SARS-COV-2, COVID-19 AND RADIATION: HISTORY, RESULTS AND PROSPECTS

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Abstract.

The history of mankind demonstrates that epidemics and pandemics have shaken civilization very systematically, at all times. This provoked a response from people to put scientific redoubts in the fight against viruses and bacteria, which (as it turned out) were the sources of diseases. At the turn of 2019-2020, humanity was invaded by a new killer, the SARS-CoV-2 coronavirus (in early China, Wuhan, and then around the world), which could overcome the barrier between animals and humans and cause COVID-19, accompanied by a combination of unusual syndromes and severe course (such as unusual pneumonia), up to to the point of lethal. Since the beginning of the disease to the present, the pandemic has affected more than 704 million people, leading to 7 million deaths, and more than 22 million people are currently suffering from one of the variants of the mutated SARS.

At the initial stage of the fight against this virus, it turned out that science and medicine (pharmacology, immunology, epidemiology), in the first months, demonstrated their inconclusiveness, and this caused specialists from various sciences, theorists and practitioners to be involved in the fight against the epidemic. Among them were physicists (specialists in radiation exposure) and physicians (radiobiologists). They suggested using the effect of small doses of X-rays to affect the virus in vivo. In the articles that appeared (Tashkent 2020, March [1] et seq.) Theoretically, a method was developed for the destruction of viral RNA using low-dose subsurface X-ray irradiation, which caused Auger cascades in phosphorus atoms embedded in the RNA. Western experimental doctors (2020, April [2] et seq.) independently revealed the really great efficiency of this method of struggle. In the following years, both theory and treatment methods were developed in a large number of details, which affected various types of com modeling. In general, these works have made a significant contribution to radiation medicine.

Introduction.

The pandemic of COVID-19 infection caused by the coronavirus poses a serious threat to the entire world, which is caused by the high rate of transmission of the virus and the rapid escalation of infections, which has led to an unprecedented strain on health systems. Severe course and mortality are caused by a high viral load and the corresponding launch of an immune response in the form of synthesis by immune cells and release into the blood of pro-inflammatory cytokines and chemokines, which takes on such an overactive character that it was defined by the term "cytokine storm". It is the latter that eventually leads to extensive damage to the lungs and other organs, causing multiple organ failure and death. Despite the fact that many pharmacological studies are currently underway, there does not seem to be an effective treatment (with the exception of supportive oxygen respiration and artificial lung ventilation systems).

Against this background, studies on the possibility of using low doses (<100 gy) of X-ray radiation for the treatment of viral pneumonia as a possible treatment method for patients with COVID-19 could not fail to attract attention [1,2]. This opinion was based on the facts of the use of X-rays for the treatment of pneumonia in the 30-40s of the twentieth century before the advent of antibiotics, which are based on 15 reports on the treatment of 863 patients with severe pneumonia of various, sometimes even unidentified, origin. Good clinical effects have been reported, including reduced mortality, usually with a short clinical onset, 1-3 days after exposure. Compared to current standards, they have a low level of evidence due to the lack of appropriate control groups in some cases and insufficient follow-up time (for example, it may take only a few hours to determine an improvement in the patient's condition, and several days to survive from the acute stage of pneumonia). In addition, not a single report on low-dose radiation therapy for pneumonia has been published for more than seven decades [3].

