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Mechanism of Action and Use of Radiomimetic Compounds

Part 1 – Alkylating Agents and Antimetabolites

Radiomimetic substances are drugs producing similar symptoms in living organisms as ionising radiation does. They constitute a special subgroup of carcinogen, mutagen, teratogen compounds; their common characteristic is to cause DNA breaks and/or to inhibit their repair. Mustard gas and its derivatives – alkylating agents – were the first known group of radiomimetic substances, later, it was observed, that some purine and pyrimidine analogues playing an antimetabolic role show a resembling outcome. Initially mustards were used in warfare, but now their usage for military purpose is prohibited by the Chemical Weapons Convention. Other radiomimetic substances have also become important tools in medicine, as they have been shown to be useful against certain pathogens and tumours. This review is a brief summary about the mechanism of action and the most common applications of alkylating agents and antimetabolites. In the coming second part, the radiomimetic substances of bacterial origin are reviewed from similar perspectives.

Keywords: **radiomimetic substances, alkylating agents, dicentric chromosome, antimetabolites**

1. Introduction

The danger of ionising radiation to human health has been well known since the last century. After Röntgen's discovery in 1895 (X-ray) and the Curie couple's in 1898 (radium), the detrimental effects of ionising radiation on biological systems were quickly revealed. The symptoms caused by ionising radiation (fever, vomiting, leukocyte depletion, burns, etc.) cannot be considered specific, that is why it is not easy to determine the radiation damage based on symptoms alone. Nor is it easy to decide whether a compound is radiomimetic, as it could cause non-specific symptoms.

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Once it had been shown to be harmful on human tissues, both the X-ray and the radium-emitted radiation types (alpha, beta and gamma radiation) began to be used as a therapeutic method to stop cell division and destroy neoplastic tissues. The principle of cancer radiotherapy was laid hereby. Subsequently, it was recognised that ionising radiation (regardless of its origin) also causes changes in exposed cells and tissues. Radiation-induced biochemical reactions cause metabolic damage, which can lead to cell death and, at higher radiation doses, even to the death of the individual.

Certain chemicals cause similar symptoms in living organisms as ionising radiation, which is why Dustin in 1947 called these chemicals radiomimetic substances.[2] The term radiomimetic seems self-evident, the word coined more than 70 years ago was also applied to later discovered compounds, although there are many targets, modes and levels of radiation effects, and radiomimetic compounds can mimic only certain segments of these effects, not all. Therefore, the use of the term radiomimetic is not always clear, and accordingly, this term is not quite common in the scientific literature.

If we compare the compounds that were originally covered by the term and that were later discovered and classified as radiomimetic substances, we see parallels and differences in their mechanism of action. Our knowledge of the molecular biological effects of ionising radiation is also expanding, so it is timely to further refine and even limit the term radiomimetic.

In 1952, Boyland listed the biological effects that can be caused by either ionising radiation or radiomimetic chemicals.[3] In the following decades, other chemicals with similar effects were discovered. In 1963, Elson published the first comprehensive review of radiomimetic substances, beginning with Boyland's work, which he expanded.[4]

The origin of clinical radiomimetic effects can be found at the molecular level, mainly as DNA damage and its deceived repair process (chromosomal breakage, intra- and inter chromosomal translocations),[5] as well as cell-level changes (white blood cell count, cell death).[6] At the level of the body, these can lead to symptoms like in the case of radiation exposure such as fever, burning symptoms, blisters, weight loss, bone marrow hyperplasia, often coupled with leukocytopenia and immune suppression.

In case of radiation, several mechanisms have evolved over evolution to repair the damage,[7] but erroneous repairs cause permanent changes in the multiple-damaged genetic stock, so that the radiation exposure suffered can be detected by biodosimetry tools as cytogenetic and molecular biological measurements,[8] which includes

