studied the offspring of mongrel male mice exposed to 5.0 Gy radiation and nonirradiated mongrel female mice. The offspring of intact specimens served as a control. Radiation was delivered by an RUM-17 unit, at 15 mA, 200 kV, with 0.5 mm Cu and 1.0 mm Al filters, dose rate 0.98 Gy/min. In the tests of radiosensitivity, we delivered divided doses of radiation throughout the life of male $F_1$0 and F_1K, starting at the age of 3 months. The single dose constituted 2.5 Gy, and the intervals between divided doses were 2-3 or 10 days.

We assessed radiosensitivity according to mean survival time and mean dosage accrued by the time of death of the last animal in the sample. Experiments were conducted on 260 animals. We tested sensitivity to bacterial toxin by injecting intraperitoneally 50-700 μg endotoxin B-42 of S. paratyphi to mice weighing 25-27 g, with subsequent daily (for 3 days) recording ot deaths with each dose of endotoxin among F_1O and F_1K mice. We calculated endotoxin dosage that elicited death of 50% of the animals, i.e., $LD_{50/3}$, on the basis of the obtained data. The study consisted of 5 analogous experiments, in each of which we used 210 animals from each group (F_1O and F_1K). Mouse resistance to exercise was determined by their capacity for static and dynamic work. Static work capacity was evaluated by the time that a mouse could hold on to a vertical metal rod, the bottom end of which was immersed in water and to the top of which was attached a cardboard circle, which limited the animal's upward movement. We tested 82 animals in each of 8 repeats of the experiment, that or which were of the same weight, from F_1O and F_1K. We selected swimming in water at a temperature of 20°C as a dynamic work load. The tests were repeated 4 times on 70 pairs of animals to determine swimming time in F_1O and F_1K. We assessed resistance to hypoxia according to time that the mouse survived in a sealed container. We used 100 animals from each of the same groups in tests repeated 5 times.

Results and Discussion

Table 1 shows that F_1O specimens are more resistant than F_1K when there is a short interval between divided doses of radiation. With a 10-day interval, the reverse is true. We observed analogous differences in direction as a function of irradiation mode when we compared radiosensitivity of offspring of irradiated and nonirradiated male rats and drosophila [7], while the authors of [8] did so in a study of radiosensitivity of female and male mice. The lower basal metabolism in F_1O [9], which delays development of radiation damage in the case of single exposure in the opinion of the author of [10] and thus is instrumental in a higher survival rate among animals, could be the cause of inverted directions of differences between acute (or close to acute) and divided doses of radiation to F_1O and F_1K, whereas with delivery of divided doses at rather long intervals, on the contrary, there is delay in repair processes and consequently more probable death. Our results here, indicative of greater resistance of F_1O mice to hypoxia (Table 2), are also consistent with the assumption that metabolism is lower in these animals. The same table lists data on mouse resistance to endotoxin and exercise. We see that F_1O specimens have less work capacity and are more sensitive to endotoxin.

Table 1. Resistance of F_1O and F_1K mice to radiation in single dose of 2.5 Gy

INDICATOR OF RADIORESISTANCE	EXPER. NUMBER	EVERY 2-3 DAYS			EVERY 10 DAYS		
		F_1K	F_1O	t	F_1K	F_1O	t
MEAN ACCRUED DOSE, Gy	1	14,33±0,52	16,17±0,48	2,6	20,12±1,06	17,58±0,62	2,1
	2	13,75±1,0	19,58±0,62	4,0	18,16±0,51	15,81±0,82	2,4
MEAN LIFE EXPECTANCY, DAYS	1	21,3±0,8	24,2±0,8	2,5	71,1±4,0	59,8±2,2	2,5
	2	23,6±1,3	32,6±0,9	5,6	71,6±3,1	61,1±3,6	2,2

Table 2. Resistance of F_1O and F_1K mice to hypoxia, endotoxin and exercise

ANIMAL GROUP	SURVIVAL TIME WITH HYPOXIA, MIN	$LD_{50/3}$ OF ENDOTOXIN	STATIC WORK TIME, MIN	DYNAMIC WORK TIME, MIN
F_1K	55,4±2,8	388±23	10,1±1,1	12,5±0,4
F_1O	63,8±2,3	287±24	6,2±1,1	10,7±0,3
P	>0,05	0,01	0,01	>0,05

Table 3. Relative weight of adrenals in F_1O and F_1K, percentage of body weight

TREATMENT	F_1K	F_1O	*P*
CONTROL	19,7+1,3	20,8+3,2	
LETHAL DOSE OF ENDOTOXIN	29,4+1,2	26,1+1,1	0,05
NONLETHAL DOSE OF ENDOTOXIN + SWIMMING	28,8+1,0	24,3+0,8	0,05

