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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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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.

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(NDMA) METFORMIN AND (NTTP) SITAGLIPTIN INDUCED CUTANEOUS MELANOMAS: LINKS TO NITROSOGENESIS, NITROSO-PHOTOCARCINOGENESIS, ONCOPHARMACOGENESIS AND THE METABOLIC REPROGRAMMING

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Abstract.

Changing the vision, understanding, interpretation and analysis of certain data or scientific dilemmas is what is able to change the status quo and revitalize a mission, an impulse or important thoughts, thus creating the conditions for it to increase immensely the chances of bringing it to success. Or, following Albert Einstein's postulate: ″We cannot solve our problems with the same thinking we used when we created them″, we should think: ″Where does the road to success start? How do we solve or neutralize a problem? ″ And the answer is : ″ By taking a consistent and systematic approach, analyzing each component! And we eliminate every possibility of negative influence.″

These thoughts apply with full force to cancer rates in general, but also to melanoma rates in particular: the murderous tempo of globalization and modernization in medicine has not yet led to the desired decrease in these rates; on the contrary, they are rising headlong and remain largely unpredictable and difficult to regulate. The conclusion is that a solution should be sought by refracting light through another prism: that of Nitrosogenesis and Pharmaco-Oncogenesis. A step-by-step and systematic approach to solving a problem requires patience, determination, and perseverance. As this perseverance is needed mainly to overcome the general ignorance, neglect , disinterest, uneducation and uncertainty of others, rather than doubt in one's own thesis, analysis, and the need for an active approach.

Careful analysis of concepts such as ″Drug Mediated Nitrosogenesis″ and ″Onco-pharmacogenesis/Pharmaco-oncogenesis″ of skin cancer would certainly contribute to the elucidation of skin carcinogenesis in the context of polymedication of the contamination and polymorbidity worldwide. The FDA has already in 2019 taken this much needed first step of universal awareness and its ″arm″ has been taken seriously and responsibly solely by dermatologists and dermatosurgeons. It was this guild and only this guild that launched its independent, never-ending observations, logically grounded (hypo)theses, remaining to date confirmatory, unshakable, and enigmatic regarding the unit: intake of potentially contaminated medication and subsequent development of melanomas. It is this and only this branch of the medical guild that has also become the guarantor of safety and objectivity in science, and thus of safety in the fight for survival of a huge number of skin cancer patients.

Contaminated oral antidiabetic drugs in the face of Metformin and Sitagliptin do not make an exception in this respect. Similarly to cutaneous melanomas occurring (and published in the scientific literature) after combined intake (or monomedication) of/ between ranitidine, valsartan, olmesartan, candesartan, telmisartan, irbesartan, losartan, enalapril, lisinopril, perindopril, hydrochlorothiazide, nifedipine, amlodipine, propafenone, bisoprolol, nebivolol, melitracen and a number of others, we inform about another rare but not unexpected clinical observation: occurrence of cutaneous melanomas after taking another class of drugs- oral antidiabetic ones. Or after the intake of nitrosamine-contaminated antidiabetic drugs. And whether this contamination is ″real or potential″ is left to regulators and manufacturers to decide. We accept it as `real-potential' or `potentially-real' because of the fact that neither the regulators nor the manufacturers know what it is or whether it is there or how it arose.

The data shared in patients one and two in the presented scientific work are confirmatory in relation to the potential pathogenetic action of nitrosamine contaminated drugs such as 1) bisoprolol/ nebivolol/ candesartan/ hydrochlorothiazide and amlodipine, as well as 2) furosemide in the direction of cutaneous melanoma.

Patient 3 in fact also represents the first formally described patient with subsequent melanoma development worldwide, having developed it following intake of potentially/actually nitrosamine-contaminated metformin and metformin/sitagliptin (both drugs are themed in the FDA's Potentially Contaminated Drug Bulletin: 1) metformin, multiple times between 2020-21, due to its contamination with NDMA and 2) sitagliptin, as of September 2022, due to its contamination with NTTP).

It should not be seen as surprising to anyone that the intake of relatively similar carcinogens/nitrosamines or NDSRIs, but as an unofficial component of heterogeneous drugs, produces a relatively monomorphic clinical picture- that of cutaneous melanoma. Or to put it metaphorically: ″ The wolf changes its hair, but not its mood.″ A carcinogen remains a carcinogen, regardless of whether it is ingested in a lemonade, a tablet, a sandwich, or a bonbon. Similarly to the intake of nitrosamines in food.

Future studies should address the important tasks/dilemmas to elucidate 1) the phototoxic/photocarcinogenic effect of unmetabolized nitrosamines identified in drug formulations; 2) the phototoxic/photocarcinogenic effect of DNA adducts generated after their metabolization, and 3) the availability of specific DNA adducts in lesional/tumor tissue and blood of patients after ingestion of nitroso-containing drug formulations.

This level of evidence is likely to lead to a reconsideration of the arguments for the introduction of permanent elimination regimes for nitrosamines in medicines. Metabolic reprogramming (and its relationship to UVB radiation) due to the availability of nitrosamines in cigarette smoke is also currently a proven reality.

Based on the available clinicopathological correlations, we believe that nitrosamines in drugs have a similar effect and are part of the key pathway activating skin carcinogenesis under the influence of solar radiation. Intake of contaminated medication is associated with skin cancer generation and progression. It is up to regulators and manufacturers to justify the merits and benefits of the self-imposed presence of carcinogens in drugs or the benefits of such drugs. Apart from the ″cancer-generating benefit″, of course, which is already widely known. And let us not forget that : ″A lie stops being a lie and becomes a truth the moment it is officially refuted.″

Key words. Metformin, sitagliptin, photocarcinogenicity, p53, Nitrosamines, NDMA, bisoprolol, nebivolol, candesartan, hydrochlorothiazide, amlodipine, furosemide, NDSRIs.

Introduction.

Oncopharmagogenesis and Nitrosogenesis of cancer in general and skin cancer in particular continue to be intriguing new scientific concepts [1,2]. Their medical relevance is also due to the ever-growing body of scientific data that is indicative of the relationship: nitrosamines-cancer or nitrosamines-mutations and cancer [3-6].

