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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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METASTATIC NODULAR MELANOMA DEVELOPING ON NEVUS SPILUS DURING INTAKE OF BETA BLOCKERS (BISOPROLOL/ NEBIVOLOL) AND ACE INHIBITORS (PERINDOPRIL). POTENTIAL LINKS TO THE DRUG RELATED NITROSOGENESIS/CARCINOGENESIS, DUNNING-KRUGER EFFECT AND GENETIC WEAPONS OF THE NEW GENERATION

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Abstract.

Drug-induced Nitrosogenesis/Carcinogenesis turns out to be a ubiquitous, pervasive, large-scale, poorly controllable concept for the academic community, which underlies the long-term, permanent modification of the human genome by contact with nitrosamines/NDSRIs, which ultimately leads to the generation of diverse cancers, but also melanoma in particular. The discovery of a (currently) unclassifiable number of nitroso derivatives/ genome modifiers in the most commonly distributed drugs worldwide (in about 300 preparations according to the FDA/ includes beta blockers/ bisoprolol/ nebivolol and ace inhibitors/ perindopril) , their forced tolerability, attributed as a necessity or lack of alternative also to the present (but also to future periods), and their proven carcinogenicity (already 70 years ago), suggest a kind of creepy form of experiment to which public health is subjected worldwide.

The creation of a universal nitroso-comfort of pharmaceutical companies and the regulation of a permanent intake of carcinogens in drugs for years to come , but also decades back, suggest possible cartel agreements between the regulation/ distribution unit and that of production cycles.

These ″agreements″ are becoming increasingly evident and in all likelihood position nitrosogenesis from a until recently unknown element, to a pathogenetic factor of paramount importance. Melanoma could be viewed precisely as the controlled end gene-modified product of drug-mediated nitrosogenesis/ carcinogenesis, proven to be a locoregional (but not only) phenomenon hundreds if not thousands of times. The dilemma stays: Are the nitrosamines in drugs genetic weapons , ethnic bioweapons for silent war ?

The nitrosogenesis concerning melanoma leads to the logical conclusion that cancer is in fact a largely controlled set event or, according to others, a forced necessity of evolutionary globalization processes to purge the population in certain regions. In favor of this statement indicative are namely: 1) lack of regulatory control / results of such conducted, 2) complete information veil for the end user regarding contamination with carcinogens / nitrosamines in certain batches or all batches of drugs, 3) misinformation and lack of transparency regarding the concept of nitrosogenesis also for the academic community, as well as 4) the impunity to pharmaceutical conglomerates after criminal negligence/controlled criminogenicity proven thousands of times by the FDA/EMA leading to regulatory controlled drug mediated genocide of the human population in certain areas on a daily basis. And most important of all: 5) the lack of refusal to eliminate these drugs, i.e. - the imposition of forced tolerance at any cost.

It is extremely unfortunate that the mentioned and identified grotesque/ situation, its tolerance on a global scale, lead to a misjudgement of the significance of real tumor inducers within the global health map/ /statistics as well as melanoma. The focus of prevention is being displaced, while the incidence of cancer in general and that of melanoma is skyrocketing. Nitrosamines could be defined as the newest , modern, until recently invisible and unknown, but -controllable form of genetic weapon to modify the human genome.

Because of these very facts, the likelihood that clinicians and the academic community are in the frozen and permanent state of the Dunning-Kruger effect is very real.

Certain globalization regulatory elements create problems and assignments that must be solved ″competently″ by incompetent, fully regulatable compartments. As their state of competence depends again and entirely on ″their incompetence″. Until now. After the formalization of the concept of Nitrosogenesis (as a form of genetic weapon) and melanoma for example, but not only, it remains to be seen whether universal incompetence will become a guarantee of competence and the survival. Or- will it remain again at the level of globalized, criminally conditioned, appointed and regulated from above ″competent incompetence″.

The dilemmas to regulators and manufacturers remain open : Is it competent to take drugs that contain carcinogens/ nitrosamines? Is it competent for this issue to continue for decades with impunity? Is it competent for regulators not to inform consumers about the presence of carcinogens/genome modifiers in medicines for decades? Is it competent for certain regions to be affected by nitrosamine contamination and not others? Is it competent not to reflect this in regional and global health bulletins on side effects? Is it competent to make thousands of times the profits from the modified genetic map business, regulated and legally initiated through the intake of carcinogens? Is it competent to have the concentration of carcinogens within polymedication exceeding many times the daily allowable doses of carcinogens and have no solution for this?

Is it competent , when the intake of nitrosamines in medicines is associated with the generation of melanomas and heterogeneous cancers- to have no alternative to this or when one is available- to conceal it skillfully? Is it competent to determine carcinogenic activity based on mutagenic tests? Is it competent to be polyincompetent within a framework of mass (in)competence?