Thus, according to several of the parameters of general adaptability that we studied, the offspring of irradiated male mice was inferior to the offspring of intact parents (resistance to radiation with long intervals between divided doses, resistance to endotoxin, exercise); according to other parameters the differences were indicative of greater resistance of F_1O (irradiation at short intervals, hypoxia). Use of additional factors enabled us to demonstrate the relativity of this advantage in offspring of irradiated males. In a special series of experiments, the mice were irradiated every other day in a dosage of 2.5 Gy, and on the days when they were not exposed we measured the intensity of their basal metabolism in a special experimental device. This procedure acted as a stressor on the animals. Under such conditions, F_1O were more radiosensitive than F_1K, as could be seen by the mean accreted radiation dose: 11.4±0.7 Gy for F_1O and 14.0±0.5 Gy for F_1K ($P>0.95$). At the same time, with an analogous mode of irradiation but in the absence of an additional factor, these differences were reversed: 17.3±0.4 Gy for F_1O and 10.5±0.6 for F_1K ($P>0.99$). We also observed such inversion of direction of differences between compared groups in our study of animal resistance to hypoxia. If the mice were submitted to graded exercise (swimming for 3 min) before placing them in a sealed container, under subsequent hypoxic conditions F_1O survived for 44.2±2.1 min, versus 50.2±2.4 min in the F_1K group. The differences between groups were reversed without preliminary swimming (Table 2).

Animal resistance to the deleterious effects of different factors is determined by the functional state of the hypothalamo-hypophyseo-adrenal system. One of the most typical reactions to a stressor is adrenal hypertrophy. As can be seen from the data in Table 3, relative weight of F_1O adrenals was negligibly greater than in F_1K. At the same time, stressors elicited less hypertrophy of this gland, which is indicative of limited compensatory capabilities in offspring of irradiated mice. Our findings are consistent with the results of morphological investigation [11], which showed that the relative weight of the adrenals was greater in offspring of irradiated rabbits and that there were histological differences in the adrenal cortex of these animals, as compared

to the control. However, it should be noted that in the cited work the offspring of irradiated females was studied and, consequently, we cannot rule out the influence of the irradiated mother on the fetus.

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RADIOPROTECTIVE AND TOXICOLOGICAL PROPERTIES OF PHENYLETHYLAMINE DERIVATIVES MODIFIED WITH ALPHA AMINO ACIDS

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82 (manuscript received 4 May 80) pp 269-275

[Article by T. Yu. Il'yuchenok, K. S. Shadurskiy, S. V. Rogozhin, V. G. Yashunskiy, L. M. Frigidova, V. I. Butayeva and Yu. A. Davidovich, Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk]

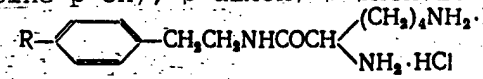
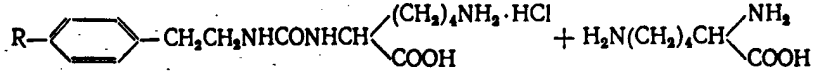
[Text] For several years we have been searching for radioprotective agents among derivatives of α- and β-phenylethylamine [1-4]. A continuation of this search resulted in synthesis of 27 chemical compounds modified by α-amino acids, which was effected at the Institute of Hetero-organic Compounds, USSR Academy of Sciences. In recent years, it was demonstrated that some amino acids have marked radioprotective activity [5]. They began to be used extensively to correct some of the undesirable properties (reduce irritating and ulcer-producing activity, lower toxicity, improve solubility, etc.), as well as to enhance the efficacy of drugs.

We submit here the results of investigation of toxicity and radioprotective properties of α-amino acid derivatives of β-phenylethylamine, which differ from one another in substituent in the para position of the benzene ring.

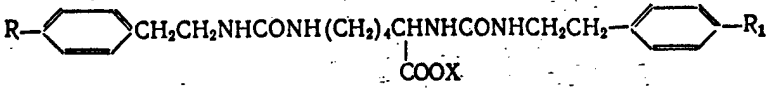
Material and Methods

Experiments were conducted on 2830 mongrel female mice weighing 20-24 g. Distilled water served as solvent for most compounds (I-VII, XI, XV-XVII and XX), as well as a combination of such water and dimethylsulfoxide with Tween-80 (VIII, IX, XIX, XXII-XXVII) or polyvinyl alcohol (XII). Acute toxicity was determined using the intraperitoneal route of administration; LD_{16}, $LD_{50}\pm m$ and LD_{84} were calculated by the method in [6]. Radioprotective properties were studied by the principles adopted in our country of conducting screening studies [7]. The compounds were given in doses of 1/2 and 1/8 LD_{16} intraperitoneally or subcutaneously 10-20 min prior to γ-irradiation in a dosage of 10 Gy at a dose rate of 0.01 Gy/min. Efficacy of protection was evaluated on the basis of percentile survival of mice (30 days) and mean survival time of animals that died. The obtained data were submitted to statistical processing.

