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Risks of transmission of blood-borne viral infections via blood transfusion, organ and tissue transplantation

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The article presents the data on the rates of blood-borne viral infections (BBVI) in potential organ donors and blood donors at the N.V.Sklifosovsky Research Institute for Emergency Medicine in the period from 2008 to 2014. Differences in BBVI rates and multidirectional trends in the proportion of infected individuals were seen in different age groups of blood donors and potential organ donors. We analyzed the established algorithm for laboratory testing of potential organ donors for BBVI in the Russian Federation and major risks for BBVI transmission in organ and tissue transplantation. We have shown that the current algorithm of screening for BBVI in organ donors does not detect these infections during a "window period", nor their occult forms. We studied the causes of occult BBVI forms and their significance for clinical transplantation.

Keywords: blood donor, potential organ donor, blood-borne viral infections, HIV-infection, PCR, occult hepatitis B.

Introduction

Organ donation in Russia constitutes a serious challenge due to the shortage of donor organs, improper management of available potential organ donors, and a continuously growing number of patients in need for transplantation [1-4]. A large number of potential organ donors are discarded because of the presence of absolute medical contraindications. The most common cause for discard from donation is the presence of a *BBVI* in a donor, including human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C (HCV). According to data presented by N.D.Yushchuk et al. [5], from 3 to 5 million people with chronic HBV infection, and from 1.5 to 3 million people with chronic HCV infection reside in Russia nowadays. The epidemic situation with spreading HIV infection remains extremely tense [6].

Under the current legal acts and regulations, only the patients of Resuscitation Wards or Intensive Care Units (ICUs) in whom the clinical evidence of brain death or circulatory arrest have been documented can be considered potential organ donors [3]. However, such patients were found to have higher rates of BBVI laboratory markers than patients from any other clinical department [7]. The issue is particularly important for emergency clinics and hospitals participating in the Programme of organ donor selection and regularly admitting patients with various injuries incompatible with life, including the patients positive for BBVI. A high prevalence of infectious diseases among potential organ donors entails a high epidemic risk of infection transmission from donor to recipient while transplanting an infected organ or tissue.

The laboratory screening of potential organ donors for the presence of BBVI is exercised in Russia in accordance with the *Regulations on medical*

screening of blood, plasma, and blood cell donors approved by the Russian Healthcare Ministry on 16.11.1998, and being already outdated. [8]. This document stipulates testing for BBVI serological markers only, using enzyme immunoassay (EIA) systems recommended by the Russian Federation Healthcare Ministry for screening the blood, organ and tissue donors. The main screening markers include: anti-HIV antibody/antigen for HIV infection, HBV surface antigen (HBsAg) for HBV infection, and anti-HCV antibodies for HCV infection.

The outdated Regulations have been replaced by a new Procedure for the medical screening for the donors of blood and its components (the RF Healthcare Ministry Order № 364 of 14.09.2001 *"On approval of the medical screening for the donors of blood and its components"*, the RF Healthcare Ministry Order № 175n of 16.04.2008 *"On Amendments to the RF Healthcare Ministry Order № 364 of 14.09.2001 "On approval of the medical screening for the donors of blood and its components"*) that mandates additional testing of donated plasma for nucleic acids of HIV, HBV, and HCV.

Of note, while using serology blood tests only for donor screening, the risk of BBVI pathogen transmissions from the donor to a recipient still remains [9-14]. This statement is true both for donor testing by means of EIA during the "serological window period", and for the cases of latent (silent, occult) BBVI infection. Latent infections remain a crucial problem for transplantation due to the risk infection transmission from the donor whose disease is not detectable in clinical or laboratory examination.

The objective was to analyze the risks of BBVI transmissions via blood transfusion, organ and tissue transplantation.

Material and Methods

According to Letter № 21181405 of Moscow Healthcare Committee of Health Moscow dated 02.12.1996, the Laboratory of Clinical Immunology of the N.V.Sklifosovsky Research Institute for Emergency Medicine was designated to test for BBVI the serum samples taken from potential donors and delivered from Moscow Organ Donation Coordination Center (MODCC), and taken from the blood donors in the N.V.Sklifosovsky Research Institute for Emergency Medicine. The standard serological screening of donors involves tests for HIV infection (anti-HIV antigen and antibodies), for HBV (HBsAg), HCV (anti-HCV antibodies of classes IgM and IgG), and for syphilis (tests using cardiolipin antigen, and tests for detecting specific antibodies to *Treponema pallidum*). According to existing Regulations, in addition to the standard testing procedure for infectious diseases in the biological material, the blood samples of organ and tissue donors from MODCC are tested for laboratory markers of hepatitis A (Anti-HAV antibodies of IgM class), and CMV infection (anti-CMV antibodies of classes IgM and IgG). Blood donors are additionally tested for BBVI by applying a molecular biology technology, namely the polymerase chain reaction (PCR) in real time (Real-time PCR), using Cobas 201 system, Roche Diagnostics (Switzerland), or using transcription-mediated amplification (TMA) technique, Procleix Panther system, Novartis Diagnostics (Switzerland).