We report systemically administered drugs for the treatment of high blood pressure from the group of beta blockers (bisoprolol/ nebivolol) and ACE inhibitors (perindopril) that have been identified by regulators in the face of FDA as hypothetically contaminated with nitrosamines/ NDSRIs with a carcinogenic potency between 4 and 5, respectively. Within this cumulative intake, (which according to the regulators was not at risk of developing cancerous forms), similar to other cases in the

world literature, the patient developed a relatively short-term, metastatic nevus spilus-based nodular melanoma.

The paper analyses not only the role of nitrosogenesis , but also that of two pregnancies and painful sunburns as potential cofactors for melanoma genesis.

Academic attention is drawn to the potential impact of drug-mediated nitrosogenesis/carcinogenesis. Nitrosamines in the framework of polycontamination and polymedication could also be identified as one of the most effective, until recently unknown, modern generation genetic weapons for modifying the human genome and controlling cancer. Moreover, they could be controllably applied and skillfully targeted. At least until now. The officialization of carcinogens in more than 250 of the most common drugs and the clinico-pathological correlations concerning the development of cancer/melanoma in poorly controlled geographical regions represent a kind of in vivo prospective study to determine precisely the real carcinogenic role of nitrosamines to date.

Key words. Nodular melanoma, nevus spilus, bisoprolol, nebivolol, perindopril, Nitrosogenesis, nitrosamines, NDSRIs, polycontamination, polymedication, adverse drug events, genetic weapons.

Introduction.

Nevus spilus is, as a rule, a benign lesion within which, however, according to a number of literatures, melanoma of the skin could also develop [1,2].

In addition to thin melanomas, the literature also describes the development of nodular melanomas within the nevus spilus, some of which show a tendency to metastasis followed by a lethal outcome [3,4].

The causes or risk factors for the development of melanomas based on nevus spilus are little known and not well studied at present.

Starting from the fact that melanoma as a disease is multifactorial, ″solving the puzzle″ is complex and not always possible precisely because of the complex nature of the issues concerning its pathogenesis.

Standard conceptions of melanoma pathogenesis, which include: 1) the role of solar radiation/painful sunburn [5], 2) light skin Fitzpatrick type 1 or 2 [5], 3) red hair/blue eyes [5], 4) dysplastic nevus syndrome/FAMM syndrome [5], 5) Xeroderma pigmentosum [6,7], the presence of congenital nevi [8], reflect in all likelihood only ″one side of this coin″. And this side of the coin is probably not the ″leading pathogenetic one″ either.

These commonly known factors often do not provide an explanation for the subsequent lack of effectiveness/efficacy following conformity to certain stereotypes of protective behaviour or a particular type of prevention.

Until recently, the lack of effectiveness of prevention programs did not lead anyone to think in the direction of seeking other explanations for the occurrence of melanomas and skin cancer in general. Or in the direction of nitrosogenesis.

Of interest so far are the following facts and possible correlations: 1) The lack of effect, minimal to no detectable effect in the last decades after the applied maximum prevention (by elimination, minimization of some of the factors such as solar radiation for example).

The absence of this preventive effect could probably be reflected most simply by a quick look at the recently formalized predicted incidence of melanoma of the skin relative to the year 2040 [9]. It is more than frightening [9] and largely inexplicable: whereas in 2020 the statistics for melanomas worldwide record 325,000 new melanomas/57,000 deaths , its projected incidence, but relative to 2040, is more than frightening: 510,000 predicted new cases/96,000 deaths [9].

In practice, these data emphasize, albeit indirectly, the following: 1) prevention to date and over the years has been ineffective/inefficient/insufficient and/or 2) the causes of melanomas are other, fundamentally different or : both statements are simultaneously valid. Melanoma nitrosogenesis is a good answer to both questions.

Starting from the motto that mutations in melanomas are mainly acquired [10], elucidation of their exogenous genesis would probably lead to a dramatic drop in the incidence of melanomas worldwide.

Nitrosamines, as contaminants/cofactors in some of the most commonly distributed antihypertensive drugs worldwide (includes perindopril and bisoprolol), have been repeatedly described as possible triggers of melanomas as well [11,12]. They are known as exogenous mutagens, carcinogens, and some of the best-known modifiers of the human genome to the academic community.

The facts that 1) regulators currently enforce their forced presence in patients' drug menus, despite their proven carcinogenic activity in humans and animals in vivo, accompanied by 2) the fact that in certain geographical regions such as Turkey, for example, the absence of any contamination when testing heterogeneous preparations of one particular antihypertensive class [13], is indicative of only one: contamination could be controllable, completely absent or - purposely controllable and present, but it is also forcefully imposed. In its last described variant , this type of directionality could also be defined or interpreted as a genetic, biological, even according to some claims - ″ethnically determined weapon″.

