GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 6 (351) Июнь 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 6 (351) 2024

Содержание:

Tan Minh Hoang, Hung Dinh Kieu, Vu Nguyen, Trung Kien Tran, Tan Chor Ngee, Ha Dai Duong.
CLINICAL AND IMAGING OUTCOMES OF XLIF SURGERY FOR LUMBAR SPINAL STENOSIS……..……6-11

Nino Totadze, Rishu Bansal.
NUTRITION AND PHYSICAL ACTIVITY OF PREGNANT WOMEN INCLUDING BARIATRIC SURGERY……...…….12-17

Arpine Muradyan.
THE EFFECT OF DIFFERENT FITNESS TRAINING PROGRAMS AND FREQUENCY ON HEALTH-RELATED QUALITY OF LIFE……
……..…….18-22

Serhii Terekhov, Andrii Proshchenko, Nina Proshchenko.
ANALYSIS OF THE USE OF COMPLEX DIGITAL TECHNOLOGIES IN THE DIAGNOSIS AND TREATMENT OF OCCLUSAL ANOMALIES…….…….23-32

Vahe Ashot Ter-Minasyan.
FERTILITY FUNCTIONS IN 4VHPV VACCINATED ARMENIAN COHORT…….……..……33-37

Alaa S. Mahdi, Ahmed H. Salman, Zahraa K. Al-Hassani, Hayder A.H. Jalil.
DECODING PEDIATRIC MENINGITIS UNRAVELING THE INTRICACIES OF ANTIMICROBIAL RESISTANCE IN IRAQI PEDIATRIC PATIENTS…….…….38-43

Rajab A. Alzahrani, Soliman shreed Soliman, Saadi Rabea Saadi AlGhamdi, Mohammed Abdullah S Alzahrani, Abdullah Mohammed B Alghamdi, Ibrahim Abdulaziz A Alghamdi, Essam Mohammed S Alghamdi, Musab Mohammed B Alzahrani, Yahya Ahmed Salem Alzahrani, Mujtaba Alrayah Fadlalla, Mohammed A. Alghamdi.
EFFECT OF ENLARGED ADENOIDS AND TONSILS ON BLOOD OXYGEN SATURATION IN AL BAHA, SAUDI ARABIA…….……..44-48

Sivakumar Palanisamy, Priyatharshni Subramani, Prabhu Narasimman, Manikkampatti Palanisamy Murugesan.
ADVANCEMENT IN ALPHA-SYNUCLEIN PROTEOMICS: EXPLORING ANALYTICAL TECHNIQUES AND THEIR CLINICAL IMPLICATIONS IN PARKINSON'S DISEASE…….…….49-54

Teremetskyi VI, Frolova OH, Batryn OV, Myrza SS, Matviichuk AV, Ryzhenko OS.
VECTORS OF DEVELOPMENT OF THE UNIFIED MEDICAL INFORMATION SPACE…….…….55-60

Rajaa Hussein Fayadh, Rawnaq Thamer Kadium, H. N. K. AL-Salman, Falah Hassan Shari.
HPLC METHOD FOR THE QUANTIFICATION OF SOME ACTIVE FLAVONOIDS IN ETHYL ACETATE EXTRACT OF LEAVES OF BUTEA *MONOSPERMA* LINN…….……61-64

Tchernev G, Ivanov L, Broshtilova V.
MULTIPLE KERATINOCYTIC CANCERS AFTER INTAKE OF ANTIHYPERTENSIVES (LISINOPRIL/ BISOPROLOL/HCT) AND ANTIARRHYTMICS (PROPAFENONE): THE IMPORTANT NEW LINKS TO THE NITROSO-CONTAMINATION AND THE METABOLIC REPROGRAMMING OF THE FUTURE CANCER CELL……...65-71

Maryam A. Faiq, Nehad N. Hilal, Mohammed T. Dawood.
LEVELS OF OSTEOPROTEGERIN AND IRISIN IN POSTMENOPAUSAL OSTEOPOROSIS WOMEN…..…….72-75

Tianhua Du, Guangren Zhou, Shouzhi Wu, Haining Ni.
UNDERSTAND THE CURRENT SITUATION OF STUDENTS' PHYSICAL FITNESS TEST AND MEASURES TO IMPROVE THEIR PHYSICAL FITNESS TEST SCORES…….…….76-79