Chemical structure, toxicity and radioprotective properties of compounds I-XXVII when given intraperitoneally 10-20 min prior to single total-body exposure to external γ-radiation in a dosage of of 10 Gy at dose rate of 0.01 Gy/min

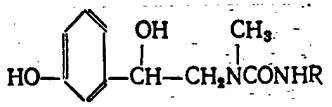
COMPOUND	R	LD_{16} $LD_{50} \pm M$, LD_{84} MG/KG	INTOXICATION SIGNS	n	DOSE MG/KG	SURVIVAL %	SURVIVAL TIME FOR MICE THAT DIED, DAYS
	L-lysine p-oxy, p-alkoxy-β-phenylethylamide hydrochlorides						
							
I	H—	292,0		30	K	20,0±7,4	10,2±0,9
		320,0±11,3	Seizures	10	146,0	0,0±0,0	10,2±1,5
		354,0		20	36,5	10,0±14,1	13,6±1,6
II	HO—	720,0		30	K	20,0±7,4	11,4±0,7
		850,0±49,0	Seizures	10	360,0	0,0±0,0	12,0±1,6
		990,0		20	90,0	25,0±9,9	9,1±1,0
III	CH_3O-	143,0		30	K	23,3±7,9	10,2±0,9
		195,0±22,4	Seizures	10	71,5	0,0±0,0	9,1±1,1
		266,0		20	18,0	25,0±9,9	12,9±1,1
IV	C_3H_7O—	174,0		30	K	23,0±7,9	10,2±0,9
		207,0±13,4	Seizures	10	87,0	0,0±0,0	8,7±2,8
		248,0		20	21,6	30,0±15,3	12,7±0,7
V	$C_5H_{11}O$—	83,0		30	K	40,0±9,1	13,5±2,0
		99,0±6,3	Depression	10	41,0	0,0±0,0	10,6±1,1
		118,0		20	10,0	40,0±11,2	15,0±7,0
VI	$C_7H_{15}O$	27,0		30	K	40,0±9,1	13,5±2,0
		40,5±5,9	Depression	10	14,0	0,0±0,0	9,9±0,8
		60,0		20	3,4	55,0±11,4	11,0±0,7
	Hydrochlorides of lysine salts of N^{α}-p-alkoxy-β-phenylethylcarbamyl derivatives of L-lysine						
							
VII	CH_3O—	304,0		20	K*	50,0±11,4	13,8±1,3
		372,0±26,0	Seizures	10	152,0	40,0±16,3	12,5±0,5
		430,0		10	38,0	0,0±0,0	8,7±1,1
VIII	C_3H_7O—	238,0		20	K*	50,0±11,4	13,8±1,3
		480,0±69,7	Depression	10	164,0	80,0±13,3	10,5±0,0
		710,0		10	41,0	20,0±13,3	11,7±0,9
IX	$C_5H_{11}O$—	119,0		20	K*	50,0±11,4	13,8±1,3
		161,0±18,1	Depression	10	60,0	60,0±16,3	10,1±3,4
		218,0		10	15,0	40,0±16,3	12,0±1,1
X	$C_7H_{15}O$—	210,		20	K*	55,0±11,4	9,9±1,4
		226,0±5,4	Depression	10	105,0	70,0±15,2	10,2±2,8
		244,0		10	26,0	90,0±10,0**	10,8±1,4

Lysine and sodium salts of bis-N^{α}, N^{ε}-p-alkoxy-β-phenylethylcarbamyl derivatives of L-lysine



XI	R=R₁—OH COOH X—NH₂(CH₂)₄CHNH₂	940 — —	Seizures	40 10 30	K• 470,0 117,0	10,0±4,8 0,0±0,0 26,6±8,2	15,8±0,1 18,1±2,7 10,7±1,1
XII	R=R₁—OCH₃ X—H	250,0 373,0±56,0 560,0	Depression	30 10 20	K 125,0 31,0	6,0±4,4 0,0±0,0 5,0±5,0	11,6±1,0 10,3±0,8 11,6±1,0
XIII	R=R₁—OCH₃ COOH X—NH₂(CH₂)₄CHNH₂	515,0 545,0±10,9 575,0	Depression	30 20 20	K 272,0 64,0	3,0±3,2 20,0±9,2 30,0±10,5**	10,2±0,7 10,6±1,2 11,0±1,1
XIV	R=R₁—OCH₃ X—Na	605,0 675,0±80,0 750,0	Depression	40 20 20	K 302,0 76,0	7,5±4,2 5,0±5,0 20,0±9,2	13,4±1,3 10,4±2,8 12,7±1,6
XV	R=R₁—OC₃H₇ COOH X—NH₂(CH₂)₄CHNH₂	940 — —	Depression	20 10 10	K• 470,0 117,0	40,0±11.2 60,0±16,3 20,0±13,3	16,2±1,8 13,0±4,8 13,1±1,1
XVI	R=R₁—OC₅H₁₁ COOH X—NH₂(CH₂)₄CHNH₂	420 — —	Depression	30 10 10	K• 210,0 52,0	0,0±0,0 0,0±0,0 20,0±13,3	16,7±1,2 11,6±2,5 17,1±1,8
XVII	R=R₁—OC₇H₁₅ COOH X—NH₂(CH₂)₄CHNH₂	940 — —	Depression	20 10 10	K• 470,0 117,0	40,0±11,2 70,0±15,3 30,0±15,3	16,2±1,8 13,0±2,9 12,6±2,4