2 Pierre Dustin, 'Some New Aspects of Mitotic Poisoning', *Nature* 159 (1947), 796.
3 Eric Boyland, 'Azione biologica delle radiazioni e delle sostanze radiomimetiche', *Endeavour* 11 (1952), 87.
4 Leslie A Elson, *Radiation and Radiomimetic Chemicals: Comparative Physiological Effects* (Washington, D.C.: Butterworths, 1963), 1.
5 Leila Benkhaled et al., 'Induction of complete and incomplete chromosome aberrations by bleomycin in human lymphocytes', *Mutation Research* 637, no 1–2 (2008), 134.
6 Elson, *Radiation and Radiomimetic Chemicals,* 1.
7 Howard H Y Chang et al., 'Non-homologous DNA end joining and alternative pathways to double-strand break repair', *Nature Reviews Molecular Cell Biology* 18 (2017), 495.
8 Gábor Deli, 'Cytogenetic Detection Tools for Effects of Ionizing Radiation on Human', *Hadmérnök* 13, no 3 (2018), 180.

chromosomal aberration, micronucleus, FISH and comet assay, gamma H2AX assay, mRNA markers, mitochondrial DNA changes.[9]

The molecular effects of ionising radiation can be direct or indirect. A direct effect is when radiation itself causes DNA breaks; an indirect effect is when it does so through free radicals generated by ionising radiation, i.e. reactive oxygen species (ROS). Oxidative stress disrupts ROS homeostasis, modulates the expression of various transcription factors, and leads to damage to lipids, protective cellular proteins and DNA.[10] ROS chemically reacts with DNA, causing permanent damage.[11]

A single high linear energy transfer (LET) particle can generate multiple double strand DNA breaks (DSB) in a relatively small region of the nucleus. Chromatin packaging can bring widely spaced DNA segments into proximity with one another, increasing the likelihood that both segments might be damaged by the same high LET particle.[12] Ionising radiation produces DSB in close temporal and spatial proximity along 'tracks' while traversing the nucleus and, hence, maximising the possibility of the interaction of processes at the damaged DNA sites and their effectiveness in the induction of dicentric chromosome (DIC).[13] The great majority of chemical mutagens, on the other hand, are incapable of inducing DSB in the first place. Because the DNA breaks caused by chemicals occur randomly, they are not as close to each other in space, as in the case of radiation.[14] Due to its catalyst-like effect, bleomycin (a radiomimetic of bacterial origin which will be discussed in the next part of this article) can induce DIC.

2. Characteristics of radiomimetic compounds

2.1. Alkylating agents

Alkylation is the chemical process in which hydrogen is replaced by an alkyl group. This alkyl group can be a simple alkyl radical (CH3, C2H5-), or a more complex, branched, ring structure as well.[15]

Alkylating agents are electrophilic and can be covalently attached to electron-rich functional groups of various target molecules. If these nucleophilic target groups are readily available, both the newly attached and leaving functional group may be temporarily bound to the target molecule at the same time. Thus, the replacement

[9] Gábor Deli, 'Az ionizáló sugárzás emberi szervezetre gyakorolt hatásának korszerű kimutatási lehetőségei' [Up-to-date Detection Possibilities of the Effect of Ionizing Radiation on the Human Body], *Honvédorvos* 71, no 1–2 (2019), 32.

[10] Dharambir Kashyap et al., 'Role of Reactive Oxygen Species in Cancer Progression', *Current Pharmacology Reports* 5 (2019), 79.

[11] Edouard I Azzam et al., 'Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury', *Cancer Letters* 327, no 1–2 (2012), 48.

[12] Wendy J Cannan and David S Pederson, 'Mechanisms and Consequences of Double-strand DNA Break Formation in Chromatin', *Journal of Cellular Physiology* 231, no 1 (2016), 14.

[13] Wolfgang Hoffmann and Inge Schmitz-Feuerhake, 'How radiation-specific is the dicentric assay?', *Journal of Exposure Analysis and Environmental Epidemiology* 9 (1999), 118.

[14] Ibid.

[15] Elson, *Radiation and Radiomimetic Chemicals,* 6.

takes place in one step, i.e. in the first-order. First-order alkylating agents are aromatic and aliphatic nitrogen containing compounds and sulfur mustards. The reaction is second-order if, due to the structural conditions, the part to be replaced must first leave its original position, allowing the alkyl group to be attached. These include ethyleneimines and epoxides, alkyl methanesulfonates and alpha-halogenated acids, ketones.[16]

Electron-rich molecules or ions (e.g. OH-, H_2O, halogenides, alcohols, thiols and amines) and the proteins and nucleic acids that carry them are ideal targets for the nucleophilic substitution.