Sosonna L.O, Boiagina O.D, Yurevych N.O, Schevtsov O.O, Avilova O.V, Konoval N.S, Sukhina I.S.
INDIVIDUAL ANATOMICAL VARIABILITY OF THE ANTEROPOSTERIOR LATERAL DIMENSIONS OF THE FACIAL SKULL IN MATURE ADULTS…….…….80-84

Zhanat Ispayeva, Raikhan Bekmagambetova, Mereke Mustafina, Elena Kovzel, Galiya Tusupbekova, Marina Morenko, Timur Saliev, Shynar Tanabayeva, Ildar Fakhradiyev.
RELIABILITY AND VALIDITY OF THE KAZAKH-LANGUAGE ACT QUESTIONNAIRE AS AN ASTHMA CONTROL TOOL.....85-90

Khitaryan D.S, Stepanyan L.S, Khachatryan M.M, Barbaryan M.S.
JUDO AS AN ALTERNATIVE INTERVENTION MODEL TO PREVENT BULLYING AT SCHOOLS: A PILOT STUDY……..91-95

Rania M. Tuama, Entedhar R. Sarhat.
THE ROLE OF MYONECTIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS…….....96-99

Rongmin Xu,Shundong Li, Anhua Zheng, Lianping He.
EFFECT OF XIAOYAO PILLS COMBINED WITH ALENDRONATE ON BONE DENSITY IN POSTMENOPAUSAL PATIENTS WITH OSTEOPOROSIS…….…….100-101

Nino Kiria, Teona Avaliani, Nino Bablishvili, Nino Chichiveishvili, Giorgi Phichkhaia, Lali Sharvadze, Nana Kiria.
EFFICACY AND SAFETY OF SILVER NANOCOMPOSITES ON RIFAMPICIN-RESISTANT M. TUBERCULOSIS STRAI NS…….……102-108

Dubivska S.S, Hryhorov Y.B, Lazyrskyi V.O, Dotsenko D.G, Lebid P.B.
THE INFLUENCE OF CHANGES IN CARBOHYDRATE METABOLISM INDICATORS IN PATIENTS WITH POLYTRAUMA COMPLICATED BY ALCOHOLIC DELIRIUM ON THE CHOICE OF THE SEDATION METHOD…….....…….109-115

Karapetyan A.G, Danielyan M.H, Badalyan B.Yu, Simonyan K.V, Grigoryan V.S, Simonyan M.A, Dallakyan A.M, Simonyan G.M, Simonyan R.M.
PROTECTIVE EFFECT OF A NEW SUPEROXIDE-PRODUCING ENZYME COMPLEX FROM RASPBERRY IN RATS WITH THIRD-DEGREE THERMAL BURNS.....……..116-124

Sura Z. Salih, Nehad N. Hilal.
EVALUATION OF SERUM VASPIN LEVEL IN IRAQI WOMEN WITH GESTATIONAL DIABETES MELLITUS…...……125-130

Tchernev G, Ivanov L.
MUSTARDE ROTATION FLAP AS ADEQUATE OPTION FOR HIGH-RISK BCC NEAR THE LOWER EYE LID: THE ADDITIONAL INTAKE OF N-NITROSO-FOLIC-ACID AND N-NITROSO-RIVOROXABAN AS COFACTORS/ TRIGGERS OF THE METABOLIC REPROGRAMMING OF THE FUTURE CANCER CELL….....…….131-137

Nazym Ailbayeva, Aliya Alimbaeva, Saule Rakhyzhanova, Nazym Kudaibergenova, Duman Berikuly, Sayat Tanatarov, Zaure Dushimova, Timur Saliev, Shynar Tanabayeva, Sergey Lee, Ildar Fakhradiyev.
THE IMPACT OF BIRTH WEIGHT ON INFANT MORTALITY IN KAZAKHSTAN…….....……..138-145

Voloshyn-Gaponov I.K, Lantukh I.V, Mikhanovska N.G, Gulbs O.A, Malieieva O.V, Dikhtiarenko S.Yu, Kobets O.V, Malieiev D.V.
PSYCHOTHERAPEUTICAL FEATURES OF PERSONS WITH MULTIPLE SCLEROSIS AND HEPATOCEREBRAL DEGENERATION.....146-151

Sevak Sanasar Shahbazyan.
COMPARATIVE ANALYSIS OF EFFECTS INDUCED BY STANDARD AND MODIFIED LAPAROSCOPIC SLEEVE GASTRECTOMY PERFORMANCE ON SHORT TERM AND DISTAL COMPLICATIONS IN PATIENTS WITH 3RD DEGREE OF MORBID OBESITY…….....…….152-157