In these older studies, the reported doses were usually in the range of 20 to several hundred X-rays, which, taking into account attenuation through the chest wall, would probably lead to average doses in the lungs in the range of tens to <100 cGy. It was shown that low doses of X-rays reduced mortality from pneumonia from an average of 30 to 10 percent. Some reports noted rapid relief of symptoms within a few hours. Historical reports suggest that the optimal dose may be between 0.35 and 0.5 Gy, while higher doses may have the opposite effect and may cause increased inflammation. Subsequently, due to the threat of nuclear war, studies of the pathogenesis of radiation sickness were conducted, which included the study of the modulation of the immune system function under the influence of various doses of radiation. Currently, the main hypothesis of the effect of low-dose X-ray therapy is that X-rays can cause a counteraction or stimulation of an inflammatory reaction depending on the applied dose (the hypothesis of macrophage polarization $MM1/MM2$). Low doses of radiation therapy can induce the anti–inflammatory phenotype of macrophage immune cells, regardless of whether they are performed locally in the inflamed area or throughout the body. Studies conducted in both in vivo and in vitro models demonstrated a three-phase dose-response curve in which a low dose of X-ray therapy (<1 Gy) and a high dose of X-ray therapy (> 10 Gy) caused an anti-inflammatory phenotype, while a moderate dose of X-ray therapy (1-10 Gy) caused a pro-inflammatory phenotype. According to this hypothesis, both phenotypes can be induced under the influence of radiation therapy, but the final result depends on the radiation dose, the tissue microenvironment, and possibly on individual characteristics (Figure 1).

At the same time, this hypothesis completely lacks information about the possibility of **direct** radiation exposure directly to a pathological agent, namely, viruses, which, strictly speaking, cause an immune reaction, and since the mutation capacity of the genetic carrier of viruses is 5-6 times higher than that of the nuclear apparatus of cells, it is possible that the mechanism This plays a role in the immune response.

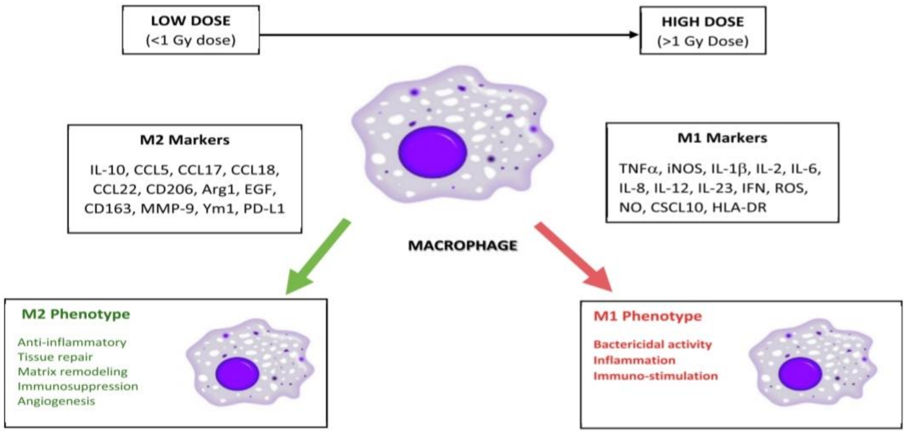

Figure 1. Radiation dose and macrophage polarization [3]

Thus, taking into account the inactivation of the SARS-CoV-2 virus, it becomes necessary to focus on the already known data on the radiation inactivation of other viruses. Very often, the tobacco masaika virus was such a guideline in radiation biology, but the data on it did not cause optimism, because for its destruction it required a set of X-ray doses up to 2 gray (!). However, optimism regarding the inactivation of SARS-CoV-2 came from indirect data, namely: already in In January 2020, Chinese researchers studied the genome of this virus (see [4]). It turned out that his RNA, which is a carrier of genetic data, looks very special (Figure 2).