α-Amino acid derivatives of mezaton [neosynephrine]



XVIII	—CH₂COOH	1550,0 1665,0±53,3	Depression Depression	10 10	K 834,5	0,0±0,0 0,0±0,0	10,2±0,7 11,4±1,0
XIX	—CHCOOH CH₂CH₂SCH₃	1170	Depression	10 10 10	K 585,0 146,0	0,0±0,0 20,0±13,3 0,0±0,0	11,2±1,0 15,4±3,3 9,9±0,9
XX	—CH(CH₂)₄NHCONCH₂CH—⟨⟩—OH COOH CH₃ OH	1400	Depression	20 10 10	K 700,0 175,0	0,0±0,0 0,0±0,0 0,0±0,0	9,0±0,5 7,3±1,0 7,8±1,1
XXI	—CH₃·HCl	298,0 384,0±27,9 495,0	Seizures	20 20	K 192,0	0,0±0,0 0,0±0,0	13,1±1,2 10,5±0,7

End of Table

COMPOUND	R	LD_{16} LD_{50} ± M LD_{84} MG/KG	INTOXICATION SIGNS	n	DOSE MG/KG	SURVIVAL, %	SURVIVAL TIME, DAYS
Derivatives of 3-p-alkoxy-β-phenylethyl-2,4-imidazoline diones							
XXII	R=R_1—OCH_3	1400,0	Depression	50	K*	12,0±4,6	15,1±0,9
		—		40	700,0	15,0±5,7	13,6±1,3
		—		10	175,0	0,0±0,0	15,9±0,9
XXIII	R=R_1—OC_3H_7	940	Seizures	80	K*	7,5±2,9	16,0±0,7
		—		20	470,0	15,0±8,2	13,9±2,4
		—		60	117,0	28,3±5,9	13,3±1,2
							15,2±0,8
XXIV	R=R_1—OC_5H_{11}	620	Depression	90	K*	7,7±2,8	12,2±1,4
		—		50	310,0	32,0±6,7**	11,5±1,1
		—		40	77,0	42,5±7,9**	13,1±1,0
XXV	R=R_1—OC_7H_{15}	940	Depression	30	K*	23,3±7,9	13,2±0,9
		—		30	470,0	30,0±8,5	14,2±2,6
		—		10	117,0	10,0±10,0	
XXVI	$C_5H_{11}O$—	940	Depression	40	K*	15,0±5,1	12,8±0,9
		—		10	470,0	50,0±16,7	11,0±2,4
		—		30	117,0	26,7±8,2	13,6±0,8
XXVII	$C_7H_{15}O$—	940	Depression	40	K*	17,5±6,1	15,2±0,9
		—		10	470,0	20,0±13,3	14,4±1,5
		—		30	117,0	23,3±7,9	12,5±1,0

*Compound given by hypodermic injection.
**Reliable in relation to control, with P<0.05.

Results and Discussion

As can be seen from the Table, the tested compounds can be arbitrarily divided into four groups of β-phenylethylamine derivatives modified by L-lysine, L-isoleucine, L-methionine and glycine.

The first group consists of hydrochlorides [chlorine hydrates] of L-lysine β-phenylethylamides containing a hydroxyl radical (compound II) or alkoxy groups (compounds III-VI) in the para position of the benzene ring. It has been determined that LD_{50} constitutes 320 mg/kg for L-lysine β-phenylethylamide (compound I). Addition of hydroxyl radical to the benzene ring of L-lysine β-phenylethylamide (compound II) was instrumental in lowering toxicity 2.7 fold. Substitution of hydroxyl with alkoxy groups led to increase in toxic properties, and the β-phenylethylamide derivative of L-lysine was found to be the most toxic (LD_{50} = 40.5 mg/kg), and it contained a heptoxy group in the para position (compound VI).

The second group consists of hydrochlorides of lysine salts of β-phenylethylcarbamyl derivatives of L-lysine (compounds VII-X), in which there are alkoxy groups in the para position that have an increasing odd number of atoms of carbon (from C_1 to C_7). These compounds are less toxic by an average of 1.6-5 fold than the corresponding hydrochlorides of α-lysine β-phenylethylamide (compounds III-VI).

The third group consists of lysine and sodium salts of bis-para-alkoxy-β-phenylethylcarbamides of L-lysine, glycine and L-methionine (compounds XVIII-XXI). The toxicity of the former is in the range of 373 to 940 mg/kg. It should be noted that substances with a free carboxyl group (compounds XII and XIII) are more toxic than their salt (compound XIV). The α-amino acid derivatives of mezaton (compounds XVIII-XX) have low toxicity (LD_{50} in the range of 1170-1665 mg/kg); they had a depressing effect on the central nervous system, as compared to mezaton (compound XXI), which, on the contrary elicited excitation and was considerably more toxic than the former (LD_{50} = 384 mg/kg). The last group includes para-oxy- and para-alkoxy-β-phenylethyl-2,4-imidazoline diones, substituted residues of α-amino acids in the fifth position (compounds XXII-XXVII). Their toxicity is in the range of 620-1400 mg/kg.