The photocarcinogenic or genotoxic, mutagenic effect of certain nitrosamines such as nitrosomorpholine, for example, is even- just as an information availability in the scientific space, an extremely worrying fact [7]. Nitrosamines are metabolized in the liver to carcinogenic metabolites that may subsequently exert their genotoxic effects [8]. As a result of this metabolisation and subsequent interaction with given cells in a given organism (human for example, but not only), DNA adducts are produced which, if not repaired, can become a powerful generator of carcinogenesis [8].

According to the literature, some nitrosamines affect key regulatory genes, such as p53 for example.

Thus, in practice, the initial changes in the genome/germline of the tumor cell could not be neutralized in time and gave rise to the neoplastic tumor cell and subsequently to the neoplastic cell clone.

Also of interest is the fact that certain nitrosamines are organ-specific in action, in fact showing a certain carcinogenic selectivity or organotropicity [9]. In order to clarify their selectivity, disclosure and cataloguing of their availability on drug packaging should be the first order of priority (mainly for regulators). This would then become an extremely powerful stimulus to science worldwide: the search for a pathogenetic relationship between a defined formal intake of a carcinogen and the subsequent development of cancer.

The carcinogenic effects of nitrosamines, and in particular of NDMA/NDEA, on members of the animal kingdom ranging from the rainbow trout to the monkey were already known some 50 years ago [10]. What, at present, leads us to believe that their action in humans will be different remains unclear?

Clinicopathological correlations between intake of drugs contaminated with ″similar to analogous nitrosamines″ and the subsequent development of skin cancer and melanoma in particular could also be viewed as categorically analogous and reciprocal to animal tests [11-14].

For dermatological science, however, some important dilemmas remain regarding nitrosamines and their pathogenetic relevance to skin cancer, such as:

1. Does certain nitrosamine/its metabolites have a triggering point to absorb photons and trigger phototoxicity?

2. Does it or its metabolites have the potential for 2.1. systemic bioavailability and/or 2.2. accumulate in skin to trigger skin cancer?

This is what would largely clarify whether concepts such as Photo-Nitroso Carcinogenesis make sense to be further elaborated and thoroughly analyzed in depth for their subsequent future definitive elimination.

The phototoxicity of nitrosamines is a known, but nonspecific effect of theirs, known since as far back as 1972 [15]. The photo-nitroso-genotoxicity of the nitrosamines present in drugs is currently of great interest: is it a reality or rather a myth?

However, the concomitant intake of drugs in the context of polymorbidity, in practice, brings the organism into contact with mutagens and carcinogens in (in all likelihood) sufficiently high concentrations that are or could also be regarded as triggers of carcinogenesis. These carcinogens could, by common sense, possibly accumulate in the blood and deposit in certain skin structures, contributing to phenomena such as Nitroso Photo-Toxicity, for example.

The overlapping mutational patterns of nitrosamine-induced mutations in humans in general (RAS and p53) [16], with those responsible for the manifestation of melanoma and keratinocytic cancers (again, the same genes) [17-20], are one piece of albeit indirect evidence that nitrosamines could safely be considered a pathogenetic cofactor for skin cancer, regardless of their phototoxicity.

Exclusion of their photo-carcinogenicity would not invalidate this role but would probably limit somewhat only their pathogenetic significance overall. However, this `exclusion' has yet to be achieved.

Distinguishing the mutagenic from the carcinogenic or genotoxic action of nitrosamines is also important (but also problematic) because of the fact that not every mutation is equivalent to a carcinogenic action, and that not every carcinogen could be classified as a mutagen [21-23].

Similarly for genotoxic substances: not all genotoxic substances are mutagens, although all mutagens are thought to be genotoxic by definition [24].

Different nitrosamines have different effects: from mutagenic, to mutagenic-carcinogenic, genotoxic, or purely carcinogenic- to the complete absence of each of these [24-26]. Nitrosamines have also been identified as genotoxic chemicals, while also being described as possible potent human and animal carcinogens [25]. Some nitrosamines are also potent mutagens [26].

The combined (in the context of polymedication and polymorbidity) or concurrent intake of nitrosamines with mutagenic effects followed by the intake of ″those″ with direct carcinogenic/genotoxic effects, for example (heterogeneous class of drugs/ heterogeneous class of carcinogens/mutagens), suggests precisely the possible stepwise elimination of genome

defense systems (in the face of p53, for example), thus indirectly setting the stage for chromosomal aberrations or uncontrolled proliferation to persist and manifesting clinically subsequently as skin cancer, for example (metabolic reprogramming of the cancer cell).

Pure Nitrosogenesis could hardly be differentiated from Photocarcinogenesis/Nitroso-Photocarcinogenesis. If the Nitroso-Photo-Carcinogenesis thesis is not confirmed in the near future, then the purely mutagenic, mutagenic-carcinogenic and/or directly carcinogenic non-mutagenic nitrosamines (in drugs) and their relevance to skin cancer, will be left hanging again and regardless - and again with full force.

The recently established reciprocity between the Ames mutagenicity test and the rodent carcinogenicity data are encouraging [27], however, their applicability/reciprocity in humans should not be viewed at or as 100% as a definite ″clean coin″. The Ames test is a test of mutagenicity in bacteria, and the rodent genome, in principle, in terms of sensitivity/susceptibility to mutations, could not be regarded as completely identical to that of humans. Rodent tests are not conducted against a background of concurrent intake of multimedication that is or could be potentially contaminated. That is, the explanation of the complex nature of the clinical picture is lost, as is the complex assessment of the processes involved in carcinogenesis. Thus, multifactorial interactions and influences are limited and cannot be considered equivalent to those in humans.

We present 3 cases of patients with melanomas of the skin that developed and progressed in the context of intake of potentially nitrosamine-contaminated (according to the FDA list) drugs. We comment on the possible relevance of drug mediated Nitrosogenesis to melanoma generation. Or its relationship to Oncopharmacogenesis/ Pharmaco-Oncogenesis.

Case 1.

A 59-year-old female presented to the dermatology department with primary complaints of darkly pigmented nodular tumor formations located in the left axillar region.

Medical history of hypertensive heart without (congestive) heart failure; chronic duodenal ulcer, without hemorrhage and perforation; kidney stone; left-sided nephrolithiasis was reported.