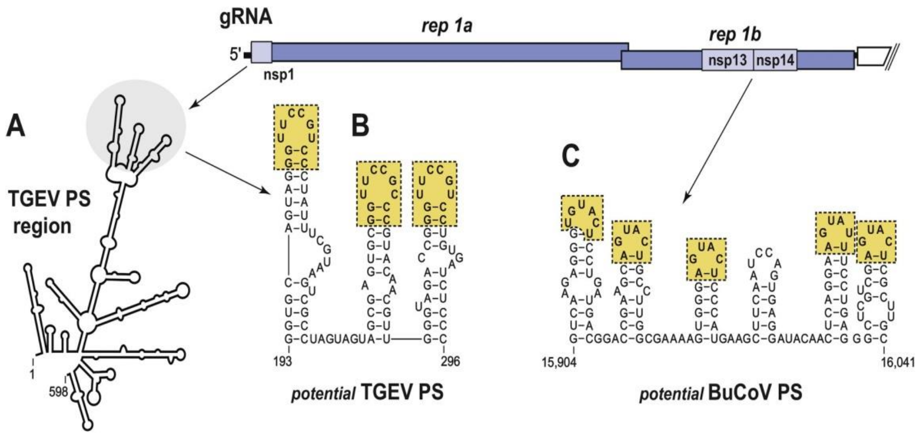

Figure 2. Various coronavirus diseases. The modular architecture (A) and the corresponding macromolecular configurations (B) and (C), including pins and loops, are shown. All these configurations correspond to conformational units, the complexity of which radically increases the cross-section of biopolymer destruction, see [4,5].

Research methods.

Features of SARS-CoV-2 that have opened up new possibilities for low-dose X-ray treatments. The analysis of the radiation damage of the virus in previous studies [1,3] was based on the standard model of their RNA viruses as a linear macromolecule, which is precisely the case for SARS-CoV-2. Indeed, numerous studies of the SARS-CoV-2 genome show the extreme nonlinearity (local deformity such as bending and torsion, as well as the fractal sequence of nucleotide bases – all of which represent synergy) of its RNA molecule, which is associated with the need to accommodate a large RNA molecule (30,000 bp) in a small cell volume – see Figure 2. This strong local deformation (bending, torsion), combined with the heterogeneity of the nucleotide bases along the RNA, radically change the nature of the radiation response to ionizing effects, the so-called subthreshold radiation [1,5]. As we showed in [1.5], the cross-section (probability) of Auger destruction of the local RNA region is determined by the expression:

$$\sigma_d = \sigma_K \alpha_K \exp(-\tau_+/\tau_e) + \sigma_L \hat{\alpha}_L \exp(-\tau_+/\tau_e) \qquad (1)$$

The nature of this multi–stage phenomenon consists in the primary ionization of the deep shells of multi-electron atoms on RNA (in particular, the phosphorus ion shells K and L), after which, as a result of the Auger cascade, a large positive charge is localized in the valence shell of the phosphorus atom, a "Coulomb explosion" occurs and the local region (even the locus) is destroyed, while in which the RNA loses its properties programmed by this locus. By selecting the radiation parameters, you can select the desired locus, in particular, damage a locus that corresponds to the "claw protein" that opens the cells of the body. In the previous formula σ_K and σ_L are the ionization cross sections of K and L shells, α_K and $\hat{\alpha}_L$ are the Auger cascade probabilities, τ_e is the time of electronic neutralization (flooding), $\tau_+ \approx 5 \cdot 10^{-14}$c. It is fundamentally important that the value of τ_e in the deformed and undeformed regions of RNA differs by orders of magnitude, and in the deformed regions τ_e is greater, since flooding/neutralization is difficult here. As a result, the destruction cross section (σ_d) in the deformed areas is 1000 times or more higher than the corresponding values in the undeformed areas. Thus, the low probabilities of RNA strand breaks estimated by previous authors [2,3] simply do not correspond to the characteristics of RNA in SARS-CoV-2. Thus, an analysis of the effect of low-dose radiation in COVID-19 is inconceivable without taking into account the death (modification) of the viruses themselves during irradiation. Taking into account the destruction of the virus itself during therapeutic treatment, together with the concept of macrophage polarization (M_1/M_2), undoubtedly opens up new possibilities for radiation therapy.

Modeling of epidemics by mathematical ecology methods.