A convulsive effect was observed with administration of L-lysine β-phenylethylamide (compound I) and its derivatives, which contain in the para position hydroxy, methoxy and propoxy groups (compounds II-IV); this effect persisted in the group of β-phenylethylcarbamyl derivatives of L-lysine only in compound VII. Bis-β-phenylethylcarbamyl derivatives (compounds XI-XVIII) and β-phenylethyl-2,4-imidazoline dione (compounds XXII-XXVII) had an inhibitory effect on the central nervous system, with the exception of compounds XI-XXIII.

Studies of radioprotective activity revealed that lysine salts of bis-N^{α},N^{ε}-p-methoxyphenylethylcarbamide of L-lysine (compound XIII), N^{α}-p-heptoxyphenylethylcarbamyl-L-lysine (X), as well as p-pentoxy-3-β-phenylethyl-2,4-imidazoline dione-5-p-pentoxy-3-phenylethylcarbamyl-L-lysine (compound XXIV), were the most effective and protected 25-35% of the animals against death.

It was previously established that LD_{50} for β-phenylethylamine is 146 mg/kg. The change to tyramine was associated with drastic decrease of toxicity (LD_{50} = 1140 mg/kg), which again increased when the hydroxyl in the benzene

ring of β-phenylethylamine was replaced with an alkoxy group, and the compound with a heptoxy group in the para position was the most toxic (LD_{50} = 52.5 mg/kg) [1, 3].

The nature of change in toxic properties of L-lysine derivatives of β-phenylethylamine (compounds I-VI) was analogous to that of the original amines, with the exception of L-lysine derivatives of β-phenylethylamine containing a hydroxyl radical (compound II) or heptoxy group (compound VI) in the para position, which were 1.3 times more toxic than the corresponding amines. Hydrochlorides of lysine salts of β-phenylethylcarbamyl derivatives of L-lysine containing an alkoxy group in the para position with an increasing odd number of atoms of carbon (compounds VII-X) were 1.6-5 times less toxic than the corresponding hydrochlorides of L-lysine β-phenylethylamide (compounds III-VI) and the original amines.

Thus, modification by L-lysine and other α-amino acids (isoleucine, methionine, glycine) of β-phenylethylamine derivatives led to change in their effects on the central nervous system and considerable decrease in toxicity, with the exception of compounds II and VI. Of all the compounds tested, essentially the para-pentoxy (compound XXIV), para-heptoxy (compound X) and para-methoxy (compound XIII) amino acid derivatives of β-phenylethylamine had the most radioprotective activity. Our studies revealed that the route of modification of chemical compounds with amino acids and, apparently, peptides consisting of 2-3 amino acids is of great practical interest, and it should be used in development of new radioprotective agents and agents for treatment of radiation lesions. Polypeptides themselves will be of even greater interest as radioprotective and therapeutic agents. Studies in this area have only begun.

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CSO: 1840/74

UDC 577.391:547.963.3

RADIOTAXONS AND GENOME STABILITY

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 4 Aug 81) pp 147-154

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[Abstract] Mathematical treatment was accorded to the relationship between cellular radiosusceptibility (D_o) and the level of structural organization of the genome. The results demonstrated that in the case of ionizing radiation radiotaxons can be defined in terms of specific genome stability, in eV units, and is given by $K = D_oC$, where C is the quantity of DNA per genome and K (in eV) is the amount of energy absorbed by the DNA necessary to produce one elementary lesion. Each radiotaxon encompasses a group of organisms with an identical (or close to identical) specific genome stability value. From the smallest viruses with the simplest genome organization (K = 100 eV) to the much more complex diploid eukaryotic cells (including that of man; K = 61000 eV) there is a 600-fold increase in the K value. Figures 4; references 19: 9 Russian, 10 Western.
[75-12172]

UDC 577.391:577.15:611.41/42

MECHANISMS OF THYMOCYTE CHROMATIN DEGRADATION IN IRRADIATED RATS. PART 3. POSTRADIATION ACTIVATION OF DNA AUTOLYSIS IN ISOLATED THYMOCYTE NUCLEI

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 20 Oct 80) pp 160-164

NIKONOVA, L. V., NELIPOVICH, P. A. and UMANSKIY, S. R., Institute of Biological Physics, USSR Academy of Sciences, Pushchino

[Abstract] Wistar rats exposed to ^{60}Co gamma irradiation (10 Gy) were employed in studies of the effects of radiation on DNA degradation in

thymocytes. Evaluation of the resultant data showed that at least two enzyme systems are responsible for DNA degradation: a) an acid nuclease independent of divalent cation activation and, b) a Ca/Mg-dependent endonuclease. Irradiation enhanced DNA degradation by the Ca/Mg-dependent enzyme. In both control and irradiated animals thymocytic Ca/Mg-dependent nuclease was inhibited by administration of cylcophosphamide, indicating that irradiation potentiated the protein-synthesizing mechanisms which resulted in enhanced Ca/Mg-dependent nuclease activity in the thymocytes of the irradiated rats. Figures 5; references 9: 4 Russian, 5 Western. [75-12172]