The alkylation of DNA, which is responsible for the antitumor activity of these compounds, can lead to formation of covalent cross-links between and within the DNA strands. During the DNA repair, or in case of cell division, such cross-linkages can result in DSBs in the DNA,[17] which cause programmed cell death.[18] Their effect is independent of the cell cycle; the proportion of cells killed depends on the dose used.[19] The alkyl group is attached to the N-7 nitrogen of the guanine in the DNA chain.[20]

The mustard gas (Figure 1) was first described in the 19th century,[21] but it was developed as a weapon only during the First World War; and it was later shown to reduce the number of white blood cells present in the circulation. When examining the biological effects of mustard gas and nitrogen mustards, it has been found that these and some related chemicals can induce remarkably similar cytological damage like the one caused by ionising radiation.

Figure 1: Mustard gas and nitrogen mustard are alkylating agents
Source: Elson, Radiation and Radiomimetic Chemicals, 5., edited

Note: They can cause DNA damage as they covalently link to guanine residues in DNA strands.

The discovery of this radiomimetic effect of nitrogen mustard was followed by the discovery that nitrogen and sulfur mustards cause mutations in Drosophila,[22] and cause

[16] Georg F Weber, 'DNA Damaging Drugs', in *Molecular Therapies of Cancer* (Cham: Springer, 2015), 9.
[17] Giovanna Damia and Maurizio D'Incalci, 'Mechanisms of resistance to alkylating agents', *Cytotechnology* 27, no 1–3 (1998), 166.
[18] Natsuko Kondo et al., 'DNA damage induced by alkylating agents and repair pathways', *Journal of Nucleic Acids* (2010), 2.
[19] Vikas Malhotra and Michael C Perry, 'Classical Chemotherapy: Mechanisms, Toxicities and the Therapeutic Window', *Cancer Biology & Therapy* 2, sup1 (2003), 2.
[20] Carmen Avendaño and Carlos Menendez, *Medicinal Chemistry of Anticancer Drugs* (Amsterdam: Elsevier, 2015), 238.
[21] Dirk Steinritz and Horst Thiermann, 'Sulfur Mustard', in *Critical Care Toxicology,* ed. by Jeffrey Brent, Keith Burkhart, Paul Dargan, Benjamin Hatten, Bruno Megarbane, Robert Palmer and Julian White (Cham: Springer, 2017), 2683.
[22] Charlotte Auerbach, J M Robson and J G Carr, 'The Chemical Production of Mutations', *Science* 105, no 2723 (1947), 244.

chromosomal damage like those caused by radiation.[23] Their medical use is based on this effect, and in 1942 animal and then clinical trials began to cure lymphoma.[24]

Mustard derivatives are chemically highly active and react easily with various organic and inorganic compounds. They react quickly with water, what makes them inert.

Mustard gas, or sulfur mustard [Bis(2-chloroethyl) sulfide, C4H8Cl2S] and its analogues, are blistering agents that can damage cells by alkylating macromolecules (DNA, RNA) initiating oxidative stress, glutathione release and inflammatory processes. Like ionising radiation and many other radiomimetic compounds, such as busulfan, cyclophosphamide and nitrogen mustard, the sulfur mustard and its analogues damage particularly the rapidly dividing cells and tissues (e.g. genital organs and foetus). Men exposed to sulfur mustard showed a lower sperm count and testosterone levels within a few weeks after respiratory exposure. For example, the gender ratio of newborns changed,[25] and the number of birth defects increased after the use of mustard gas in Iraq.[26]

In addition to nitrogen mustard, other alkylating agents are used in chemotherapy, such as nitrosureas, alkyl sulfonates and platinum-based agents. The well-known alkylating agents are listed in Table 1.

Table 1: Alkylating agents based on Antineoplastic Agents

Source: 'Antineoplastic Agents', in LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases, 2012.

Alkylating agents					
Nitrogen mustards	**Nitroseureas**	**Alkyl sulfonates**	**Platinum based drugs**	**Ethylenamine and methyl-enamine derivatives**	**Triazenes**
cyclophos-phamide	carmustin	busulfan	cisplatin	altretamine	dacarbazine
chlormethine	lomustin		carboplatin	thiotepa	procarbazine
uramustin	streptozocin		nedaplatin		temozolomide
melphalan			oxaliplatin		
chlorambucil			satraplatin		
mechloret-hamine					
ifosfamide					

[23] Cyril D Darlington and Peo C Koller, 'The chemical breakage of chromosomes', *Heredity* 1 (1947), 190.