Qutaiba A. Qasim.
ANTIOXIDANTS, LIPID PROFILES, AND GLUCOSE LEVELS, AS WELL AS PERSISTENT INFLAMMATION, ARE CENTRAL TO THE LINK BETWEEN DIABETES MELLITUS TYPE II AND OXIDATIVE STRESS…….....……..157-161

Stepanyan L.S, Khitaryan D.S.
RESEARCH ON PSYCHOLOGICAL WELL-BEING AND EMOTIONAL PROFILE OF ADOLESCENTS IN THE CONTEXT OF SCHOOL BULLYING…….....…….162-166

Yi Jin, Zhi Luo, Hua-Qin Su, Cui-Ping Li, Cai-Li Wang, Li-Fen Zhang, Feng-Lian Peng, Lian-Ping He, Xiang-Hu Wang.
SERUM CALCIUM WAS NEGATIVELY ASSOCIATED WITH SERUM IRON AMONG GENERAL POPULATION: FINDINGS FROM A CROSS-SECTIONSTUDY…….....……167-169

Stela Dzotsenidze, Lali Pkhaladze, Jenaro Kristesashvili, Nina Davidovi, Samer Hammoude, Marika Zurmukhtashvili.
FUNCTIONAL STATE OF THE REPRODUCTIVE SYSTEM AFTER UNILATERAL OOPHORECTOMY…….....……170-174

GEORGIAN MEDICAL NEWS
No 6 (351) 2024

MUSTARDE ROTATION FLAP AS ADEQUATE OPTION FOR HIGH-RISK BCC NEAR THE LOWER EYE LID: THE ADDITIONAL INTAKE OF N-NITROSO-FOLIC-ACID AND N-NITROSO-RIVOROXABAN AS COFACTORS/ TRIGGERS OF THE METABOLIC REPROGRAMMING OF THE FUTURE CANCER CELL

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Abstract.

Contamination of a heterogeneous class of drugs with nitrosamines of an also different type underlies or defines the occurrence of drug-induced skin cancer Nitrosogenesis or keratinocyte cancer Oncopharmacogenesis. Further identification of some of these carcinogens in drugs as both phototoxic and genotoxic in turn defines concepts such as Drug-Mediated Nitroso-Photo Carcinogenesis. Its first formal representative was and remains at present Nitrosomorpholine (Nmor).

Unfortunately, further data on the propensity of individual nitrosamines and/or their derivatives to absorb photons and generate phototoxicity are lacking. The simultaneous intake of a heterogeneous class of drugs in the context of Nitrosocontamination, now officially announced by regulators, makes the initiation of cutaneous carcinogenesis a perfectly possible scenario. Continuous, permanent intake of several types of carcinogens/mutagens or nitrosamines in the context of potential / or real Nitrosocontamination is probably able to activate certain oncogenes such as RAS oncogenes and neutralize certain tumor suppressor genes such as p53. We report another case of a female patient who developed over the years 3 high-risk basal cell carcinomas in the facial area in a stepwise fashion in the context of potentially contaminated drug treatment with ACE inhibitor/ Ramipril/, Beta blocker/ bisoprolol/, anticoagulant/ rivaroxaban/ and folic acid.

The possible role of Nitroso contamination in polymedication in the context of drug related Nitroso-Photocarcinogenesis for the triggering of multiple basal cell carcinomas is commented. The performed Mustardé rotation flap for the tumour near the lower eyelid was with optimal final reconstructive result.

Nitroso-Folic acid and Nitroso- Riviroxabanan are described for the first time in the medical literature as possible key elements that could have an activating effect on skin carcinogenesis on the background of the so-called metabolic reprogramming of the future tumour cell.

Key words. Nitroso Rivoroxaban, Nitroso-Folic acid, Nitroso-Ramipril, Nitroso-Bisoprolol, p53, RAS, Mustarde rotation flap, dermatologic surgery.

Introduction.

Basal cell carcinoma (BCC) is one of the most frequently diagnosed cutaneous malignancies among the Caucasian population [1]. Over the past 30 years, the incidence rate has increased by 20% to 80% [2]. BCC predominantly occurs on sun-exposed areas of the skin, with rare instances found on mucous membranes, palms or soles [2]. This tumor is characterized by its slow growth and infrequent metastatic potential [2]. While basal cell carcinoma is rarely fatal, it can cause significant local damage to the underlying tissues if left untreated [2]. Patients with previous history of basal cell carcinoma are 10 times more likely to develop a subsequent basal cell carcinoma compared to patients without history of non-melanoma skin cancer (NMSC) [2].