UDC 577.391:001.572

MODELING POSTRADIATION CELL RECOVERY AND EFFECTIVE DOSE DIMINUTION PRINCIPLE. PART 1. CELL RECOVERY MODELS IN ACUTE IRRADIATION

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 5 May 80) pp 187-193

ANDREYEV, A. D. and KUTLAKHMEDOV, Yu. A., Institute of Plant Physiology, Ukrainian SSR Academy of Sciences, Kiev

[Abstract] A number of mathematical models are considered for cell recovery following acute irradiation applied according to the effective dose diminution principle. A general model is derived for cell recovery which is based on experimental data and indicates the impossibility of predicting the time of occurrence of an irreversible radiation-induced lesion, since that type of injury may occur immediately after irradiation or at any time in the course of recovery. Figures 1; references 12: 9 Russian, 3 Western. [75-12172]

UDC 577.391:612.419:612.418

LATE PROLIFERATIVE ACTIVITY OF HEMOPOIETIC CFUs OF BALB/c AND CBA MICE AFTER LONG-TERM IRRADIATION

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 11 Aug 80) pp 199-202

MUKSINOVA, K. N.

[Abstract] Studies were conducted on the proliferative activities of splenic and bone marrow colony forming units (CFU) of BALB/c and CBA male mice subjected to long-term Cs-137 gamma irradiation for a total dose of 9.71 Gy (0.485 Gy/day). Evaluation of total cell counts and the CFUs over a 12 month period following irradiation revealed that in the case of the BALB/c mice the

proliferative activity of the CFUs remained elevated, whereas that of the CBA mice showed a gradual decline to background levels. These observations were interpreted to reflect different regulatory mechanisms in the hemopoietic systems of these mouse lines. Figures 2; references 9: 3 Russian, 6 Western. [75-12172]

UDC 577.391:661.879

CERTAIN PATHOPHYSIOLOGICAL AND BIOCHEMICAL CHANGES IN DOGS WITH VARIABLE RESPIRATORY EXPOSURE TO Pu-239 AND Am-241 NITRATES

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 28 Apr 80) pp 209-214

KALMYKOVA, Z. I., TOKARSKAYA, Z. B., BULDAKOV, L. A., NIFATOV, A. P. and VEDENEYEV, V. S.

[Abstract] Respiratory function and blood protein and enzyme patterns were investigated in outbred dogs following respiratory exposure to various doses of polymeric Pu-239 and monomeric Am-241 nitrates. Animals exposed to high levels of Pu-239 or Am-241 (74 kBq/kg and higher) died within half a year from fibrotic suppurative pneumonia and pulmonary sclerosis; animals exposed to intermediate levels of Pu-239 (25 $\pm$ 2.2 kBq/kg) died within 524 $\pm$ 45 days from lobar pneumonia and pulmonary sclerosis, whereas animals exposed to 52 $\pm$ 8.5 kBq/kg of Am-241 died within 562 $\pm$ 96 days from respiratory insufficiency, cirrhosis, and pulmonary sclerosis. Low levels of Pu-239 (8 $\pm$ 0.3 kBq/kg) led to death within 1568 $\pm$ 68 days from pulmonary cancer, and in the case of Am-241 exposure (15 $\pm$ 0.7 kBq/kg) death occurred within 1645 $\pm$ 47 days from osteosarcoma. Dysproteinemia and alterations in serum transaminases and sorbitol dehydrogenase reflected respiratory insufficiency and damage to the lungs and to secondary sites of radionuclide deposition (primarily the liver). Figures 3; references 16: 1 Ukrainian, 12 Russian, 3 Western.
[75-12172]

UDC 577.391:591:477:539.124

FUNCTIONAL CRITERIA IN THE EVALUATION OF CUTANEOUS RADIATION INJURY

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 7 Jul 80) pp 226-229

SUDAKOVA, V. O. and RAPPOPORT, I. A.

[Abstract] Outbred male rats were used to evaluate the usefulness of skin neutralizing activity of applied alkaline solution as an indicator of beta radiation (krypton-85; 30 and 60 Gy) damage. The results showed that over

a 30-day period the depression of neutralizing activity can be correlated with the degree of radiation-induced damage to the skin, and that the neutralization test may have balue in the clinical evaluation of radiation dermatitis. Figures 2; references 14: 13 Russian, 1 Western. [75-12172]

UDC 577.391:661.879:595.5

BIOLOGICAL ACTION OF RADIOACTIVE CARBON. PART 1. BIOLOGICAL EFFECTS OF LONG-TERM C-14 INTAKE

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 16 Sep 80) pp 230-234

VASILENKO, I. Ya., TUROVA, V. I., POLUBOYARINOVA, Z. I. (Deceased), BUGRYSHEV, P. F., ZHOROVA, Ye. S., KALISTRATOVA, V. S., ZHUKOVA, I. V., LYUBIMOVA-GERASIMOVA, R. M., TISHCHENKO, G. S., ISTOMINA, A. G., SHAL'NOVA, G. A. and KUZ'MINA, T. D.