This article focuses on the role of actual/potential nitrosamine contamination of the patient's medication for previously diagnosed arterial hypertension as a possible significant cofactor for melanoma.

Case report.

We report a 51-year-old female patient with a congenital pigmentary malformation localized laterally thoracic on the right, which has changed significantly in shape and color over the past year (Figures 1a,1b). The change of the lesion in practice proved to be the reason for the patient's visit to the outpatient dermatology and dermatological surgery clinic. The age of the so-called mole is about 10 years of age, and the data on this occasion are not entirely certain or definite.

The patient informs of 2 available pregnancies to date (at 38 and 44 years), within which the intensity of pigmentation changes slightly and progressively becomes more intense, but the size of the lesion does not change overall.

There is also evidence of 2-3 painful sunburns 30 years ago, however these did not affect the area of pigmentation that was covered by the patient's bra/swimsuit (according to history).

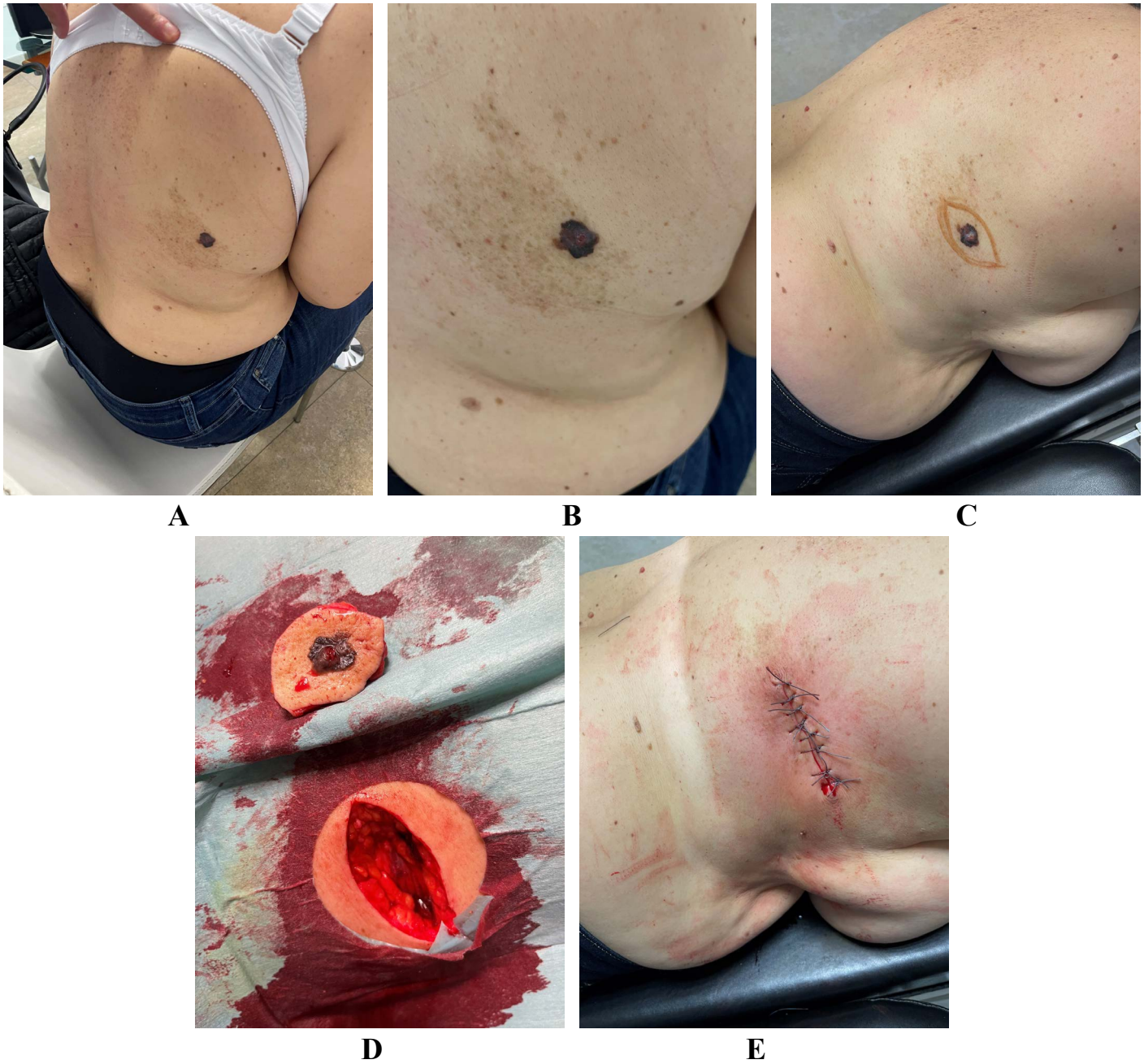

Figure 1. 1a. *Nodular melanoma developed within a nevus spilus.*
1b. *Advanced metastatic nodular melanoma with thoracic right localization, developed on the basis of nevus spilus.*
1c. *Marking of surgical resection field.*
1d. *Surgical removal of the tumour lesion with a near field of surgical security.*
1e. *Postoperative finding after closure of the defect using single skin sutures.*