For the arterial hypertension, the patient was on systemic therapy from 2021 with bisoprolol fumarate 5 mg once daily administrated for 1 year, then switched to nebivolol 5 mg once daily for another 1 year, when the therapy is switched again to bisoprolol fumarate 5 mg once daily administrated for another year until February 2024. In March the therapy regimen was replaced with bisoprolol fumarate 5 mg twice daily, candesartan cilexetil/hydrochlorothiazide 16 mg/12.5 mg once in the morning, amlodipine 5 mg once in the evening, and clopidogrel 75 mg once in the evening. Additionally, esomeprazole 20 mg on an empty stomach once daily in the morning was administrated for the duodenal ulcer.

In April 2022, the patient was admitted to the oncodermatology department for surgical excision of a pigmented cutaneous lesion located on the back, intrascapularly (Figure 1). The patient describes the lesion as a birthmark that has been progressively growing for the past two years and has been bleeding for the past year prior to the consultation. The lesion was clinically diagnosed as a nodular melanoma measuring 10/18 mm, exhibiting ulceration and bleeding, without regression. At the time of the physical exam, regional lymph nodes were not palpable. The lesion was surgically removed under local anesthesia (Figure 1). Upon histological examination, the lesion was confirmed as a nodular melanoma with a diameter of 30 mm, Breslow thickness of 13 mm, Clark level 4 (reticular derma), with ulceration, mitoses 6/2 mm, staged as pT4bN0M0 llC. Sentinel lymph node biopsy was not performed because of the wish of the patient.

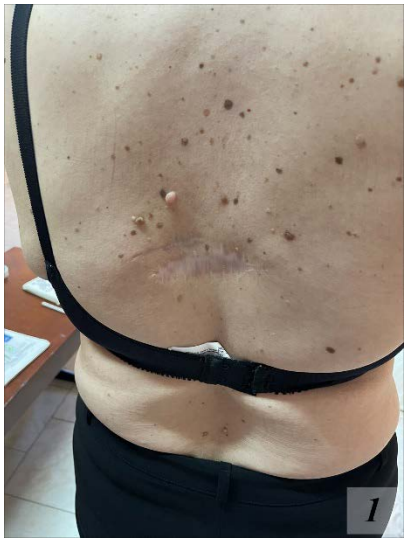

Figure 1. *Two scar tissues from previous surgical interventions in the dorsal region of the back. Multiple pinkish-brownish pigmented lesions were noted over the entire back area.*

In September 2022 (5 months after the surgical intervention), a clinical suspected satellite metastasis near the surgical scar was observed, leading to its surgical excision (Figure 1).

In January 2023 (4 month later), following a respiratory infection, the patient noticed swelling near the scar tissue and enlarged of lymph nodes in both armpits. Antibiotic therapy was initiated, resulting in reduction of the lymph node sizes. Subsequently, a PET/CT scan revealed secondary involvement, indicating local recurrence in the surgical scar and in both axillar regions.

In May 2023 (4 month later), the patient underwent radical excision of the lesion around the primary site, which measured 28 mm x 23 mm to the left of the midline. In June, a surgical intervention in both axillary regions were scheduled. A radical lymph node dissection was performed, involving the removal of level 2 and 3 lymph nodes. The histopathological verification confirmed the diagnosis of malignant melanoma with the presence of BRAF mutation (BRAF +). Subsequently, the patient was referred to the radiation department for a course of radiation treatment for 1 month using IMRT ARC with 50 Gy for both left and right axillae.

In November 2023 (6 months later), two metastatic lymph nodes on the left axillary were identified on a follow-up PET/CT scan. A radical axillary excision was performed. The excised lymph nodes were sent for a histopathological verification,

resulting in axillary lymph node macrometastases from malignant melanoma, pN3c. The infiltration extended beyond the capsule into the perinodal soft tissues.

In February 2024 (2 months later), a restaging PET/CT scan was conducted, revealing a new metabolically active lesion in the left mammary gland with potential involvement of the pectoral muscle. No evidence of lymphatic dissemination or dermal recurrences was observed.

In April 2024 (2 months after the PET/CT), the patient presented to our dermatological department with clinically suspected lesions for recurrent nodular melanoma in the left axillar region (Figures 2a,2b).

Figure 2a,b. Preoperative view.
2a,b: *Two well-defined dark nodules and multiple small slightly raised pigmented lesions in the left axillary region.*
(a) Preoperative view
(b) Intraoperative view: the lesions that were going to be removed are preoperatively marked.

The dermatological examination revealed two scar tissues from the previous two surgical interventions in the dorsal region of the back (Figure 1). Additionally, two well-defined dark nodules and multiple small slightly raised pigmented lesions in the left axillary region were observed (Figure 2a).

The patient was recommended surgical removal of the lesions under local anesthesia with lidocaine. The lesions were preoperatively marked (Figure 2b) and removed with elliptical excisions (Figure 3a) followed by closure of the remaining defects with single interrupted sutures (Figure 3b). The postoperative period went without complications. Daily wound dressings with povidone iodine were applied, and suture removal was performed after 14 days.

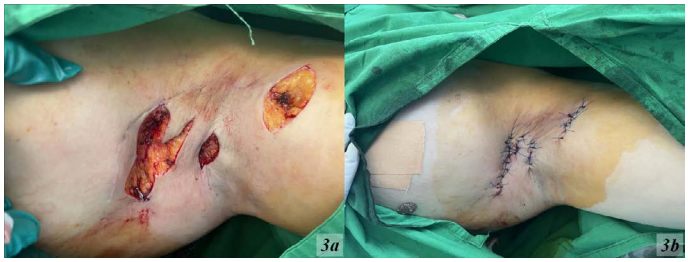

Figure 3a,b. *Surgical removal with multiple elliptical excisions of the preoperatively marked lesions followed by closure of the remaining defects with single interrupted sutures.*

Histopathological verification of all resected lesions was indicative of melanoma metastases. CT with contrast showed a possible proliferative process of the left mammary gland and a nodule in the right lung as possibly related to the underlying disease. The patient was restaged as stage 4 and referred to the medical oncology department to start targeted therapy with BRAF/MEK inhibitors.

Case 2.

A 76-year-old male presented to the dermatology department with a tumor-like formation on his back area, the duration of which was unclear. He reports constant bleeding from this lesion over the past 1 month.

Medical history of arterial hypertension, congestive heart failure, paroxysmal atrial fibrillation, chronic alcoholism, liver cirrhosis, and alcoholic polyneuropathy were reported.