We retrospectively reviewed the results of screening for BBVI in blood donors and potential organ donors for the period of 2008-2014. The prevalence of mono- and multiple BBVI cases was assessed by the absolute number of detected infection cases, the detection rate (F), calculated as the number of identified individuals positive for an infection per 100 screened

donors, and the index of the total detection rate F_{sum} (F_{HIV} + F_{HBV} + F_{HCV} + $F_{syphilis}$). The detection of laboratory markers for multiple BBVI was defined as the fact of more than one infectious diseases simultaneously (mixed infection). Statistical data processing was performed using Graph Pad Prism 6 Software (Graph Pad Software, USA). The statistical significance of differences in BBVI detection rates between the compared groups of donors was assessed using χ^2 test (Pearson's Chi-squared test, two-tailed P values). The differences were considered statistically significant at 95% probability ($p < 0.05$).

Results

In the period from 2008 to 2014, 3479 blood serum samples from potential organ donors and 75,622 blood serum samples from blood donors were tested for BBVI laboratory markers in the Laboratory Diagnostic Department of the N.V.Sklifosovsky Research Institute for Emergency Medicine (Table. 1, 2). The BBVIs detected in potential organ donors in the study period were the following: HIV infection in 1.1% of cases (n=38), HBV, HCV infections, and syphilis in 2.8% (n=97), 11.5% (n=399), and 5.1% (n=176), respectively. Mixed BBVIs were documented in 1.5% (n=53) of cases (Table.1). The most common mixed infection detected (70% of the total number of detected mixed-forms) was the combination of HIV and HCV infections. In the study period, the total detection rate for BBVI mono-infection ranged from 19.2 to 23.5%, and the detection rate of mixed infection was significantly lower and ranged between 0.9-1.9%. In potential organ donors, the detection rate of laboratory markers for HCV infection was many-fold higher ($p<0.0001$; Pearson's Chi-squared test, two-tailed P values), than those for HIV and HBV infections. No statistical significant

differences between the detection rates of HIV and HBV infections were observed. A 14.6% increase in the detection rates of monoinfection in potential organ donors was observed in 2014 when compared to 2008.

Table 1. The results of testing potential organ donors for blood-borne viral infections (BBVIs).

Infectious disease test/ Year	2008		2009		2010		2011		2012		2013		2014	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
HIV	5	10	10	20	6	eleven	3	0.6	7	15	5	10	3	0.6
HBV	16	3.1	9	18	13	2.4	20	3.8	14	3.1	17	3.5	10	2.1
HCV	48	100	54	11.0	66	12.0	67	12.8	57	12.4	66	13.6	55	11.5
Syphilis	26	5.3	22	4.5	29	5.3	32	6.1	thirty	6.5	21	4.3	16	3.4
HBV + HCV	1	0.2	2	0.4	1	0.2	2	0.4	4	0.9	1	0.2	1	0.2
HIV + HCV	5	10	4	0.8	4	0.7	7	13	4	0.9	8	16	5	1.1
HIV + HBV + HCV	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2
HIV + HBV	1	0.2	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Negative for BBVI markers	388	79.2	392	79.3	430	78.3	392	74.8	343	74.7	369	75.8	385	80.9
Total tested	490	100	494	100	549	100	524	100	459	100	487	100	476	100

The incidence of BBVI among potential organ donors in different age groups had differently directed trends over time showing a statistically significant decrease in the proportion of infected donors in the age group under 30 years old ($p < 0.05$; Pearson's Chi-Squared test for trend, two-tailed P values), and the increase in other age groups (Table. 3). The detection rate of infection markers in men was significantly higher ($p<0.05$) in all age categories.

The results of testing serum samples from blood donors in the N.V.Sklifosovsky Research Institute for Emergency Medicine, by using

serological and molecular biology diagnostic methods are presented in Tables 2 and 4. During the study period, HIV infection in blood donors was found in 0.08% of cases (n=57), HBV-, HCV-infection, and syphilis were detected in 0.15% (n=117), 0.5% (n=348), and 0.2% of cases (n=185), respectively. Mixed BBVI forms were documented in 0.005% of cases (n=4). Total infection detection rate varied from 0.5 to 2.7% for mono-BBVIs, and from 0 to 0.02% for mixed forms (Table 2). In contrast to the potential organ donors, the total detection rate in blood donors had a statistically significant downward trend during the study period ($p<0.0001$; Pearson's Chi-Squared test for trend, two-tailed P values), and decreased from 2.66% in 2008 to 0.50% in 2014, i.e. 5.3-fold.