One of the burns was adjacent to the pigmentation and was associated with formation of bullae.

The patient had seen a dermatologist 10 years previously regarding the pigmentation, and no definitive assessment of the lesion's dignity was made during this examination, but her follow-up and eventual surgical removal was recommended.

Sporadic mechanical irritation of the lesion was also present on several occasions over the years but was not accompanied by bleeding.

The lesion has changed in shape, size, and intensity in recent months (about 4 months) , with the area also becoming slightly sensitive to touch.

As a concomitant disease, arterial hypertension is known to have a duration of about 10-15 years. Medication intake on this occasion was irregular.

The patient's systemic medication for the past years includes : 1) Bisoprolol 5 mg / perindopril 10 mg from 3-4 months / to date ; 2) 11 years ago first started with the intake of : bisoprolol 5 mg once daily for about 3 years (also taken during pregnancy), followed by 3) nebivolol 5 mg once daily for a period of 2 years (after delivery), after which this intake was discontinued.

During the dermatological examination, a brown patch of melanization dotted by smaller dark black macules measuring 10 by 15 cm was found. In one part of the lesion there was

a nodular tumour formation with a diameter of 2 by 1.8 cm, asymmetrical location, relatively clear demarcation from healthy tissue, heterogeneous colour: central nodular brownish grey area, projecting in the periphery at 11:00 and 17:00, surrounded in the rest by intense black pigmentation; significant elevation of the lesion on palpation in the central area (Figures 1a,1b). Dermatoscopically: absence of melanocytic network, heterogeneous coloration, grey-pink regression areas. On the basis of clinic and dermoscopy, the working diagnosis was nodular melanoma developed within the nevus pilus lesion. Preoperative screening and staging were performed, and CT with contrast revealed dissemination of the process into the lungs, and the lesions were determined to be metastatic: evidence of focal lesions in the lung parenchyma with secondary features. Medially in the left lung , in the area of the 8th segment, a circular lesion of 22 mm is seen. Peripherally in the right lung, several nodular lesions measuring up to about 3 mm are seen in the upper and middle lung fields. In the mediastinum, single lymph nodes measuring up to 5 mm are visualized paratracheally and are not pathognomonic.

The lesion suspicious for nodular melanoma was surgically removed under local anesthesia with a surgical margin of no more than 1 cm (proven distant metastases) (Figures. 1c-1e), with histopathologic evidence favoring: poorly demarcated, asymmetric melanocytic lesion represented by compact parakeratosis, overlying atrophic epidermis with underlying nodular proliferation with large , atypical melanocytes with marked pleomorphism, centrally located nucleoli with nucleoli forming atypical mitoses, areas of desmoplastic degeneration and necrosis demarcated by moderately prominent lymphocytic, well-vascularized stroma and peripheral extensive areas of regression. Clean resection lines. No evidence of perineural and lymphovascular invasion. Clark IV , Breslow 2,28 mm, high mitotic index, stage IV / M1b -Distant metastasis to lung with or without M1a sites of disease/. Braf test negative. The patient was referred to the regional cancer center for follow-up and pembrolizumab infusions.

Discussion.

Regarding the carcinogenic action of the two classes of drugs mentioned above - ACE inhibitors (perindopril) and beta blockers (bisoprolol/nebivolol), which are the subject of discussion within the presented work, the following could be mentioned: 1) phototoxicity has been associated according to various literature data with subsequent DNA damage, which could in fact give rise to a malignant cell clone [14], and that: 2) beta blockers have a photosensitive effect and could also be associated with the development of melanomas [15]. Photosensitivity and phototoxicity are one side of the issue concerning drug intake and melanoma development.

Similar observations have been made on the development of cutaneous melanomas or melanoma precursors lesions like the dysplastic nevi after systemic administration or intake of ACE inhibitors [12,16].

These data are confirmed in one of the enigmatic articles of our time-that of Beatrice Nardone, who associated the intake of ACE inhibitors with the risk of developing cutaneous melanomas: unadjusted OR (95% CI): 2.42 (2.00-2.95)/adjusted OR (95% CI): 1.71 (0.97-3.00) [17]. Unfortunately, this analysis was not accompanied by a concurrent test for the absence or presence of nitrosamines in the preparations [17].