The history of mankind shows that at all times it has been accompanied by epidemics caused by viruses and bacteria [3, 6-8]. Apart from pharmacology, epidemiology, immunology (vaccination), sanitary hygiene, etc. have always played a very significant role among the various methods of countering the epidemic. Epidemiology occupies a more than worthy place in this list, allowing either statistically or semi-experimentally to identify the weaknesses of microorganisms in relation to their biology, the interaction of the "microorganism-host" type, and much more [7]. There are many methods of epidemiology (in the sense of theory), and each of them serves to solve specific problems [8]. Interesting results are obtained when classical methods of epidemiology are combined with such new ideas as fractals, synergetics, and catastrophe theory [9, 10]. This part demonstrates a combination of ecosystem theory, synergetics, biophysics, and radiation physics.

Let's consider the evolution of viruses (type 1) capable of "producing" virus 2 with the help of mutation, both in the absence of vaccination and with it. The simplest system of equations that takes into account the intraspecific competition of virus 1 and its type 2 mutant is illustrated as [10]:

$$\begin{cases} \dot{X}_1 = K_1 X_1 (N_0 - X_1 - \beta X_2) - X_1/d_1 \\ \dot{X}_2 = K_2 X_2 (N_0 - X_2 - \beta X_1) - X_2/d_2 \end{cases} \qquad (2)$$

Here N_0 is a common food resource, $(d_{1,2})^{-1}$ – the probabilities of virus death are "1" and "2"; all values with tildes (« $\dot{}$ ») refer to vaccination.

We especially note that we will describe the birth of a mutation using the Heavisaid function $\Theta(t-\tau)$, a threshold function equal to 1 for $t \geq \tau$ and 0 for all other t.

We will take into account the probabilities of the absence or presence of vaccination

$$1/d_{1,2} = 1/d_{1,2}^{0} + [\Theta(t - \tilde{\tau}_{1,2})]/\tilde{d}_{1,2} \quad (3)$$

A detailed analysis of the system of equations (2) provides interesting information (Figure 3)

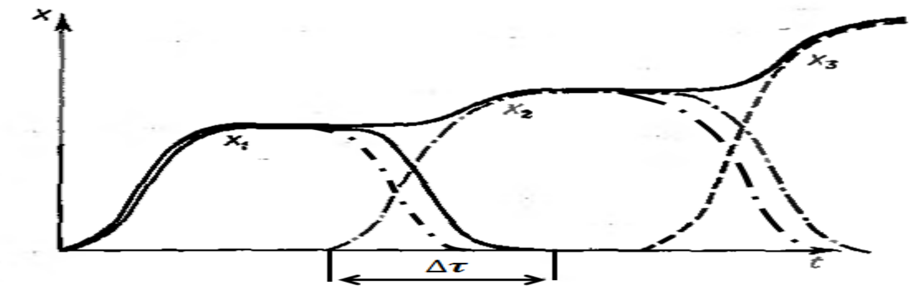

Figure 3. The evolution of the virus, taking into account the mutation during vaccination (dotted line) and without it (solid line), the growth of the virus of the third type (dashed line).

Figure 3 shows that virus 1 and the mutant of this virus 2 compete in terms of food resources ("host" cells), and the presence of vaccination against virus 1 facilitates the victory of virus 2 (in intraspecific competition) earlier than without vaccination (1), and its growth during vaccination (accelerated). The later inclusion of vaccination "2" leads to the existence of "PDW", **a particularly dangerous window** when the "owner" (person) is completely defenseless (a "window" with a time interval of $\Delta\tau$).

This circumstance requires the involvement of fundamentally different methods of influencing the virus during the period of $\Delta\tau$. It is precisely this method that is the classic method of **radiation nanotechnology**, such as subthreshold irradiation, namely low-energy, low–dose X-ray irradiation of the SARS-2V virus in vivo - in a cell (low dose irradiation $D \leq 0{,}5$ Gray, energy ≈3 keV). Fundamentally, this results in a "Coulomb explosion" of the local RNA region based on the Auger effect, which does not damage the surrounding healthy tissue of the host cell [10-11]. This method, proposed in [12-13], is actively used in a number of foreign clinics [8]. It is assumed that low-dose X-ray therapy (RT) will be useful in the fight against other viruses and bacteria.