The patient is on systemic therapy with amiodarone hydrochloride 200 mg once daily for the past 8 months prior to the consultation; apixaban 5 mg twice daily for the past 8 months; furosemide 40 mg (potency category 4) twice daily in the morning for the past 8 months; spironolacton 50 mg twice daily for the past 8 months; pantoprazole 40 mg once daily for the past 8 months; benfotiamine (fat-soluble vitamin B1 derivative)/ pyridoxine hydrochloride (vitamin B6)/ Cyanocobalamin (vitamin B12) once daily for the past 3 months; passiflora 100 mg twice daily for the past 3 months; and pregabalin 75 mg once daily for the past 3 months.

The dermatological examination revealed a pedunculated round tumor formation measuring 2 cm by 1.8 cm. The lesion was spontaneously bleeding and had surface ulceration (Figure 4a-c). No palpable enlargement of lymph nodes was observed.

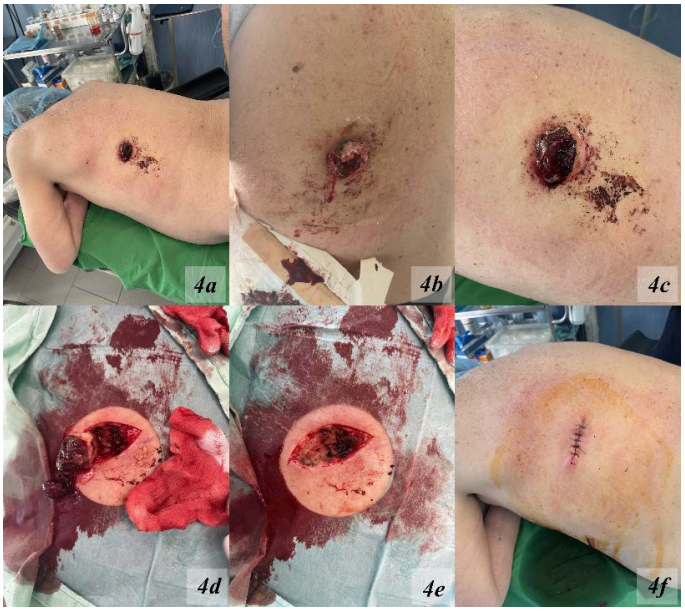

Figure 4a-f. Intraoperative view: *A polypoid melanoma measuring 2 cm by 1.8 cm, with spontaneous bleeding and surface ulceration (a-c). The melanoma is removed with an elliptical excision (d,e) and the remaining defect is closed by single interrupted sutures (f). Histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*

The patient was recommended surgical excision of the lesion under local anesthesia.

The apixaban was discontinued one day before the surgical intervention and switched to nadroparin calcium 0.4 mg administered twice daily.

The tumorous lesion located on the back was surgically removed with an elliptical excision under local anesthesia with lidocaine 2% with surgical safety margin of 0.5 cm in all directions (Figure 4d,e). The remaining defect was closed with single interrupted sutures (Figure 4f). The histopathological results revealed polypoid, well-circumscribed lesion represented by extensive epidermal necrosis covered by a parakeratotic crust, a compact proliferation of large epitheloid atypical melanocytes with marked pleiomorphism, discohesion, and areas of extensive necrosis located in a well-vascularized, melanophage-rich stroma (Figure 7a,7b). The resection lines were clear. Ulceration was noted, along with a high mitotic index. The Breslow thickness was >7 mm. Additionally, the S-100 protein level was measured at 0.151 mcg/l, exceeding the refence range of up to 0.10 mcg/l. Immunohistochemistry for Sox -10 and Ki-67 were positive (Figure 5 and 6).

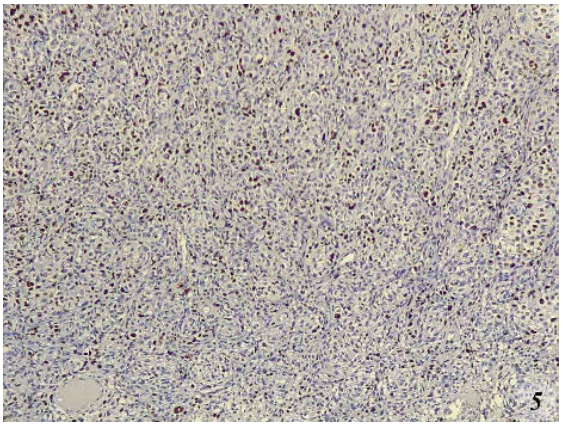

Figure 5. *Polypoid melanoma. Sox-10 x 100 – tumor cells intensively stain with Sox-10.*

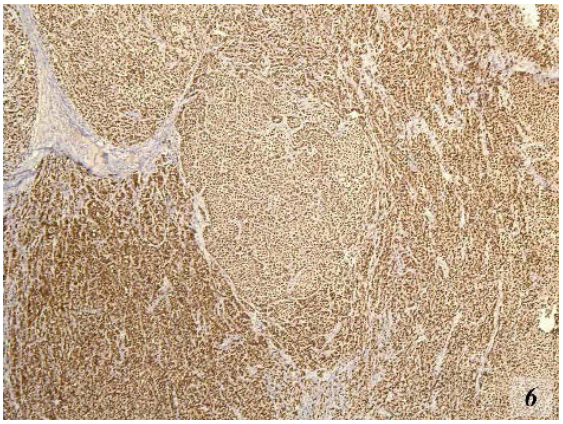

Figure 6. *Polypoid melanoma. Ki-67 x 100 – highproliferation activity demonstrated by Ki-67.*

This histological picture corresponded to a polypoid melanoma, staged as T4bNxMx. A whole-body CT scan was recommended, and patient was sent for reexcision and sentinel lymph node biopsy in the oncosurgical unit.

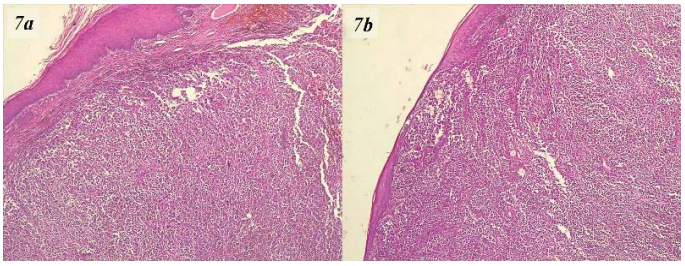

Figure 7a,b. *Polypoid melanoma. H&E x 40.*
7a: *Diffuse dermal infiltrate of large, atypical melanocytes with intraepidermal pagetoid spreading and consumption/ Histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*
7b: *Severe atypical melanocytes with pleiomorphism, disperse chromatin and atypical mitoses/ Histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*

Case 3.