[Abstract] From the age of three months, outbred rats were exposed to C-14 glucose via drinking water for the duration of their lifetime, in doses ranging from 1.3×10^1 to 1.3×10^4 Bq/day, to simulate the effects of atmospheric increases in C-14 levels resulting from the development of nuclear energy. Over their lifetime, 76% of the animals developed mammary cancer, and various histopathologic changes were noted in the other organs and tissues, particularly those involved in the elimination of C-14 from the body (lungs, kidneys). Figures 3; references 10: 6 Russian, 4 Western. [75-12172]

UDC 577.391:612.112.94:547.963.3

EFFECTS ON DNA SYNTHESIS OF IRRADIATION OF HUMAN LYMPHOCYTES IN G_o AND G_1 PHASES OF THE MITOTIC CYCLE

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 25 Aug 80) pp 243-246

LYCHEV, V. A. and PORYADKOVA, N. A., Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk

[Abstract] Cultured lymphocytes from healthy human donors were subjected to γ-irradiation (1, 2, or 4 Gy) in the G_o of G_1 phase and the number of cells subsequently entering the S phase were evaluated after PGA stimulation (Difro, USA). Autoradiographic data showed that exposure of cells at the end of the G_1 (1 and 2 Gy scheme) had a more profound inhibitory effect on DNA synthesis than irradiation of the cells in the G_o phase. However, the reverse effect was seen with 4 Gy irradiation. Variation in the rate of

irradiation (0.05, 0.51, or 2.19 Gy/min) had no noticeable effect on the results. Figures 1; references 9: 2 Russian, 7 Western.
[75-12172]

UDC 577.391:621.039.58:663.12/14

RADIOPROTECTIVE MECHANISMS OF 2-AMINO-2-THIAZOLINE IN YEAST EXPERIMENTS

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 18 Nov 80) pp 257-258

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[Abstract] Radioprotective effects of 2-amino-2-thiazoline (AT) on Saccharomyces cerevisiae and the lack of such an effect on Pichia guilliermondii were investigated by determination of the levels of biogenic amines known to have radioprotective functions following exposure of the cells (10^5/ml) to AT (10^{-3} M) for 30 min at 30°C. The results showed that AT induced an increase in the histamine and serotonin levels of S. cerevisiae by 87 and 50%, respectively; no significant changes were noted in P. guilliermondii. It appears, therefore, that the radioprotective effects of AT in the case of S. cerevisiae can be ascribed to AT-mediated elevation of serotonin and histamine, and that the lack of a radiprotective effect in the case of P. guilliermondii is due to ineffectiveness with respect to these biogenic amines. References 6 (Russian).
[75-12172]

UDC 577.391:591.434

DEVELOPMENTAL ASPECTS OF LATE SEQUELAE OF SUPRALETHAL IRRADIATION DIRECTED PRIMARILY AT THE ABDOMEN

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 3 Oct 80) pp 258-261

KUDRYAVTSEV, V. D. and YARILIN, A. A., Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk

[Abstract] Studies were conducted on the effectiveness of therapy directed at the 'intestinal phase' of radiation sickness in prolonging life of male Wistar rats subjected to supralethal Co-60 gamma irradiation (10 Gy to the abdomen, 5 Gy to the rest of the body). Untreated animals presented with 60% mortality within 3-5 days, with the remaining animals succumbing by day 7. Intense antibacterial therapy (kanamycin) in combination with massive administration of salt and protein solutions limited 'intestinal death' to 17% and resulted in a 60% survival figure by day 30; the mean survival time

for this group was 107 ± 9.7 days. Animals pretreated with kanamycin had a mean survival time of 139 ± 9.3 days. These findings were interpreted to indicate that early treatment, intended to overcome fulminating infections because of intestinal radiation-induced lesions, prolonged the survival times of lethally-irradiated Wistar rats, but that eventually the animals succumbed because of inadequate immunity. References 12: 7 Russian, 5 Western.
[75-12172]

UDC 577.391

COMBINED EFFECTS ON RATS OF TRITIUM OXIDE, NOISE, AND HEAT

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 3 Mar 81) pp 275-277

TSAPKOV, M. M., KALISTRATOVA, V. S. and TISHCHENKO, G. S.