On the role of natural and man-made radiation effects on the SARS-2V coronavirus and Covid-19 pneumonia.

When thinking about the mechanism of selective radiation exposure described above, we suggested that there should be a correlation between the suppression of covid incidence in local areas of different continents where natural or man-made radiation is present. We have carried out work on mapping both radiation sources and disease bulletins (the first according to the IAEA documents, the second according to the Internet), and it seems to us that such a correlation with COVID is really being suppressed. As an example below, the situation concerning Kazakhstan will be demonstrated.

To determine the degree of radiation exposure in this complex multifactorial process of COVID infection, we combined a map of the infection areas of the population of these countries with the localization of the developed uranium ore deposits.

As you can see (Figure 4), in the list of regions of Kazakhstan, the Turkestan region occupies the last place in terms of the incidence of COVID infection, where almost 85% of the country's operating uranium mines are concentrated. Since the level of vaccination differed little between the regions of this country, we considered that the degree of morbidity may depend on the number of the population or the density of its residence. However, the population of this region is more than 2 million people, which is slightly less than the most populated Almaty region. Moreover, this calculation does not include cities with a population of over a million people located on the territory of these regions and for which the incidence rate is shown separately. A comparison of the incidence among 3 millionaire cities showed that the incidence rate per 100,000 people for Shymkent was almost 2-4 times lower than for other cities. This indicates that the incidence of COVID infection is decreasing in the territory where uranium is mined, and this does not depend on the density of the population.

According to the IAEA, uranium ores in Kazakhstan are found in sandy soil and are extracted by underground leaching. This is the cheapest way to extract uranium, but it may not be completely environmentally friendly, since it can increase the radioactivity of groundwater. Apparently, it was the increase in the radioactive background, albeit to a small extent, that caused the lower incidence of COVID infection in the neighboring (Turkestan) regions of Kazakhstan.

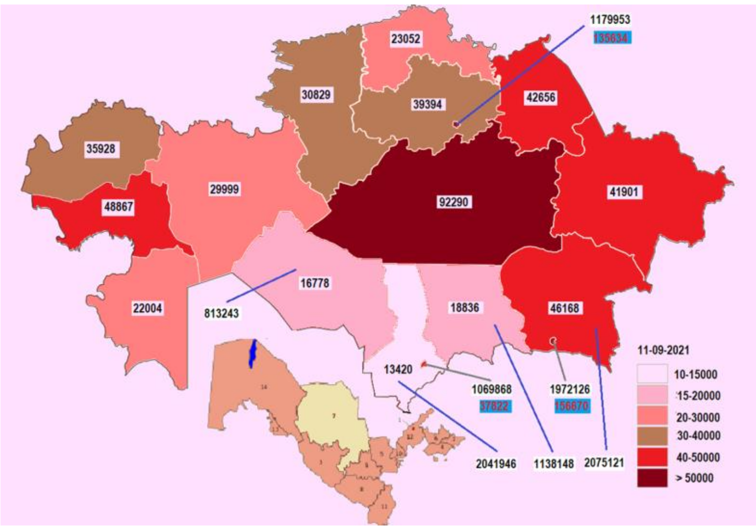

Figure 4. The incidence of COVID-19 in the regions of Kazakhstan.

This is also evidenced by the fact of a lower incidence in the Talas region compared to other regions of Kyrgyzstan, where an enterprise processing uranium ore mined in Kazakhstan is located.

The results and their discussion.