The primary risk factors for developing keratinocytic tumors include ultraviolet radiation, immunosupression or a compromised immune system, skin microbiome alterations, pigmentary factors, and aging [1].

Ultraviolet (UV) radiation is a well-known causative environmental carcinogen associated with the development of keratinocyte cancers [1]. Chronic exposure to UV radiation leads to direct DNA damage, generates reactive oxygen species that cause indirect DNA damage, and results in dose-dependent suppression of the cutaneous immune system [2].

Several tumor suppressor genes and proto-oncogenes are involved in the pathogenesis of basal cell carcinoma [3]. Key components of the Hedgehog signaling pathway, such as PTCH1 and SMO, play crucial roles, along with the TP53 tumor suppressor gene and members of the RAS proto-oncogene family [3]. Recent studies are also exploring new genes linked to basal cell carcinoma carcinogenesis, including PTPN14 and LATS1, both effectors of the Hippo-YAP signaling pathway, and MYCN [3]. Additionally, recent findings have highlighted frequent non-coding mutations in the regulatory promoter regions of the TERT and DPH3-OXNAD1 genes [3].

Oral corticosteroid use has been identified as a potential risk factor for developing basal cell carcinoma, with an estimated incidence rate ratio (IRR) of 1.15 (95% CI: 1.07-1.25) [4]. Similarly, methotrexate use has been linked to an elevated risk of developing bcc, with an adjusted odds ratio (OR) of 1.29 (1.20-1.38) [5]. The risk was estimated higher with higher cumulative doses of the medication [5].

However, these environmental risk factors and complex carcinogenic processes can take considerable time to manifest phenotypically. These observations, along with other recent findings, support the (hypo)thesis that skin carcinogenesis, particularly in the context of polymedication, may be triggered by additional causative agents, currently known as nitrosamines [6].

It is well-established that exposure to a combination of medications contaminated with carcinogens can act as a “cocktail” of carcinogenic agents, which may include both photocarcinogenic and genotoxic components. Clinicopathological evidence suggests that such exposure

is linked to the development of both keratinocytic [7] and melanocytic [8] skin cancers also.

In the treatment of skin cancer, particularly basal cell carcinoma, several therapeutic options are available depending on the disease stage and characteristics: for localized disease is recommended surgical excision with margin evaluation, Mohs Micrografic surgery, radiation therapy, curettage and electrodesiccation, cryosurgery, photodynamic therapy, topical 5-fluorouracil, topical imiquimod, and carbon dioxide laser; for metastatic or locally advanced disease – hedgehog pathway inhibitors; and for recurrent nonmetastatic disease – surgical excision or Mohs Micrographic surgery [9].

In cases of locally destructive or high-risk BCC near the lower eyelid for example, or when the primary defect is sufficiently large, the melolabial advancement flap has proven to be an effective one-step treatment option [10].

In this case report, we explore some new aspects and thesis about the complex pathogenesis of keratinocytic cancer, focusing on the potential role of drug-induced Nitrosogenesis associated with the use of 1) folic acid, 2) ramipril, 3) bisoprolol, and 4) rivaroxaban. We also discuss the impact of possible contaminants in these medications in the context of the modern concept on tumor cell metabolic reprogramming.

Case report.

A 74-year-old female came to the dermatology department with primary complaint of a basal cell carcinoma under the left lower eyelid, histologically confirmed three years prior. The tumor had been treated unsuccessfully with imiquimod 5% cream. In the past six months, the patient reported rapid growth of the tumor formation.

The patient reports having urticarial systemic vasculitis since 2010, arterial hypertension since 2008; a basal cell carcinoma on the upper cheek dating from 2009-2010 and subsequent surgically removed in 2018; and another basal cell carcinoma in the left temporal region since 2021, successfully treated with imiquimod. Additionally, she has a history of arterial fibrillation and heart failure from 2023. She reports allergies to metamizole sodium, acetylsalicylic acid, and nimesulide.

The patient's systemic medication regimen includes bisoprolol fumarate 5 mg, two tablets daily since 2023 (previously taken as one tablet daily from 2008 to 2018); eplerenone 25 mg, one tablet daily since 2023; methylprednisolone 4 mg, one tablet daily according to a prescribed scheme since 2010; etoricoxib 60 mg, taken once every two weeks since 2023; rivaroxaban 20 mg, one tablet daily since the beginning of 2023; methotrexate 2.5 mg, two tablets once a week; digoxin 0.25 mg, half a tablet once daily; ramipril 5 mg, one tablet as needed since 2023; and folic acid and vitamin D, both taken since 2023 (previously from 2020 to 2022).