[24] Alfred Gilman, 'The initial clinical trial of nitrogen mustard', *The American Journal of Surgery* 105, no 5 (1963), 574.

[25] Ramesh C Gupta, *Handbook of Toxicology of Chemical Warfare Agents,* 2nd edition (Amsterdam: Academic Press, 2015), 37.

[26] Kamyar Ghabili et al., 'Mustard gas toxicity: the acute and chronic pathological effects', *Journal of Applied Toxicology* 30, no 7 (2010), 627.

2.2. Antimetabolites

Since radiation-induced cytological damage is closely related to the effects on the nucleus (this is clearly visible in the morphological changes of the chromosomes), some cytological effects of radiation can be induced by compounds that disrupt the normal metabolism of nucleic acids, especially DNA. Many antimetabolic compounds are being tested as a possible chemotherapeutic agent, particularly as anti-leukemia agents. A few of these compounds are listed below in Table 2.[27]

Table 2: Radiomimetic antimetabolites based on Antineoplastic Agents
Source: 'Antineoplastic Agents'.

Antimetabolites		
Purine analogues	**Pyrimidine analogues**	**Folic acid antagonists (Antifolates)**
6-mercaptopurine	5-fluorouracil (5-FU)	methotrexate
azathioprine	floxuridine	pemetrexed
mercaptopurine	cytosine-arabinoside	pralatrexate
fludarabine	6-azauracil	trimetrexate
thioguanine	gemcitabine	edatrexat
cladribine	azacitidine	raltitrexed
	capecitabine	
	cytarabine	
	decitabine	
	trifluridine/tipracil	

Antimetabolites inhibit DNA synthesis by showing structural similarity to molecules that play a key role in DNA synthesis. The cellular enzymes are incapable of distinguishing them from their normal counterparts and insert them into the DNA, where they make the normal functions impossible.[28] Because of the inhibition of DNA synthesis, the cell is unable to divide as well. In contrast to alkylating agents, the effect of antimetabolites is cell-cycle dependent, affecting only cells that are in the S phase (synthesising DNA for cell division).[29]

2.2.1. Purine analogues

One of the best-known purine analogues is 6-mercaptopurine, a structural analogue of hypoxantine. It inhibits de novo purine biosynthesis.[30] The compound shows

[27] Elson, *Radiation and Radiomimetic Chemicals,* 11.
[28] William B Parker, 'Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer', *Chemical Reviews* 109, no 7 (2009), 2883.
[29] Malhotra and Perry, 'Classical Chemotherapy', 3.
[30] Leonard S Jacob, *Pharmacology. The National Series for Independent Studies,* 4th edition (Philadelphia: Williams & Wilkins, 1996), 260.

radiomimetic effects, for example on its effect on mucosa and bone marrow, also causes liver damage. The mechanism is fundamentally different from that of acute radiation syndrome.[31] Amsacrine (synonyms: m-AMSA, acridinyl anisidide) intercalate into DNA and inhibits topoisomerase II, resulting in DNA double-strand breaks.[32] It is an antineoplastic agent, has been used in acute lymphoblastic leukemia.[33]

The 2-amino-6-mercaptopurine (thioguanine) is a guanine analogue and disrupts the synthesis of DNA and RNA. Its effect on haemopoietic organs is more reminiscent of the effects of radiation. Fatal injuries such as agranulocytosis and thrombocytopenia caused by bone marrow damage, similar to whole-body irradiation, have been observed in animal experiments. However, other damage by thioguanine can be distinguished from radiation induced damages by the fact that lesion in lymphoid tissues and intestinal epithelium are not prominent.[34]

Common side effects are bone marrow suppression, liver problems and inflammation in the mouth.[35]

2.2.2. Pyrimidine analogues

A well described example of the pyrimidine analogue type antimetabolites is 5-fluorouracil described by Heidelberger et al. in 1957. The compound inhibits thymidylate synthase, hereby the DNA synthesis and growth of certain tumours and attenuates the aggravation of leukemia.[36] The 5-fluorouracil also has radiomimetic effects: it causes a decrease in leukocyte and erythrocyte count with its inhibiting effect of the bone marrow on haemopoietic tissues.[37] It is used to treat a variety of solid tumours such as breast, head-and-neck and digestive cancers either in neo-adjuvant, adjuvant or metastatic settings.[38] 5-fluorouracil sensitises tumour cells towards double stranded DNA breaks by interfering with homologous recombination repair.[39]

2.2.3. Folic acid antagonists

Aminopterin and its methyl derivative methotrexate are well-known folic acid antagonists which have a radiomimetic effect on hematopoietic organs.