It remains an open question whether this relationship (melanoma/medication) is due to the currently known phototoxicity/photosensitivity (followed by painful sunburns and permanent DNA damage of the cells) or rather to additional factors identified as present in the drug packaging: the so-called nitrosamines or NDSRIS, the genome modifiers [18]. Or perhaps to both factors mentioned?

It is these nitrosamines that are associated with melanoma generation and within the intake of NDMA-contaminated valsartan [19].

But also, with the generation of melanomas after intake of potentially/actually nitrosamine-contaminated irbesartan, Olmesartan, and candesartan [20-24].

ACE inhibitors and beta blockers contaminated with NDSRIs should not be an exception in this respect and could in fact, analogous to the data shared above, lead to the induction of cutaneous melanomas [11,12,16,17]. The unifying link remains the nitrosamines or NDSRIs: compounds that are genome modifiers and could be considered as chemical weapons for gene modification and genome impact or, according to some experts, even as the modern expansive, speculative term-ethnic bioweapons, due to their sporadic or geographically targeted and in all likelihood temporally limited impact. This impact could only be captured through strict, regular regulatory control, not through the absolutely liberal regulatory regimes currently reigning, created by the EMA and the FDA.

The following facts would be of interest to the scientific community:

1) elucidation of the exact concentration of nitrosamines/ NDSRIs in each medication (beta blocker/ ACE inhibitor)/ batch of medications, 2) elucidation of polycontamination within polymedication and polymorbidity for specific periods/ could also be calculated by clinicians in an accurate description of the nitroso-residue in the components of the medications/ determination of the total cumulative intake for a specific period, as well as 3) the determination of the carcinogenic activity of the relevant contaminant/ determined by the FDA in 2023, but unfortunately not on the drug packaging.

The fact that the FDA has 1) established reference values for carcinogens/nitrosamines, 2) established a daily permissible dose that is not desirable to be exceeded, and 3) the carcinogenic potency of the nitroso components found in drugs, is indicative of the fact that ″this information is known″ (nitrosamines in drugs and associated clinical cancers) , but is not currently generally available to the scientific community and end-users [18]. Why has the presence of genome modifiers been tolerated for decades in medicines? Why might this contamination be practically completely absent in certain regions? Why is there a lack of official data on the controlled availability of genome modifiers in the most commonly distributed medicines globally and by geographic region?

One should not ignore the in vivo observations of a British collective as far back as 1987 [25], which made a connection between 1) the contact of certain groups of patients with

nitrosamines contained in cutting oil (as additive ingredients) and the development of bladder cancer.

Similarly, several cohort studies on workers engaged in oil refineries have reported an increased incidence for the development of melanomas [26].

Epidemiological follow-up from Great Britain also found a significant association between the working environment in oil refineries/ contact with nitrosamines/ and melanoma-induced mortality [27]. According to these data, all deaths of patients affected by skin cancer are due to melanomas [27].

Nitrosogenesis of skin cancer and melanoma in particular is in all likelihood one of the most significant factors/ cofactors in generating skin tumors [16,17,19]. This is evidenced by data from the past [20-24,28-29], but also by data from the present [11,12], which are retrospective/prospective in nature and would be difficult to refute scientifically.

Photosensitivity/phototoxicity within the real/potential contamination of a particular drug class with nitrosamines/ NDSRIs (in certain patients) could be easily differentiated from the actual mutagenic/carcinogenic action of the available nitrosamines/NDSRIs carcinogens, namely due to the fact that : the parallel or subsequent development of cutaneous melanomas in combination with second-type tumors such as colon cancer [30,31], Kaposi's sarcoma [30] or prostate cancer [32] could not be explained in any way by concepts such as phototoxicity or photosensitivity, due to the particular anatomy of the compartments where these tumors arise. The actual contamination with nitrosamines in these classes of drugs remains the leading thesis. Or thesis- taboo even at the moment- for both the academic community and the end consumer.

Polycontamination within polymedication and polymorbidity remain the most resonant explanation for the generation of melanomas through persistent, intense, prolonged contact with known mutagens, carcinogens, or so-called nitrosamines, modifiers of the human genome. Regardless of the class of drugs involved.

Drug-induced carcinogenesis, paraphrased definitively by the FDA as a reality/availability in 2018 [33], reconfirmed in 2023 [18], is and the most significant and irrefutable evidence of the relevance of nitrosogenesis to the generation of skin cancers and melanomas in particular.