[Abstract] The effects of noise (100-300 db, 500 Hz) and/or heat (40°C for 2 h/day for 60 days with rel. hum. 18-25%) were investigated on outbred rats with respect to modification of the physiologic response to a single intraperitoneal administration of tritium oxide (TO; 2.2 MBq/g). The results showed that TO alone had no effect on serum cholinesterase activity or hepatic glycogen levels over a 60 day period of observation. However, the combination of noise and TO depressed cholinesterase and hepatic glycogen in the early stages (days 1-14), followed by recovery (days 30-60). The combinations heat + TO or heat + TO + noise resulted in elevated hepatic glycogen levels (day 14), suggesting enhanced glycogenesis or carbohydrate mobilization from other tissues, while serum cholinesterase showed initial depression (days 1-3), followed by recovery and subsequent late depression (day 60). The latter features were interpreted to indicate phasic changes in hepatic protein metabolism induced by the combined factors. These observations indicate that environmental factors can significantly alter the physiological reaction to TO administration and should be considered in evaluating the effects of TO. Figures 1; references 10: 5 Russian, 5 Western.
[75-12172]

UDC 577.391:611.41/42:616-001.17

STRUCTURAL CHANGES IN THE THYMUS OF IRRADIATED ANIMALS ADDITIONALLY SUBJECTED TO THERMAL TRAUMA

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 8 Sep 80) pp 278-279

BUDAGOV, R. S., Scientific Research Institute of Medical Radiology, USSR Academy of Medical Sciences, Obninsk

[Abstract] An evaluation was made of changes in thymic structure in male Wistar rats subjected to Co-60 gamma irradiation (5.5 Gy), photic burn covering 15% of body surface, or to both with the photic burn applied within 10-20 min of irradiation. The results showed that the thymic changes in rats exposed to both factors were essentially identical, but that the thermal component contributed to thymocyte loss from the cortical areas of the thymus and slowed repopulation of the cortical and medullary areas. Thermal trauma alone led to transient changes which affected only the cortical area; it was apparent after 3 h, and involved the loss of less than 9% of the thymocytes. The net effect of thermal trauma in conjunction with irradiation appears to be to delay immune recovery. References 5: 4 Russian, 1 Western. [75-12172]

UDC 577.391:621.039.58

EFFECTS OF INTRAGASTRIC ADMINISTRATION OF POORLY ABSORBED ANTIBIOTICS ON INTESTINAL BACTERIA IN IRRADIATED MICE

Moscow RADIOBIOLOGIYA in Russian Vol 22, No 2, Mar-Apr 82
(manuscript received 9 Dec 80) pp 280-283

KHANYKOV, A. V., NASONOVA, T. A., NEVINNAYA, A. P., TYURIN, Ye. A., STREL'NIKOV, V. A. and IVANOV, A. A.

[Abstract] The effects of intragastric administration of poorly absorbed antibiotics (gentamicin, ristomycin, nystatin) on fecal flora and survival rates were investigated in (CBA x C57Bl)F_1 and outbred mice subjected to Co-60 gamma irradiation (7.68 or 8.64 Gy). The antibiotics were first administered 3 days after irradiation and continued for 20 days. The 30 days survival rate of the animals on antibiotics was 50% higher than that of untreated animals, while concomitant examination of stool samples showed marked depression of coliform counts. Abrupt termination of antibiotic therapy on day 20 or a gradual dose decrease from day 12 to 21 resulted in the rebound of coliform counts, particularly in the former case. Animals treated on day 21 (after termination of antibiotic therapy) with bifidum-bakterin [sic] (0.5 human dose/day for 4 days) showed statistically significant

depression of coliform counts. Discontinuation of bifidumbakterin was also accompanied by a coliform rebound. These observation point to possible control of endogenous infections in irradiated animals with poorly absorbed antibiotics and bifidumbakterin. Figures 2; references 7: 1 Czech, 6 Russian.
[75-12172]

UDC 591.158 + 591.445

PROBLEMS IN STRESS GENETICS. PART 5: GENETICS OF ADRENOCORTICAL REACTIVITY DURING EMOTIONAL STRESS OF RATS

Moscow GENETIKA in Russian Vol 18, No 8, Aug 82
(manuscript received 25 May 81) pp 1326-1333

MARKEL', A. L. and BORODIN, P. M., Institute of Cytology and Genetics, Siberian Division, USSR Academy of Sciences, Novosibirsk

[Abstract] The goal of present study was to perform genetic analysis of the reactivity of corticosteroidal function of the adrenal gland of rats under conditions of stress. Three lines of 3-4 months-old male rats were studied: Wistar (Wag), August (Aug) and Sprague-Dawley (SD) and their F_1 reciprocal hybrids. The base line corticosteroidal function was determined only on parental lines keeping the rats in isolation for 1-2 weeks. The emotional stress was created either by a 30 min immobilization or by putting a number of rats into the same cage. The plasma levels of glucocorticoids in peripheral blood were determined after decapitation along with levels of adrenal gland secretions in vitro. The base line function was similar in all three genotypes. After stress, however, the genotypes demonstrated significant variability in the in vitro secretions of adrenal gland as well as in the levels of plasma corticoids. Using the Griffing model for analysis of the matrix of diallel crossings, it was shown that the genetic variation in the adrenocortical activity under stress was determined by the distribution of genes with additive action. During the immobilization stress a statistically significant variance of specific combinational ability of lines was noted: a domination was observed of the line with low corticosteroid activity. Evidently some alleles determining high stress reactivity in the inbred Aug line were recessive in respect to corresponding alleles determining low reactivity in the Wag line. References 32: 12 Russian, 20 Western. [136-7813]

CSO: 1840

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