She requested physical examination and further therapeutic approach to be established.

The dermatological examination revealed a tumor-like formation under the left eyelid, measuring 2.5 cm in diameter, with a pearly border, erosions, and superficial telangiectasias (Figure 1). In the area of the left medial corner of the eye, a smaller tumor-like formation of 0.5 mm was observed. Additionally, hypopigmentation measuring 2 cm in diameter was noted in the left temporal region, corresponding to the basal cell carcinoma that was successfully treated with imiquimod (Figure 1). Enlarged lymph nodes were not palpable.

An MRI of the facial skull revealed changes in the area of the lower eyelid of the left orbit consistent with a volumetric process. No focal pathological changes were observed in the brain parenchyma supra- and subtentorially. The skin and subcutaneous tissue showed infiltration, but there was no evidence of involvement of the underlying tissues like muscles and bone structures.

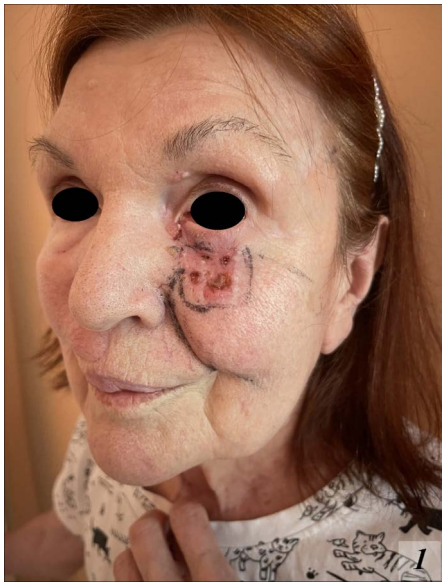

Figure 1. *A tumor-like formation under the left eyelid, measuring 2.5 cm in diameter, with a pearly border, erosions, and superficial telangiectasias. In the area of the left medial corner of the eye, a smaller tumor-like formation of 0.5 mm is also observed. Additionally, hypopigmentation from a previously treated bcc, measuring 2 cm in diameter is noted in the left temporal region.*

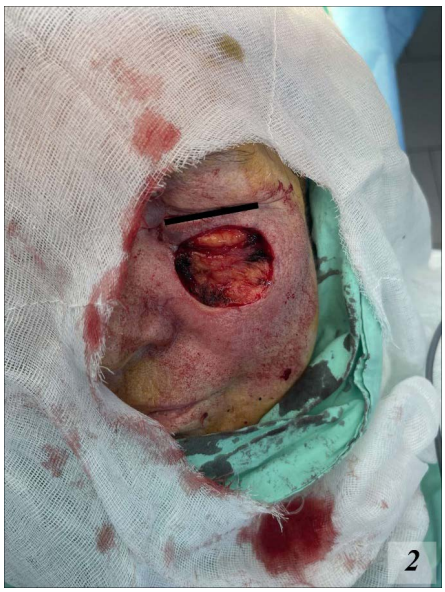

Figure 2. *Primary circular skin defect after oval excision with a 4 mm safety margin of the tumor formation under the left lower eyelid.*

The patient was recommended surgical excision of the lesion under the left eyelid.

Preoperatively, the patient was consulted by a cardiologist who adjusted her medication, switching from rivaroxaban 20 mg to nadroparin calcium solution 0.4, administered twice daily.

After thorough disinfection of the operative field and under local anesthesia with 1% lidocaine, the tumor formation under the left lower eyelid was removed with an oval excision with a 4 mm safety margin (Figure 2). Hemostasis was achieved, and a Mustardé rotation flap was used to reconstruct the primary circular skin defect (Figure 3). The remaining skin defect was then closed with using single interrupted sutures (Figure 4, 5). A sterile povidone-iodine dressing was applied. The excised material was sent for histological certification, which confirmed ulcero-nodular basal cell carcinoma. Postoperatively, to accelerate the resorption of the edema, the patient was prescribed desloratidine 5 mg once daily, methylprednisolone 20 mg intravenously in 300 ml of 0.9% NaCl once daily, and famotidine 20 mg twice daily. The postoperative period was uneventful.