A 71-year-old male presented to the dermatology department with primary complaint of a slowly growing lesion in the back area and a hyperpigmented plaque in the neck area, which he noticed a year ago (Figures 8a-c). He also noted having a mole on the right forearm since 2016 (Figure 8d).

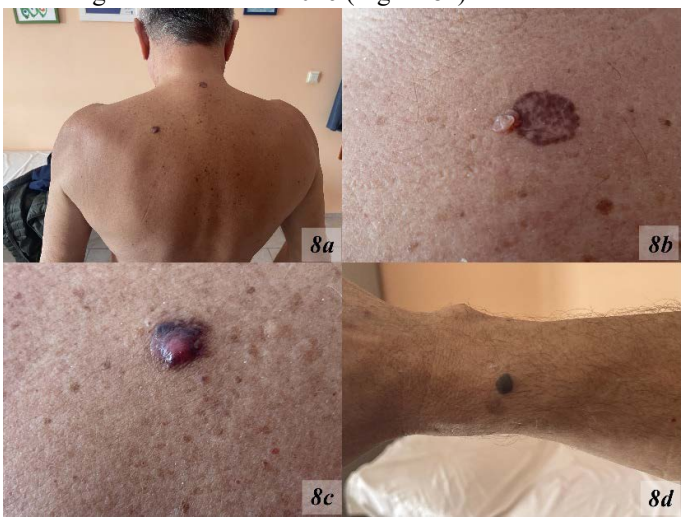

Figure 8a-d. *Dermatological examination.*
8a: *Nevus with irregular borders and uneven pigmentation centrally in the back area at the level of C7.*
8b: *Nodular melanoma at the level of Th12, 4 cm to the left, with uneven borders, inhomogeneous pigmentation, and measured 1.5 cm in size.*
8c,d: *Blue nevus located on the right forearm area.*

Medical history of diabetes since 2008 was reported. The patient is on systemic therapy with metformin hydrochloride 850 mg administrated three times a day in the period of 2008 until 2016. Later he was switched to sitagliptin/metformin hydrochloride 50 mg/ 850 mg twice daily, which he has been taking up to the present day. Additionally, he was prescribed glimepiride 2 mg until 2023, after which he switched to gliclazide 30 mg administrated until present day. Thioctic acid 600 mg once daily has been part of his regimen since 2023, as well as serenoae repentis fructus extractum spissum 320 mg once daily, the duration of which is unknown.

The patient presented with a request for physical evaluation of the three lesions and further therapeutic approach to be established.

The routine blood tests were without abnormalities. The dermatological examination revealed a nevus with irregular borders and uneven pigmentation centrally in the back area, in the rear sweat trough area (Figure 8a). Left of it, one span lower, a nodular lesion with black color and peripheral brown-black pigmentation was noted. It exhibited uneven borders, inhomogeneous pigmentation, and measured 1.5 cm in size (Figure 8b). Additionally, on the right forearm, a pigmented formation clinically suspected for a blue nevus (differential diagnosis of nodular melanoma) was observed (Figure 8d). No palpable enlarged lymph nodes were detected upon examination. The two tumor formations located in the back area and the one pigmented lesion located on the right forearm area were removed with three elliptical excisions with a safety margin of no more than 5 mm surgical security field (Figures 9a-c). The remaining wound defects were closed with single interrupted sutures (Figures 9a,c). The lesions were sent for histopathological evaluation which resulted in a dermal melanocytic nevus on the neck (Figure 10), a nodular melanoma, staged T3aNxMxR0, Clark level 4, Breslow 2.9 mm, with moderate mitotic index, without ulceration (Figure 11), and a blue nevus on the right forearm (Figure 12).

Figure 9a-c. *The two tumor formations located in the back area (a) and the one pigmented lesion located on the right forearm (b) area were removed with three elliptical excisions with a safety margin of 5 mm for the lesion at Th12 level, 4 cm to the left, and 3 mm for the remaining two (the lesion on the right forearm and the C7 lesion). The remaining wound defects were closed with single interrupted sutures (a,b,c).*

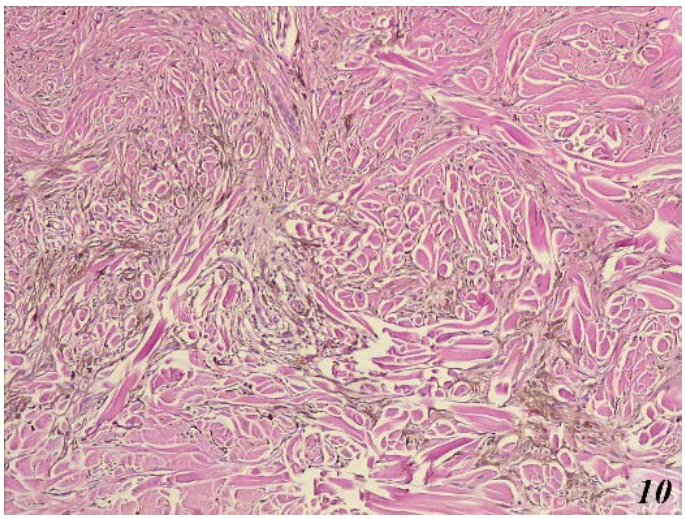

Figure 10. *Dermal nevus x HE x 40 – polypoid maturated dermal nevus/ Histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*

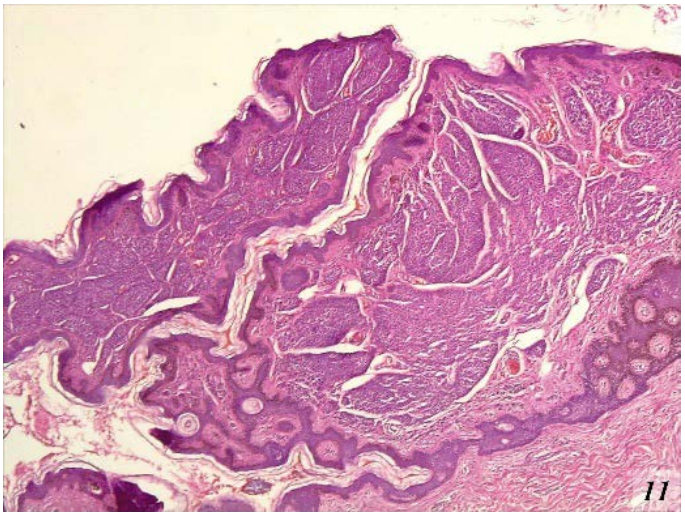

Figure 11. *Nodular melanoma x HE x 40 – large, atypical melanocytes with pleiomorphism and atypical mitosis, penetrating deep into the reticular dermis. Histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*