Its recognition, formalization and elimination should be a priority for market regulators, manufacturers, and the academic community. For now, this remains a ″pipe dream″. The disparity in worldwide statistics regarding the incidence of melanomas, but also cancer in general, is absolutely explainable through the concept: controlled contamination and nitrosogenesis.

In conclusion, we report a patient who developed advanced nevus spilus based nodular melanoma during a long-standing, irregular, at times sporadic intake of two beta blockers: nebivolol and bisoprolol, in combination with perindopril (on the last intake). It is noteworthy that all three drugs taken by the patient appear on the April 2023 FDA list of potentially contaminated drugs [18], namely: bisoprolol and nebivolol have a potential carcinogenic potency of 4, whereas perindopril has one of 5 [18].

The short-term intake (of about 4 months) of a combination drug for the treatment of high blood pressure containing bisoprolol/perindopril (potentially/actually contaminated with nitrosamines/NDSRIs), coincides with the rapid change in shape and size of the pigmented lesion in the back area.

The complex nature of melanoma pathogenesis in the case described, including 1) the painful sunburns in the past, 2) the sporadic mechanical irritation, and 3) the role of 2 pregnancies as possible potentiating cofactors of carcinogenesis, cannot be ignored. However, the significance of each factor remains difficult to determine.

Similarly, peak concentrations of nitrosamine NDSRIs (between 2 to 200 times above normal), the presence of as yet unidentified nitrosamines, or concurrent contamination with up to several nitrosamines simultaneously cannot be excluded (in the case of possible contamination of long-term and/or short-term potentially/actually contaminated antihypertensive drugs).

The lack of any data from regulators and manufacturers (to patients and physicians) regarding contamination and the exact concentrations of carcinogens in drug preparations contributes substantially to the loss of confidence of end users, indirectly supporting the thesis of real rather than possible/potential contamination.

The relatively short-term manifestation of melanomas after intake of potentially/actually contaminated antihypertensive drugs such as beta blockers and ACE inhibitors (whose carcinogenic potency is classified according to FDA as 4 or 5) does not preclude the presence of peak concentrations of carcinogens to condition this phenotypic manifestation. The results shared challenge the significance of the tests performed by the FDA to determine carcinogenic potency and its significance.

The problem with nitrosamine impurities, or so-called (NDSRIs), is that there is almost no safety data [34]. This makes it difficult to set an acceptable limit for daily intake [34].

The determination of the mutagenic activity of these ingredients in drugs is globally and currently still not uniform for Europe/EMA and America/FDA, which in practice indicates the existence of deep problems.

A number of regulatory authorities are of the opinion that the determination of carcinogenic activity by using the Ames mutagenicity assay is not always indicative.

Currently, there is comment on the fact that for most drug impurities, a negative Ames test suggests that the compound will not be determined to be carcinogenic [35].

Slightly forgotten among the scientific community remains the fact that the mutagenic potential of nitrosamines/ NDSRIs could differ significantly and not correlate with their carcinogenic potential [36]. This is supported by the case we presented of a patient who took drugs with a relatively low carcinogenic potency according to the current FDA list [18] and subsequently developed advanced (metastatic) melanoma. In practice, mutagenicity tests are somewhat controversial and not conclusive or 100% conclusive in determining carcinogenic potency, as there may be considerable variability in the interpretation of the results by experts [37].

Because of this fact and when there is insufficient evidence of mutagenic activity, regulators/EMAs recommend additional tests such as (1) the CPCA test/ Carcinogenic potency categorization approach text [38] and (2) a modified Ames test. However, regardless of which category the genome modifiers

identified by these tests fall into (even if it is 5) the substances in question remain classified as mutagens. However, mutagenic activity can only be excluded by, for example, in vivo testing in transgenic rodents or duplex sequencing [36].

And similar, analogous, or somewhat equivalent experiments were done in the early 1960s and conclusively proved the carcinogenic effect of a certain type of nitrosamines in rodents [39-41]. In practice, the new forms of gene modifiers - the so-called nitrosamines / NDSRIs, should (according to the top experts of the 21st century) be ″similarly tested″ as in 1956 on mice, to prove their carcinogenic effect on humans again?

Although this carcinogenic effect has been proven in vivo in hundreds of clinical observations over the past decades and subsequent publications of real patients who took these drugs and subsequently developed melanomas (without their informed consent being signed and without even being informed) [11,12,16,17,19-24, 28-32]?

The lack of academic memory and morality definitely help this to happen, since globalization processes are perceived as something completely normal, in contrast to the less priority concepts of our time such as: 1) extended life expectancy of the patient, 2) improved quality of the patient's life and 3) the Hippocratic Oath.

Once again, the case remains illustrative of the potential, key role of drug-mediated nitrosogenesis in the generation and progression of melanoma, at least as a cofactor, and this time within the nevus spilus.