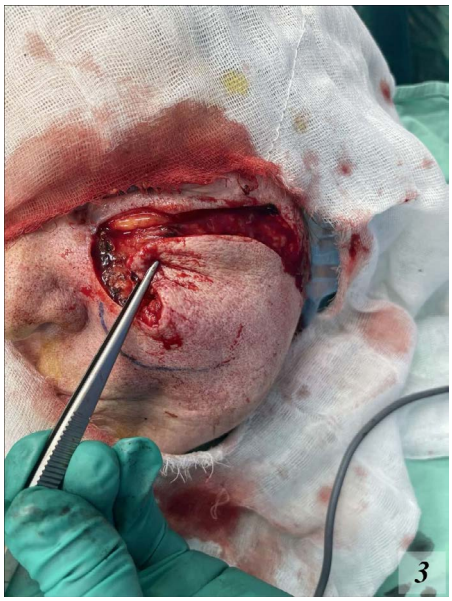

Figure 3. *Mustarde rotation flap technique used for the closure of the primary circular skin defect.*

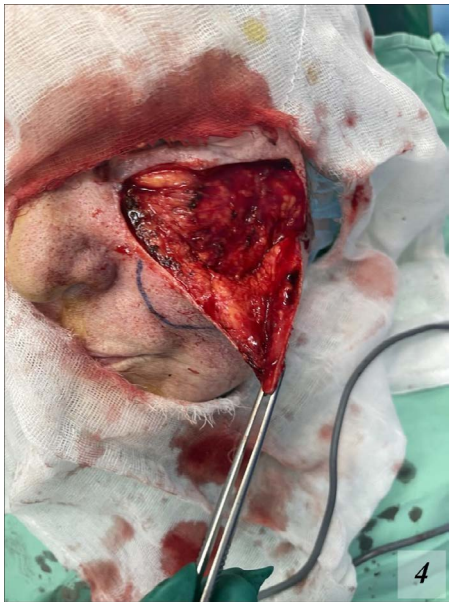

Figure 4. *Mustarde rotation flap technique used for the closure of the primary circular skin defect.*

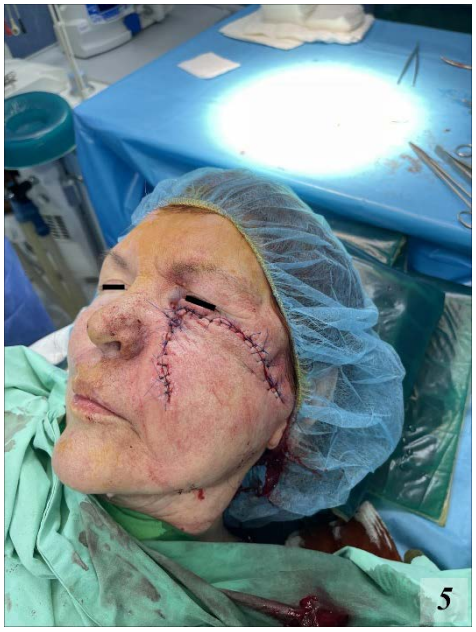

Figure 5. *The remaining skin defect is closed with single interrupted sutures.*

An ophthalmologist was consulted and surgical removal of the small additional tumor formation involving the left medial corner of the eye was planned. A whole-body contrast-enhanced CT scan for staging was negative for metastatic spread.

Discussion.

The drastically increasing incidence of keratinocytic cancer worldwide is a not unknown fact, the roots of which currently remain incompletely understood [11]. Despite massive campaigns for sunlight protection and the relatively constant intensity of the latter over the years, cancer incidence is skyrocketing [11,12]. The search for the real causes of this incidence should be focused on the identification and recognition of new environmental factors that should be able to 1) induce acquired mutations, 2) be potential photocarcinogens and/or have 3) permanent contact with the human body. And such substances were recently discovered and categorized: nitrosamines and their derivatives, localized however in pharmaceutical preparations also [13,14].

For the period 2019-2023, regulators in the face of the FDA have identified certain carcinogens/mutagens, also known as nitrosamines, that are found in heterogeneous form and concentration in about 300 of the most commonly distributed drugs worldwide [13,14].

Some of these drugs have even been found to contain more than one nitrosamine, so there is also evidence of polycontamination with more than 1 nitrosamine in a given drug [15]. One of the nitrosamines relatively recently identified as being present in drugs-nitrosomorpholine-has been shown to exhibit

interesting characteristics: genotoxic yet phototoxic before metabolisation in the liver [15,16]. Open questions remain, are the other nitrosamines identified in the drugs phototoxic and genotoxic prior to methylation in the liver, and are their subsequently formed metabolites mutagenic, carcinogenic, and/ or simultaneously phototoxic?