[31] Elson, *Radiation and Radiomimetic Chemicals,* 12.
[32] Brendan Marshall et al., 'Evidence that mAMSA induces topoisomerase action', *FEBS Letters* 161, no 1 (1983), 75.
[33] Martin Horstmann et al., 'Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children', *Haematologica* 90, no 12 (2005), 1701.
[34] Elson, *Radiation and Radiomimetic Chemicals,* 12.
[35] British National Formulary, *BNF 69,* 69th edition (London: British Medical Association, 2015), 588–592.
[36] Jacob, *Pharmacology,* 261.
[37] Elson, *Radiation and Radiomimetic Chemicals,* 13.
[38] Florian Lemaitre et al., '5-fluorouracil therapeutic drug monitoring: Update and recommendations of the STP-PT group of the SFPT and the GPCO-Unicancer', *Bulletin du Cancer* 105, no 9 (2018), 791.
[39] Upadhyayula S Srinivas et al., '5-Fluorouracil sensitizes colorectal tumor cells towards double stranded DNA breaks by interfering with homologous recombination repair', *Oncotarget* 6, no 14 (2015), 12575.

Their radiomimetic effect is weight loss, bone marrow hypoplasia and decrease in blood cell counts (especially neutrophil granulocytes).[40]

Methotrexate inhibits the formation of DNA-forming nucleotides by binding and inactivating enzymes involved in their synthesis as a substrate due to their structural similarity.

Methotrexate reversibly inhibits the function of the dihydrofolate reductase enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of this step of folic acid metabolism limits purine synthesis, DNA synthesis, cell proliferation and regeneration.

Tissues whose cells proliferate rapidly (e.g. tumour cells, bone marrow, foetal cells, urinary bladder, mucous membranes of the mouth and intestines) are more susceptible to methotrexate. If the rate of cell proliferation in malignant tissues is much higher than in intact tissues, methotrexate inhibits tumour cell proliferation without irreversible damage to non-dividing tissues.[41]

3. Application of alkylating agents and antimetabolites

3.1. Chemical warfare

Mustard gas, namely sulfur mustard, belongs to the group of cytotoxic and blistering warfare agents. Chemically pure sulfur mustard is a colourless liquid at room temperature. When used in unpurified form in warfare, it is usually yellowish brown in colour and smells like mustard, garlic or horseradish.[42]

For the first time mustard gas was produced presumably by César-Mansuète Despretz in 1822. The cytotoxic and blistering effect of mustard gas was recognised by Meyer in 1887, its development for military purposes was launched later by Fritz Haber.[43] The first military use of mustard gas took place during World War I, near Ypres, Belgium, on 12 July 1917, and the German army effectively used it against British soldiers, and later against the second French army. It was used as a warfare agent in World War I under the code H.

During World War II, the study of sulfur mustards led to the development of nitrogen mustards, such as bis(2-chloroethyl)methylamine (code HN2) and tris(2-chloroethyl)amine (code HN3). Fortunately, the use of these compounds in battlefields has not taken place.

Since the First World War, there were only isolated cases where mustard gas was used, mostly in the Middle East, for countries that were not members of the OPCW (Organisation for the Prohibition of Chemical Weapons) at the time of the incident.[44]

[40] Elson, *Radiation and Radiomimetic Chemicals,* 13.

[41] Alexei Vazquez et al., 'Overexpression of the Mitochondrial Folate and Glycine–Serine Pathway: A New Determinant of Methotrexate Selectivity in Tumors', *Cancer Research* 73, no 2 (2013), 479.

[42] National Research Council, *Acute Exposure Guideline Levels for Selected Airborne Chemicals,* Volume 3 (Washington, D.C.: The National Academies Press, 2003), 301.

[43] Steinritz and Thiermann, 'Sulfur Mustard', 2683.

[44] James A Romano et al. (eds), *Chemical Warfare Agents, Chemistry, Pharmacology, Toxicology, and Therapeutics,* 2nd edition (Boca Raton: CRC Press, 2007), 630.