Increasing evidence indicates that nitrosamines could also be considered as bioweapons or genetic weapons to lead to peak mass locoregional but also global cancer pandemics [34]. This thesis is indirectly supported by several additional alarming factors: 1) Lack of impunity for manufacturers, 2) the continued distribution of drugs that have been given the green light by regulators, 3) the initialization of the presence of gene modifiers in drugs as something inevitable and normal.

Last but not least, the possibility of nitrosamines occurring endogenously should also be mentioned, and it is currently unclear to what extent the endogenously occurring carcinogenic nitrosamines are in concentrations that are lower, higher, or equivalent to those in drugs [42]. Nevertheless, the endogenous occurrence of nitrosamines should not limit the efforts of clinicians and regulators to limit exogenous intake through drugs.

The determination of mutagenic activity is currently carried out using the Ames test, modified Ames test and in vivo mutagenicity assay [42]. It should not be forgotten, however, that carcinogenicity is not always associated with mutagenicity [42], and this somewhat renders the previously mentioned three tests questionable in relevance. In vivo animal models in rodents are the best alternative, analogous to Maggee and Barnes' ″Tests from Antiquity″ [39-42].

The clinical significance of the shared clinical finding described by us, which is not sporadic, but turns out to be just another confirmation regarding melanoma after taking potentially/ actually contaminated medicinal preparations with nitrosamines, remains indisputable. The rethinking of the pathogenesis of melanomas, according to drug-induced carcinogenesis/ nitrosogenesis, remains one of the few reasonable explanations for its alarmingly increasing frequency.

Getting out of states of ″numbness or competent incompetence″/ the Dunning-Kruger effect should be seen as a priority and sobering.

REFERENCES

1. Kordeva S, Tchernev G. Thin melanoma arising in nevus spilus: dermatosurgical approach with favourable outcome. Georgian Med News. 2023;340-341:53-55.
2. Racanelli J, Moloney M, Siegel L. Superficial spreading melanoma within a nevus spilus. J Osteopath Med. 2023;123:223-224.
3. Grinspan D, Casala A, Abulafia J, et al. Melanoma on dysplastic nevus spilus. Int J Dermatol. 1997;36:499-502.
4. Corradin MT, Zattra E, Fiorentino R, et al. Nevus spilus and melanoma: case report and review of the literature. J Cutan Med Surg. 2010;14:85-9.
5. Tran T, Song S, Texeira AJ, et al. Educational interventions to promote sun-protection behaviors in adolescents in the United States: A systematic review. Pediatr Dermatol. 2023;40:637-641.
6. https://www.mskcc.org/cancer-care/types/melanoma/risk-factors-prevention
7. Takebe H, Nishigori C, Tatsumi K. Melanoma, and other skin cancers in xeroderma pigmentosum patients and mutation in their cells. J Invest Dermatol. 1989;92:236S-238S.
8. Tannous ZS, Mihm MC Jr, Sober AJ, et al. Congenital melanocytic nevi: clinical and histopathologic features, risk of melanoma, and clinical management. J Am Acad Dermatol. 2005;52:197-203.
9. Arnold M, Singh D, Laversanne M, et al. Global Burden of Cutaneous Melanoma in 2020 and Projections to 2040. JAMA Dermatol. 2022;158:495-503.
10. Spathis A, Katoulis AC, Damaskou V, et al. BRAF Mutation Status in Primary, Recurrent, and Metastatic Malignant Melanoma and Its Relation to Histopathological Parameters. Dermatol Pract Concept. 2019;9:54-62.
11. Tchernev G. Nitrosogenesis of cutaneous melanoma: simultaneously development of primary cutaneous thick melanoma of the breast, thin melanoma/dysplastic mole of the back during parallel intake of bisoprolol, amlodipine and valsartan/ hct: nitrosamine polycontamination in the multimedication as the most powerful skin cancer trigger. Georgian Med News. 2023;339:83-88.
12. Tchernev G. A flavour of death: perindopril induced thick melanoma and bcc of the back. Potential role of the generic substance or/-and possible nitrosamine contamination as skin cancer key triggering factors. Georgian Med News. 2023;336:123-125.
13. Öncü T, Yüksel B, Binay E, et al. LC-MS/MS Investigation of nitrosamine impurities in certain Sartan group medicinal products available in Istanbul, Türkiye. Ann Pharm Fr. 2023:S0003-4509(23)00079-2.
14. Lozzi F, Di Raimondo C, Lanna C, et al. Latest Evidence Regarding the Effects of Photosensitive Drugs on the Skin: Pathogenetic Mechanisms and Clinical Manifestations. Pharmaceutics. 2020;12:1104.