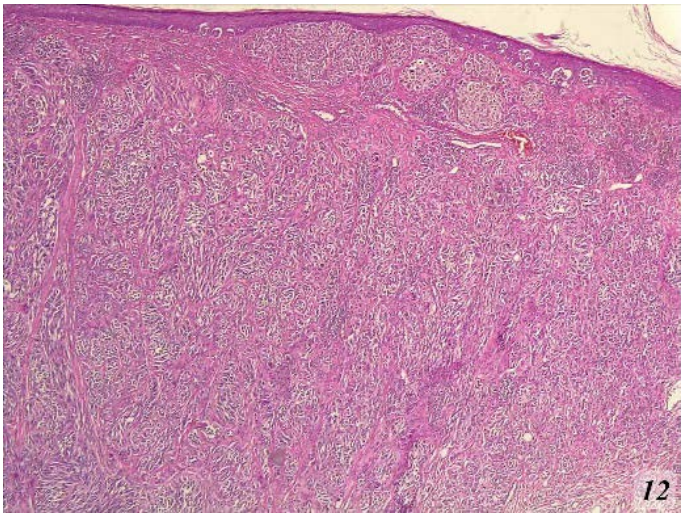

Figure 12. *Blue nevus x HE x 40 – fuziform, large dermal melanocytes intermingled into fibrotic stroma/ histopathological evaluation Assoc Prof Dr Valentina Broshtilova, 2024.*

For the lesion histologically verified as nodular melanoma, whole-body contrast-enhanced CT scan was advised to detect any metastases, followed by the removal of a sentinel lymph node. A 1.5 cm re-excision in all directions (2 to 3 weeks after hospital discharge) was also recommended.

The patient's therapy was also changed to linagliptin/metformin hydrochloride 2.5 mg/ 850 mg twice daily administrated in the morning and evening, thioctic acid 600 mg once daily, and serenoae repentis fructus extractum spissum 320 mg once daily in the morning.

Discussion.

Chemical or cutaneous carcinogenesis has been known for decades and concerns in particular the development of epithelial skin tumors as well as melanoma [28].

This carcinogenesis is based on the stepwise, multistep action of a heterogeneous number of carcinogens, including so-called nitrosamines [28].

Transplacental transfer of certain nitrosamines was associated (under experimental conditions) as early as 1969 with the subsequent development of multiple deforming tumors in the facial area (hydradenomas) [29].

This area of manifestation is, of course, relevant, or topical today with respect to the topic of contamination of a number of drugs with the mutagens/nitrosamines in question, as well as the relationships: nitrosamine and phototoxicity/ photocarcinogenicity, and/or nitrosamines and combined conditioned carcinogenicity [30]. Are nitrosamines also potent photocarcinogens?

In melanoma, this (hypo)thesis has been repeatedly described as possible and thematized specifically in relation to polymedication within the framework of polymorbidity and nitrosamine contamination [31].

The (Hypo-) thesis of the phototoxicity of nitrosamines remains valid for keratinocytic tumors according to recently published literature [32,33].

RAS and p53 mutations are among the characteristic mutations induced by certain nitrosamines/TSNAs/tobacco specific nitrosamines/ contained in cigarette smoke and directly affecting the human genome [16].

However, the same target structures/genes are also affected in skin cancer, a process observed in the context of so-called Photo-Carcinogenesis [17-21]. The overlap of these genes is key or at least seriously alarming and requires more serious analysis.

Two recent articles published in the ″nonfamous journal Nature″ comment on the revolutionary possibility of blocking specifically RAS-induced human mutations by RAS inhibitors [34,35]. One of them, RMC-7977, is applicable to all three forms of mutations: K-RAS, H-RAS, and N-RAS [35] and is in all likelihood a good solution for ductal adenocarcinoma of the pancreas [35]. However, the RAS inhibitor RMC-7977 has also proved its preclinical applicability in a number of other cancers that show RAS mutations [34], which is in fact quite encouraging.

A complete elimination regimen against the nitrosamines in the drugs, which are also, according to available scientific data, one of the inducers of p53 and RAS mutations [16], would be an even better, early, and timely solution for the human population, having an entirely preventive effect. This should also include the idea of preventing mutations from occurring or eliminating pathogenetic factors at an earlier stage.

Unfortunately, the globalising rates of today liberalise the ubiquity of carcinogens in medicines and food through the creation of permissive-coercive regimes of constant presence.

Despite being designated by the National Cancer Agency (IARC) as human carcinogens in Groups 2A and 2B [36,37], the coercive (at least for the time being) presence of nitrosamines and their derivatives remains to this day more than puzzling to the scientific community.

Nitrosamines have also been described as exacerbated mutagens according to (ICH) M7 guidelines [38].

Different enzyme systems are involved in the process of activation of heterogeneous nitrosamines in the liver. These include CYP2E1 and CYP2A6 [39-42] as well as CYP3A4 [43]. A serious and so far, unresolved element is the production of various DNA adducts after metabolization of nitroso compounds in the liver that have genotoxic effects. Such PHB DNA adducts, for example, require further investigation and analysis to elucidate their genesis and subsequent actual procarcinogenic action [44-46].

It is absolutely unclear whether these heterogeneous adducts are deposited in the skin and whether they have a photocarcinogenic effect. But it is suggested that this is entirely possible and should lie as the number one task for future research teams: typing the metabolizing enzymes and the consequent DNA adducts with carcinogenic activity, such as O6-Me-dGuo aN7-Me-dGuo, O6-POB-dGuo, and O2-POB-Thd.

O6-methylguanine (O6MeG) or 3MeA, arising after methylation of NDMA, are practically analogous carcinogenic [47-50].

Methylated DNA adducts (as a result of contact with NDMA) [51] are capable of seriously damaging human tissues [52-55] or, in practice, of causing cancer.