Producing or stockpiling sulfur mustard is prohibited by the Chemical Weapons Convention. The treaty entered into force on 29 April 1997 and accordingly, 86% of 17,440 tons of mustard gas worldwide have been destroyed by 2015.[45]

There is no information that other radiomimetic materials have been used for military purposes.

3.2. Antibiotic, antiviral and antifungal therapy

Methicillin-resistant Staphylococcus aureus (MRSA) refers to a group of gram-positive bacteria that genetically differs from other Staphylococcus aureus strains and is responsible for many, difficult-to-treat diseases. Attempts are being made to exploit the antibiotic effect of certain radiomimetic agents in the treatment of MRSA.[46]

Mechlorethamine is the prototype of nitrogen mustards. It has been used topically for treatment of mycosis fungoides.[47]

Antimetabolites are used as an antibiotic (e.g. trimethoprim) or antiviral agent (e.g. lamivudine, ribavirin) in addition to the treatment of tumours. In the latter, the selective effect is based on the inhibition of enzymes or pathways that do not occur in humans.[48]

3.3. Tumour and autoimmune therapy

In 1943, an American ship carrying mustard gas and military personnel was bombed. Tanks containing mustard gas were damaged, causing deadly poisoning in those who survived the ship's sinking. Doctors later found that mustard gas probably attacked white blood cells. Leukemia and lymphoma are types of cancer that are associated with the proliferation of white blood cells; they were still incurable diseases at that time. It has been thought any substance capable of killing healthy white blood cells could destroy cancer cells, as well.

Mustard gas was too toxic to be used on its own, but after successful animal tests, Goodman and Gilman developed a version named nitrogen mustard and looked for test subjects. They found a man who is known today only by his initials, J D. He had lymphoma; he was so sick that he could barely move because of the swollen, painful lymph nodes. The researchers gave him nitrogen mustard, and although the injections he received did not save J D's life, the treatment temporarily helped him.[49]

[45] Organisation for the Prohibition of Chemical Weapons, "Annex 3." Report of the OPCW on the Implementation of the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction in 2015 (OPCW, 2016), 42.

[46] Christina C Andros et al., 'A novel application of radiomimetic compounds as antibiotic drugs', *Journal of Pharmacy and Pharmacology* 67, no 10 (2015), 1371.

[47] Jacob, *Pharmacology,* 255.

[48] Agnieszka Wróbel et al., 'Trimethoprim and other nonclassical antifolates an excellent templat Agnieszkae for searching modifications of dihydrofolate reductase enzyme inhibitors', *The Journal of Antibiotics* 73 (2020), 5.

[49] Gilman, 'The initial clinical trial of nitrogen mustard', 574.

This way chemotherapy began with the nitrogen mustard, i.e. with a radiomimetic agent. Various derivatives of radiomimetic substances are widely used in combination chemotherapy today.

The first successful cancer chemotherapy regimen was the MOPP, introduced in 1964 for lymphomas.[50] The name comes from the initials of components: Mechlorethamine nitrogen mustard (alkylating agent, radiomimetic), Oncovin (vincristine, a vinca alkaloid, binds to tubulin), Procarbazine (triazen, alkylating agent, radiomimetic), Prednisone (glucocorticoid). Hundreds of chemotherapy regimens are in use today, defining the drugs to be used, their dosage, the frequency and duration of treatments and other considerations. There is no widely accepted naming convention for the nomenclature of chemotherapeutic regimens, standardisation has recently been proposed.[51]

Alkylating agents are frequently applied in tumour therapy. Cyclophosphamide is an essential part of many effective drug combinations in the treatment of various neoplastic disorders, and it has also been used as an immunosuppressing agent for organ transplants.[52] The high lipid solubility of some of nitrosoureas (Carmustine, Lomustine) allows penetration of the blood-brain barrier and is useful in the treatment of malignancies of the central nervous system. Dacarbazine is one of most active agents against malignant melanoma.[53]