15. Gandini S, Palli D, Spadola G, et al. Anti-hypertensive drugs and skin cancer risk: a review of the literature and meta-analysis. Crit Rev Oncol Hematol. 2018;122:1-9.
16. Tchernev G, Kordeva S. Multiple bccs and dysplastic nevi after ace inhibitors (enalapril/perindopril): the role of nitrosamine contamination/availability as substantial skin cancer triggering factor. Georgian Med News. 2023;335:90-94.
17. Nardone B, Majewski S, Kim AS, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. Drug Saf. 2017;40:249-255.
18. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related
19. Mansouri I, Botton J, Semenzato L, et al. N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 Million Valsartan Users. J Am Heart Assoc. 2022;11:e8067.
20. Tchernev G, Temelkova I. Drug-Induced Melanoma: Irbesartan Induced Cutaneous Melanoma! First Description in the World Literature! Open Access Maced J Med Sci. 2019;7:114-116.
21. Tchernev G, Temelkova I. Irbesartan Induced Cutaneous Melanoma! Second Case in the Medical Literature! Open Access Maced J Med Sci. 2019;7:121-123.
22. Tchernev G, Temelkova I. Irbesartan Induced Cutaneous Melanoma! Second Case in the Medical Literature! Open Access Maced J Med Sci. 2019;7:121-123.
23. Tchernev G, Temelkova I. Olmesartan/valsartan induced giant achromatic cutaneous melanoma: "modified" one-step surgical approach with favourable outcome. J Biol Regul Homeost Agents. 2019;33:1775-1777.
24. Tchernev G. Neighbouring melanomas and dysplastic nevus developing simultaneously after candesartan intake: nitrosamine contamination/ availability as main cause for skin cancer development and progression. Georgian Med News. 2023;336:104-107.
25. Bell CM, Jenkinson CM, Murrells TJ, et al. Aetiological factors in cutaneous malignant melanomas seen at a UK skin clinic. J Epidemiol Community Health. 1987;41:306-11.
26. Austin DF, Reynolds P. Occupation and malignant melanoma of the skin. Recent Results Cancer Res. 1986;102:98-107.
27. Rushton L, Alderson MR. An epidemiological survey of eight oil refineries in Britain. Br J Ind Med. 1981;38:225-34.
28. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. Expert Rev Clin Pharmacol. 2021;14:1075-1080.
29. Tchernev G, Patterson JW. Telmisartan/hydrochlorothiazide-induced nevus-associated cutaneous melanoma: first report in the medical literature. Expert Rev Clin Pharmacol. 2021;14:289-293.
30. Tchernev G, Poterov G. Drug induced cancers: Simultaneously development of Cutaneous Melanoma, Colon carcinoma and Kaposi Sarcoma under Valsartan/ Hydrochlorothiazide. Clin Res Dermatol Open Access. 2020;7:1-8.
31. Tchernev G, Poterov G. Antihypertensive Drugs and Cancer: Simultaneously development of Choroidal melanoma and Colon Carcinoma after Administration with Valsartan / Hydrochlorothiazide. Clin Res Dermatol Open Access. 2020;7:1-4.
32. Tchernev G, Temelkova I. Valsartan/hydrochlorothiazide induced prostate carcinoma in a patient who subsequently developed melanoma. J Biol Regul Homeost Agents. 2019;33:1125-1127.
33. https://www.science.org/content/blog-post/sartan-contamination-story
34. https://www.scmp.com/news/china/science/article/3239723/chinas-top-spy-agency-warns-gene-weapons-able-target-specific-ethnicity-or-race
35. Trejo-Martin A, Bercu JP, Thresher A, et al. Use of the bacterial reverse mutation assay to predict carcinogenicity of N-nitrosamines. Regul Toxicol Pharmacol. 2022;135:105247.
36. https://www.chemistryworld.com/news/addressing-the-saga-of-nitrosamine-contamination-in-drugs/4018123.article
37. Tennant RE, Ponting DJ, Thresher A. A deep dive into historical Ames study data for N-nitrosamine compounds. Regul Toxicol Pharmacol. 2023;143:105460.
38. https://extranet.who.int/prequal/news/update-n-nitrosamine-impurities
39. Magee PN, Barnes JM. The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosamine. Br J Cancer. 1956;10:114-22.
40. Magee PN, Barnes JM. The experimental production of tumours in the rat by dimethylnitrosamine (N-nitroso dimethylamine). Acta Unio Int Contra Cancrum. 1959;15:187-90.
41. Magee PN, Barnes JM. Induction of kidney tumours in the rat with dimethylnitrosamine (N-nitrosodimethylamine). J Pathol Bacteriol. 1962;84:19-31.
42. https://www.fda.gov/media/150932/download.