The identification of such metabolites in human lesional/ tumor tissue is possible and important, having been described in the literature nearly 50 years ago [55]]. What discourages the conduct of these investigations at present remains unclear?

The case one we described in our paper is indicative of several (somewhat at present hypothetical/speculative) elements that should be analyzed in detail: initial intake of bisoprolol and nebivolol for one year each, followed by intake of bisoprolol again for one year. Initially, melanoma develops on the basis of a nevus dating back to childhood, with onset within the beta blocker monomedication.

2 recurrences occurred twice within this monomedication. On initiation of the patient's additional combined systemic treatment with candesartan/hydrochlorothiazide and amlodipine, another 3rd recurrence occurred coincident with the initiation of the additional polymedication.

It is unclear whether this is a pure association or in fact the result of the concomitant intake of the other two (potentially nitrosamine/NDSRIs contaminated) drugs catalogued in the FDA list of potentially contaminated drug products as of 2023/2019 [56,57].

A number of articles in the medical literature have described the possible development of melanomas and dysplastic nevi as a result of taking a heterogeneous class of medications in the context of potential nitrosamine contamination [2,11,31]. It is because of this fact that the role of potential contamination within the intake of 3 potentially nitrosamine-contaminated medications should not be overlooked, at least as a possible pathogenetic scenario.

In Patient 2, we observed a lesion in the back area that was of unclear age and had been noticed only about a month ago. According to the analysis of the anamnestic data, the patient had been newly prescribed therapy with (potentially contaminated) furosemide (class 4 carcinogenic potency/ FDA bulletin 2023) since 8 months. The remaining drugs are not described and catalogued in the 2023 FDA contamination list: amiodarone, apixaban, pantoprazole, pregabalin, but they exist in the form of nitroso compounds [58-61]. It would be difficult or speculaive

to judge the validity of the pathogenetic relevance of a systemic drug intake with low carcinogenic potency (such as furosemide, for example) in the context of concomitant administration of another 4 other drugs, whose cataloguing in the drug contamination list of the FDA and carcinogenic potency are still lacking. But hypothetically speaking- this is not impossible.

The third patient described is very interesting in terms of the onset of the lesions, their evolution, and the systemic medication taken, which includes the following drugs: metformin 850 mg three times daily for 8 years/ before the onset of the lesions, subsequently changed for another 8 years to sitagliptin/ metformin hydrochloride 50 mg/ 850 mg twice daily, continued to date.

Metformin contamination with NDMA is not new and was announced long ago by the FDA [62]. Two years later, nitroso-contamination was officially announced again by the regulator in the person of the FDA and for sitagliptin: NTTP, daily acceptable intake dosage of 37 ng [63]. That of NDMA is 100 ng daily [64].

The administration of metformin in combination with amiodarone, hydrochlorothiazide and telmisartan, has also been described as a scientific publication in the context of melanoma induction [65]. Although not reflected in the title, abstract, or discussion of the referenced scientific paper [65]. It is this accurate reflection of the chronology of drug intake to a past period that allows for future accurate assessment of the data and makes it more than invaluable [65].

On the other hand, metformin intake is also associated with the development and progression of epithelial skin tumors [33,66-67].

The coincidences between metformin intake and skin cancer generation become apparently more than ″permitted for the day″ [33,65-67].

A number of publications in the literature have focused on monitoring the effect of the protective action of the active substance metformin on melanoma progression [68,69].

Some patients with melanomas and diabetes mellitus taking metformin have been followed in terms of overall survival and melanoma-specific survival [68]. The results of this paper could also be seen as indicative of the following: that cumulative pre- and postdiagnostic metformin use is associated with better overall OS survival: the HR for prediagnostic use was 0.90 (95% CI 0.86-0.95) for every 6 months of use and the HR for postdiagnostic use ranged from 0.98 (95% CI 0.97-0.98) for 0-6 months to 0.59 (0.49-0.70) for 24-30 months of use [68].

Similar to the shared article, other authors have found an association between overall survival in patients with melanoma, diabetes, and metformin use [69]. Patients treated with metformin showed, within multivariable analyses performed, one lower melanoma-specific mortality [69].

The interesting about the above international papers is that none of them denies taking metformin before the melanomas occurred [68,69], quite the contrary. Or in practice- the works are also indicative of the following statement: melanomas that occurred during or after the initiation of metformin intake are presented [68,69]. But the publications thematize the role of the drug after the onset of melanomas and its possible protective effect thereafter [68,69].

Another interesting fact is that none of these papers comment on actual or potential metformin contamination with nitrosamines as a potential cause of melanomas occurring in general or initially [68,69]. It is because of this fact that one might reasonably assume that the conclusions in the publications mentioned are somewhat limited and not sufficiently considered in terms of the complexity of the subject at issue [68,69].

But they are also absolutely and categorically indicative that thousands/hundreds of patients developed melanomas were taking metformin before the melanomas appeared [68,69]. In these papers remains inconsistent or uncommented on the fact that there is possibility that patients may have taken contaminated metformin [62,68,69] or metformin, previously also associated with the development of heterogeneous other forms of cutaneous cancer in the context of exogenous nitrosogenesis and oncopharmacogenesis [65-67]. Or it could in fact refer to NDMA-induced melanomas in NDMA-contaminated metformin [70,71].

Meanwhile other types of scientific publications concerning the antitumor effect have prevailed for years of metformin: but within these publications there is not a single tumour/melanoma patient who took metformin and went into complete remission.

Interestingly also that ranitidine, similarly to metformin, is also associated with NDMA contamination [72-75]. As with the subsequent development of melanomas and dysplastic nevi following its (ranitidine) administration and in the context of possible contamination of the polymedication [76].

Clinicians and scientists worldwide should not lose focus of the fact that a drug could contain, in addition to the active ingredient, certain carcinogens, also known as nitrosamines [62-64,71].

These ingredients remain to this day officially undeclared, but some of them have been categorized as potent carcinogens, mutagens, or genotoxic ingredients [22-25]. Because of this fact, it should not be surprising to anyone that metformin intake, according to the most serious scientific publications worldwide, is associated with the development/occurrence of melanomas [68,69]. It is another matter that these papers do not thematize melanoma pathogenesis/onset but focus primarily or entirely on overall or specific melanoma survival [68,69]. This shift of focus away from the actual data and their interpretation, should not be potentiated and accepted as a ″clean coin″ by clinicians and scientists worldwide. The critical, sharp eye of the serious researcher would not miss this important information, the interpretation of which is of invaluable pathogenetic importance.