Some expert opinions remain of concern, which are indicative of the fact that NDMA, for example, activates RAS Oncogenes prior to its metabolisation in the liver, and after its metabolisation, the resulting metabolite, methyldiazonium, is also a mutagen [17]. In practice, monocontamination of a particular drug with only one nitrosamine (NDMA), could act on the principle of either being a bicarcinogen, polycarcinogen.

The hallmark of the theses, theories or actual/ modern pathogenesis/ understandings for cancer in general, but also skin cancer in particular, is based on 1) the activation of the so-called metabolic reprogramming/initiation of a tumor clone or of a future tumor cell due to contact with factors of the external environment (mutagens/carcinogens/nitrosamines), which could disturb the balance between the processes of proliferation and programmed cell death for example [18]. For skin cancer, a major role of this reprogramming (or its initiation) of the future tumor cell is mainly attributed to the solar radiation [18].

According to the International Agency for Research on Cancer (IARC), tobacco-specific nitrosamines play a key role in the initiation phase of a variety of cancers caused virtually by inhalation from cigarette smoke [18].

Tobacco-specific nitrosamines are known to cause acquired mutations in human DNA, primarily and predominantly affecting RAS oncogenes and the tumor suppressor gene p53 [19].

However, the same genes are also the major genes found to be affected in skin cancer [20,21]. What leads medical professionals and scientists to think that nitrosamines taken as permanent, daily, long-term, polymedicated intake in the context of polymorbidity would have a different effect on the human genome compared with sporadic intake of nitrosamines similar in composition and action but taken inhaled and via tobacco, remains unclear? A significant number of publications worldwide are indicative of such a direct or indirect pathogenetic link or association.

Whether photocarcinogenesis/phototoxicity is (self-) potentiated within the so-called nitroso-photocarcinogenesis remains also unresolved, but perfectly reasonable as a thesis or starting point concerning future analyses. A number of publications have found a pathogenetic association between potentially nitrosamine-contaminated polydrug intake and the subsequent development of multiple keratinocytic cancers [22,23].

International data on this topic are not lacking. There is new evidence that it is the intake of antihypertensives that could be associated with the development of certain skin cancers such as: basal cell carcinomas, squamous cell carcinomas, dermal pleomorphic sarcoma and atypical fibroxanthoma [24].

The dilemma remains open here: does potential contamination with nitrosamines mediate the phototoxicity and photocarcinogenic effect of the drug in this case (hydrochlorothiazide)? Do these two effects concerning the presence of nitrosamines in drugs exist separately: a purely mutagenic/carcinogenic effect and a photo-nitroso-mediated toxic/carcinogenic effect?

The largely overlapping mutational patterns/target genes of nitrosamine-initiated mutations with those responsible for skin cancer are at least indicative of possible nitroso-mediated negative effects presented, but those time probably drug related.

A similar meta-analysis by an American collective in 2024 [25], is indicative of ″Increased risks were seen for basal cell carcinoma with calcium channel blockers (relative risk [RR] = 1.17, 95% confidence interval [CI] = 1. 11-1.22), diuretics (RR = 1.06, 95% CI = 1.03-1.10), and thiazides (RR = 1.10, 95% CI = 1.04-1.16); for squamous cell carcinoma with calcium channel blockers (RR = 1. 08, 95% CI = 1.01-1.14), diuretics (RR = 1.29, 95% CI = 1.17-1.43), and thiazides (RR = 1.36, 95% CI = 1.15-1.61)″ [25].

This article does not comment, however, on whether 1) the medications that were analyzed as being at risk belonged to the group of potentially nitrosamine-contaminated drugs created by the FDA, and 2) whether there was concomitant use of other, non-antihypertensive drugs also belonging to this potential contamination list]25].

An innovative and recently published study on postmenopausal hypertensive patients taking photosensitizing antihypertensives found an association between : ″Use of antihypertensives (HR [95% CI]: 1.12 [1.07-1.18]), ACE inhibitors (1.09 [1.01-1.18]), calcium channel blockers (1.13 [1.05-1.22]), diuretics (1.20 [1.12-1.27]), loop diuretics (1.17 [1.07-1.28]), and thiazides (1.17 [1.03-1.33]) were each associated with higher NMSC risk [26]. NMSC risk linearly increased with use of multiple antihypertensives (p-trend = 0.02) and with longer duration of use (p-trend < 0.01) [26]. ″

Although again not thematized as a potential cofactor for cutaneous carcinogenesis [26] and here nitrosamines, could be the mediating phototoxicity and photocarcinogenicity ″nitroso-agent″, analogous to previously shared literature data [27-29].