The above analysis of expert results, in principle, can be interpreted in two ways from a microscopic point of view. The first variant, the microscopic approach developed by us [14], is based on the idea of Auger destruction of RNA molecules when the virus is inside a human cell. Detailed microscopic analysis [14] allowed us to write an expression for the destruction cross section, which strongly depends on the degree of delocalization of the external valence electrons of RNA molecules. This mechanism belongs to the class of "direct impacts", so that their number (destroyed sites) is directly proportional to the dose.

$$N_{\text{раз}} \sim \mathcal{D} \quad (4)$$

In contrast, there is an indirect mechanism for suppressing the action of the virus, when the initial products of radiation are molecules that excite the immune system, and then these molecules enter into a chemical reaction. So with this mechanism, a differential stage is required, which violates the law of straightness noted above. Thus, if the damage rate of the virus has scaling (damage rate) $\approx \mathcal{D} = I \cdot t$

where I is the X–ray photon flux.. A detailed identification of the type of direct or indirect mechanism was carried out on an array of data from Western clinics, where changes in the course of covid-pneumonia were achieved with X-ray irradiation [1,2,8]* scaling ($I \cdot t = \mathcal{D}$) in the area of doses sufficient to suppress pneumonia was revealed with a high degree of reliability. Therefore, it can be assumed that the above (Figure 4) is also due (mainly) to a direct mechanism.

The current state of the problem.

The reliably established experimental fact of the possibility of suppressing COVID-19 pneumonia caused by the SARS-CoV-2 coronavirus is interpreted within the framework of a combined ideology of excitation of a polarizing macrophage (M_1/M_2) in combination with the destruction (modification) of the virus itself by ionizing effects on its genome. The most effective way of the latter process consists in primary K and L ionization by external subsurface X-ray radiation (with dose parameters up to 1 Gy, and with an energy of the order of 10 keV). The increased efficiency of damage to genome loci by subthreshold radiation is associated with the combined deformation of local RNA regions (the increase coefficient can be 1000 or more). The damage effect itself is a Coulomb explosion caused by the Auger cascade in the phosphorus atom. It seems that the SARS-CoV-2 and COVID-19 facilities clearly exhibit the properties of systems that are the prerogative of the COMPLEXITY approach- isn't that the difficulty of dealing with them?!

Conclusion: prospects for the application of Auger destruction in biological objects.

Radiation technology, one of the types of which is the effect of X–rays on matter, is discussed in this paper and represents an outstanding method even against the background of the variety of different directions of nanotechnology [15]. This is due to a number of fundamental circumstances. First of all, radiation exposure has a huge number of variants of irradiating particles (photons, electrons, mesons, protons, neutrons, ions, fission fragments, etc.). The parameters of these irradiation options are very diverse and adjustable: by the amount of energy and its spectrum, intensity, dose, chirality, coherence, etc. Thus, with the help of irradiation, it is possible to "drive" any substance into states that are unattainable by thermal means.

When it comes to radiation nanotechnology, three conditions must be met:

1. The structure of the irradiation object should have at least a hierarchy;
2. The effect of a gigantic increase in primary excitation should be realized;
3. The effects are especially pronounced in the case of strong disequilibrium of experimental conditions.

It is these three positions that are perfectly realized in biological environments exposed to so-called subthreshold ionizing radiation (in particular, X-rays).

The phenomenon of Auger destruction considered by us, accompanied by various effects, fully satisfies the specified criteria of radiation nanotechnology.

It should be noted that in the case of irradiation, the so-called synergism phenomenon is very often realized [16], when the **simultaneous action** of several external factors (one of which is radiation) leads to strong nonlinearity and enhanced irradiation results. The classic examples found are the following.

1. In the wild - in oncological diseases, ionizing X-ray radiation is used in combination with high-temperature heating ($T > 42^0C$) in the wild;

2. For inanimate nature, an extremely promising analysis of the operation of a Large Solar Furnace in which four factors of influence interact at once (a wide energy spectrum of solar radiation, its extremely high intensity, high temperature and its negative gradient from the center of the focal spot along the radius of the object).

It is important to note that synergism [16] together with synergetics [17] quite successfully fall under the general concept of Complexity [18].

Thanks.

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