Each antimetabolite is used in several cancer types alone or as part of a combined therapy: 6-mercaptopurine (6-MP) is marketed as Purinethol and is used to treat cancer and acute lymphoid leukemia, chronic myeloid leukemia, and other, non-tumour diseases, e.g. autoimmune diseases, Crohn's disease and ulcerative colitis. For acute lymphoid leukemia, it is generally used with methotrexate, in a regimen called POMP.[54] Common side effects include liver toxicity, vomiting, loss of appetite and inhibition of white blood cell formation in the bone marrow. There is an increased risk of future cancer and pancreatitis.[55] Tioguanine (6-thioguanine, 6-TG) is used in medicine for acute myeloid leukemia, acute lymphoid leukemia and chronic myeloid leukemia. Long term use is not recommended. Fluorouracil (5-FU) is marketed under the name Adrucil for the treatment of certain cancers. It is used intravenously for treatment of colon cancer, esophageal cancer, gastric cancer, pancreatic cancer, breast cancer and cervical cancer.[56] As a cream, it is used for the treatment of certain types of skin cancer.[57] Clinical use of aminopterin and methotrexate in leukemia has been the subject of numerous studies. Methotrexate is a folic acid antagonist antimetabolite

[50] Kenneth M Rassnick et al., 'MOPP Chemotherapy for Treatment of Resistant Lymphoma in Dogs: A Retrospective Study of 117 Cases (1989–2000)', *Journal of Veterinary Internal Medicine* 16, no 5 (2002), 576.

[51] Samuel M Rubinstein et al., 'Standardizing Chemotherapy Regimen Nomenclature: A Proposal and Evaluation of the HemOnc and National Cancer Institute Thesaurus Regimen Content', *JCO Clinical Cancer Informatics* 4 (2020), 60.

[52] Jacob, *Pharmacology,* 256.

[53] Ibid. 258.

[54] Victorio Rodriguez et al., 'POMP combination chemotherapy of adult acute leukemia', *Cancer* 32, no 1 (1973), 69.

[55] Mercaptopurine, The American Society of Health-System Pharmacists, 2016.

[56] Fluorouracil, The American Society of Health-System Pharmacists, 2016.

[57] Angela Yen Moore, 'Clinical applications for topical 5-fluorouracil in the treatment of dermatological disorders', *Journal of Dermatological Treatment* 20, no 6 (2009), 328.

used for the treatment of certain cancerous and autoimmune diseases (psoriasis, rheumatoid arthritis).

4. Conclusion

The term "radiomimetic" was originally defined based on symptoms, but there are two aspects by which we can redefine the concept. The first is whether a compound can replace any use of ionising radiation, and the second is whether its molecular biological mode of action is similar to that of ionising radiation.

The term radiomimetic now has a different meaning than it originally did 70 years ago.[58] Not even Elson has claimed that all radiomimetic compounds should produce all the effects listed by him.

Sax – the same botanist who described the formation of dicentric chromosomes by ionising radiation in 1938 – based on chromosome studies in 1966 described that caffeine and ethanol has a radiomimetic effect on the cells of the onion germ.[59] Today, caffeine is not considered a radiomimetic compound, nor is ethanol. Sax himself has already suggested that the metabolism of each species is different, which is why today a compound is considered radiomimetic if exerts its effects on humans, too.

Traditionally, antimetabolites are radiomimetic, they also act on DNA, but their effects are indirect, as opposed to alkylating agents and inorganic free radical generating compounds.

Ionising radiation not only affects DNA, but it also damages other organic compounds as proteins, lipids, etc. It reaches the deeper layers of the body quickly and unnoticed, its effect develops only with a greater or lesser delay.

There are many compounds that may be considered to belong to the group of radiomimetic agents, but their mechanism of action is not like those of radiation damage. These include, among others, corrosive surface disinfectants, which prevent repair enzymes from working by destroying almost any part of the cell, the intercalating DNA dyes that do not cause DNA breakage but result in frameshift mutations, and certain antibiotics and cytostatics that do not attack DNA but, for example, protein synthesis. These compounds are not considered radiomimetic, but this issue may still be open to debate.

The use of the term 'radiomimetic' in the scientific literature has become even more complex with the discovery of radiomimetic substances of bacterial origin. A line should be drawn to clarify the meaning and simplify the use of this term. These topics will be discussed in the next part of this article.

[58] Dustin, 'Some New Aspects', 796.
[59] Karl Sax and Hally J Sax, 'Radiomimetic beverages, drugs, and mutagens', *Proceedings of the National Academy of Sciences of the USA* 55, no 6 (1966), 1433.

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