The positive effect of this drug (metformin) could be related to the action of the active substance, while its pro-carcinogenic or mutagenic action- to the concentration found by the control authorities many times or up to 30 times elevated / within the daily intake [77]. Moreover, these concentrations are only within the monocontamination range of a single drug. And most of the patients thematized in the international articles are polymorbid, which includes the possible concomitant intake of a heterogeneous type of potentially contaminated medication, however, not accounted for in the studies [68,69]. And these data are also additionally completely missing in the shared follow-up studies that were the subject of the current analysis and interpretation.

We believe that the 3rd case presented by us is the first formal case regarding the intake of metformin potentially contaminated with NDMA.

Despite these claims of ours, in practice it appears that there are scientific data from diverse international collectives that have published in PubMed/ Medline information on hundreds of cases of melanomas occurring after initiation or within the context of metformin intake [68,69]. At the same time, these works do not pay attention to currently introduced concepts in the scientific literature such as: exogenous, drug mediated Nitrosogenesis and Oncopharmacogenesis/ Pharmaco-Oncogenesis. And these two concepts are and will be able to lead to a new understanding, interpretation, and reconsideration of the theories of melanoma and skin cancer in general.

In support of the aforementioned claims, our recently published observation of manifestation of 16 keratinocytic tumors during systemic treatment with metformin in combination with several other potentially contaminated drugs is also available [65].

A narrowed (clinical/scientific) horizon also remains the surest guarantor of the one-sidedness and inadequacy of the subsequent interpretation of a particular database and subsequent results. This inevitably leads to the favoritism of an absolutely incorrect, false, and manipulative counterthesis [68,69].

The somewhat pedestaled protective effect of metformin against keratinocytic cancers until recently [78,79] is being somewhat challenged by the most recent clinical observations formalized in JEADV/ The Journal of the European Academy of Dermatology and Venereology [80].

The divergent claims and results with respect to concepts such as benefit/risk for melanoma patients after taking metformin could be due to (or mainly explained by) the neglect of the fact that a drug could also be considered in practice as the sum of 1) the pure drug, the active substance, and 2) the additional carcinogenic impurities present in it (so-called nitrosamines/ NDSRIs).

The concentration of a given nitrosamine, as well as the persistent intake of this carcinogen over a prolonged period of time, could in all likelihood outweigh the anticarcinogenic/ antitumor effect of the active substance [81].

NDMA-induced melanomas are not a myth but remain a reality, whether the carcinogen is a constituent of Metformin [68,69], Ranitidine [76], Propafenone [30], Valsartan/ Olmesartan/ Candesartan/ Telmisartan [82-84,13] or Hydrochlorothiazide [11,85].

Metformin contamination is also a serious issue for the US drug market due to the following circumstances: 1) 90% of the drug market is based on the ″budget use″ of generics [86], and 2) it is generics that have been subjected in the past and to date to extensive scrutiny and calls for elimination by the pharmaceutical sector due to NDMA/DMF contamination [86].

As well as (3): despite the FDA's own announced recalls of nitrosamine-contaminated metformin-containing preparations, these are still available and distributed undisturbed on the pharmaceutical market [86].

The paradox is that, in practice, the end-user pays the same price for contaminated and uncontaminated metformin-containing medicinal products [86], leaving the patient himself completely uninformed regarding his inherent/legal right to be officially informed about the purity drug substances which he is taking.

Even more problematic is that regulators and manufacturers recognize which products are contaminated and which are not, but 1) do not completely neutralize contaminated products from the market, 2) do not require 100% transparency regarding contamination within a particular company's production of a particular drug that (transparency) is 100% available to end users and clinicians, and 3) do not require pharmaceutical companies to formalize and strictly follow a nitroso-contamination-free production cycle.

Precisely because of the loss of confidence in the regulatory authorities, a number of countries, including Australia, have launched their own independent observations on the contaminated medicinal preparations distributed on their territory [87]. Even more interesting is the fact that in these lists there is no complete overlap of the contaminated production with the medicines from the USA and Europe [87].

The most severe contamination in Australia, according to the current status/year 2024, is observed with the antifungal agent terbinafine, with the permissible daily dose being 18 ng/daily [87].

And this, in turn, is an indicator of serious follow-ups of skin tumors after taking terbinafine as monomedication or within contaminated polymedication of polymorbid patients, in the relevant geographic region or country.

Last but not least, the possibility of metabolic reprogramming and its relation to skin cancer should be mentioned [88]. Generally speaking, certain environmental factors are able to activate the initiation phase of cancer cells [88]. This complex game includes the inactivation of some tumor-suppressor genes as p53 for example [89] and the activation of oncogenes such as RAS oncogenes [16].

It is UVB that has been shown to initiate these processes/ metabolic reprogramming within the precancerous stage in skin cancer patients [88]. For the so-called TSNA/tobacco specific nitrosamines this is known but not studied in detail [88].

Similarly, the relationship between 1) metabolic reprogramming, 2) nitrosamines present in drugs, and 3) Phototoxicity/Photocarcinogenicity should be considered. Nitrosamine signalling due to the contamination of a number of medicinal preparations with nitrosamines and the metabolic reprogramming of cancer are likely to be the subject of future discussions and endless scientific interest.

It is these data and subsequent analyses that would lead to the rewriting of textbooks on dermatology and venereology, as well as those on skin cancers pathogenesis.

And for now, skin cancer generators remain an integral unofficial ingredient in medicines. According to one of the invariable advantages of contaminated production, all that remains is its budget or equivalent value, compared as early value to that of uncontaminated production [86]. This official statement sounds more than inadequate.

Contamination of metformin, ranitidine, angiotensin-receptor blockers, and a number of other drugs is more than disturbing and, in all likelihood, it could be just the tip of the iceberg [90]. The contaminant NDMA directly activates RAS oncogenes, and its product, methyldiazonium, activated after methylation in the

liver, is an active mutagen [90]. Who actually regulates-and why the so-far- controlled compulsory availability of carcinogens in drugs is allowed, remains unclear! The regulators of carcinogens in drugs are also the regulators of programmed and regulated death.

Elimination regimes for these carcinogens should follow the path of sound logic to become a priority and mandatory for manufacturers and regulators. Their current forced tolerance or as yet unannounced availability is proving to be one of the most serious scourges for global health care.

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