The contribution of the data presented in the current publication lies in the opportunity to further clarify/ crystallize the role of drug-triggered carcinogenesis and its broad basis.

This basis could be based not only on potentially nitrosamine-contaminated antihypertensive drugs but also on other drugs present in the list of FDA-contaminated drugs [13,14]. The same or completely overlapping skin tumors, also occurred after potentially contaminated intake of sitagliptin and/or metformin for example [30,31], as well as after polymedication with neuroleptics/ Olanzapine and antidepressants/ Velafaxine [32].

In the patient presented, the following facts are of interest: 1) The stepwise development of 3 basal cell carcinomas localized in areas exposed to solar radiation, 2) Their development in the context of or after initiation of bisoprolol, Rivoroxaban, Ramipril and folic acid, and 3) That all 4 of these medications have been described as potentially contaminated with nitrosamines of heterogeneous carcinogenic potency according to the FDA/ official bulletin and the Australian Medicines Control Agency list [13,33].

Another point of interest should be the fact that folic acid [13] and rivaroxaban [33] are new, previously undescribed drugs that, possibly and according to clinical observations, could have a potential role to model the processes of drug-mediated nitrosogenesis/carcinogenesis concerning skin cancer and basal cell carcinomas in particular. Rivoroxaban has been catalogued as a potentially nitrosamine-contaminated drug-according to the Australian Government/ Department of Health and Aged Care/ Therapeutic Goods Administration [33] lists, but not by those of the FDA and EMA. This leads us to consider that, in practice, contamination is not uniform across latitudes and affects heterogeneous medications [13,33]. This is what necessitates the establishment of nationally responsible institutions to monitor, control (and eliminate) the presence of carcinogens/ mutagens in drugs. And this availability to be officially declared in the prescriptions of the drugs or eliminated completely.

The concomitant intake of 4 potentially nitrosamine and/or nitroso derivative contaminated drugs (rivaroxaban, folic acid, bisoprolol and ramipril) should not be surprising in terms of the development of another basal cell carcinoma in the facial area (Figure 1).

The role of drug-induced nitrosogenesis/photo/nitroso-carcinogenesis in the case described is difficult to differentiate in terms of its relevance due to the concomitant long-term intake of immunosuppressants (low-dose prednisolone/methotrexate, see history) due to a past diagnosis of vasculitis.

Keratinocytic cancers are seen as a common side effect in patients on immunosuppressive medication or with weakened immunity [34,35]. However, this in no way neglects the presence of the nitrosocomponent in the polymedication of the described patient, but on the contrary, requires the urgent clarification of this issue: the simultaneous administration of a cocktail of carcinogens to influence the initiation process of the cancer cell in the context of metabolic reprogramming [18], but this time through drugs.

The contribution of the casuistic described in the publication consists in the tabulation of two other new drugs- rivoroxaban and folic acid (described as potentially contaminated with nitrosamines according to the current international regulatory lists for the control of carcinogens in medicines), distributed in the USA and Australia [13,33]. In combination with beta blockers (bisoprolol) and ACE inhibitors (ramipril), these drugs carry a risk of developing multiple keratinocytic tumors.

The complex assessment of the relevance of carcinogen intake in the context of polymedication and polycontamination (drug-mediated skin cancer nitrosogenesis) for the development of keratinocytic cancer, as well as concomitant iatrogenic immunosuppression due to the presence of vasculitis, is difficult but should by no means be neglected.

Successful surgical treatment by using a Mustardé rotation flap is a challenge for dermatologic surgeons, especially in areas close to the lower eyelid, because of the risk of developing ectropion or inadequate aesthetic results afterwards [36,37].

The advantage of this type of plastic lies in the fact that the tension is spread in a horizontal direction / towards the nose rather than in a vertical direction / towards the eye, thus preventing the formation of an ectropion of the lower eyelid [38].

Future analyses regarding the phototoxicity/nitroso-photo-mediated carcinogenicity of drug-related nitrosamines and/ or their derivatives could prove pivotal in terms of ultimately unraveling the pathogenesis of skin cancer. The phototoxic properties of most nitrosamines have been known to the scientific community since 1972 [39].

The recent identification of nitrosamine (nitrosomorpholine/ NMor) as a contaminant in drug preparations, which has potent genotoxic and phototoxic effects, is highly indicative that other members of the nitrosamine family could possess similar properties [15,16]. Recent data on this preparation define concepts such as drug-mediated Nitroso-Photo Carcinogenesis.

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