Table 2. The results of testing blood donors for the presence of blood-borne viral infections

Infectious disease test/Year	2008		2009		2010		2011		2012		2013		2014	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
HIV	6	0.10	eleven	0.12	8	0.08	7	0.06	8	0.06	eleven	0.08	6	0.05
HBV	31	0.53	33	0.37	17	0.17	15	0.13	5	0.04	9	0.07	7	0.05
HCV	65	1.12	69	0.77	46	0.46	41	0.37	34	0.25	53	0.40	40	0.31
Syphilis	53	0.91	35	0.39	35	0.35	18	0.16	23	0.17	10	0.08	eleven	0.09
HBV + HCV	0	0.00	0	0.00	1	0.01	0	0.00	0	0.00	0	0.00	0	0.00
HIV + HCV	0	0.00	1	0.01	1	0.01	0	0.00	0	0.00	1	0.01	0	0.00
HIV + HBV + HCV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
HIV + HBV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Negative for BBVI markers	5667	97.34	8792	98.33	9943	98.93	11056	99.27	13427	99.48	13181	99.37	12845	99.50
Total tested	5822	100	8941	100	10051	100	11137	100	13497	100	13265	100	12909	100

Table 3. The detection rate of BBVI markers in potential organ donors in different age groups

Year / Age group	18-30		31-40 years		41-50 years		51-60 years		Over 61 years		Total number of donors with BBVI	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
2008	34	33.3	31	30.4	27	26.5	9	8.8	1	10	102	100
2009	28	27.5	33	32.4	21	20.6	18	17.6	2	20	102	100
2010	33	27.7	37	31.1	29	24.4	18	15.1	2	1.7	119	100
2011	23	17.4	50	37.9	41	31.1	17	12.9	1	0.8	132	100
2012	19	16.4	48	41.4	34	29.3	15	12.9	0	0.0	116	100
2013	22	18.6	43	36.4	31	26.3	20	16.9	2	1.7	118	100
2014	14	15.4	35	38.5	25	27.5	15	16.5	2	2.2	91	100

Table 4. PCR/TMA test results of seronegative blood samples

Number of tests	Number of samples containing genetic material		
	HBV DNA	HIV RNA	HCV RNA
10,570	1	2	1

Molecular biology assays used for screening the donor blood samples, detected HBV DNA in 0.02% of cases, HIV RNA, and HCV RNA in 0.01% each, respectively (Table 4). In all the cases, alanine aminotransferase (ALT) levels were within normal range. In one donor who had HBV DNA detected in serum, and negative serology test for HBsAg, the antibodies for HBV capsid antigen (anti-HBc) IgG class were additionally found that was considered the evidence of chronic HBV infection (Table 5).

Table 5. Serological markers of donor blood positive for HBV DNA

No.	Screening test results for HBsAg (test-system sensitivity of 0.05 ng/mL)	PCR screening test results for HBV DNA	Anti-HBc	ALT
Donor No. 1	-	+	n / a	Normal
Donor No. 2	-	+	+	Normal

While analyzing the BBVI incidence in blood donors of different age groups, a statistically significant trend ($p<0.0001$; Pearson's Chi-Squared test for trend, two-tailed P values) to the increased proportion of infected donors was identified in the age group under 30 years old: from 20.6% in 2008 up to 50% in 2014 (Table 6). Comparison of mono- and mixed BBVI detection rates revealed the values of potential organ donors exceeding the values of blood donors in certain years by 25 times for HIV infection, 84 times by HBV, by 49 time for HCV, by 57 times for syphilis, and by 212 times for HIV + HCV.

Table 6. The detection rate of BBVI markers in blood donors in different age groups

Year / Age group	18-30		31-40 years		41-50 years		51-60 years		Over 61 years		Total number of donors with BBVI	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
2008	32	20.6	37	23.9	21	13.5	10	6.5	2	13	155	100
2009	36	24.2	53	35.6	35	23.5	23	15.4	2	13	149	100
2010	34	31.5	35	32.4	26	24.1	12	11.1	1	0.9	108	100
2011	thirty	37.0	20	24.7	26	32.1	3	3.7	2	2.5	81	100
2012	28	40.0	17	24.3	7	100	4	5.7	0	0.0	70	100
2013	37	44.0	21	25.0	21	25.0	3	3.6	1	12	84	100
2014	32	50.0	16	25.0	10	15.6	5	7.8	1	16	64	100

Discussion

Blood transfusion is one of the most common forms of tissue transplantation in medicine. Early in the XX century, a shortage of blood donors prevented a widespread blood transfusion. In 1930, doctor S.S.Yudin from the N.V.Sklifosovsky Institute for Emergency Medicine made attempts to solve the problem of donated blood shortage in the clinical practice by transfusing the blood from a suddenly died person. The idea of such blood transfusion was borrowed from doctor V.N.Shamov after his series of successful experiments performed on laboratory animals [15].

In those years, a number of important questions were addressed to the doctors with regard to the existing risk of syphilis transmission in blood transfusions from a suddenly died patient. One of the questions was related to the infectious safety of transfused blood, another one was concerned with the urgency of blood transfusion [15]. When discussing the infectious safety of blood transfusion from a patient who died suddenly, Professor V.N.Shamov expressed his point of view to Doctor S.S.Yudin "... There have not been a case yet when the blood transfusion on life-saving indications would have been refused by the patient concerned or his/her relatives only because there was no time to investigate the blood donor for syphilis. A probable risk of getting infected is better than an almost sure death". [15] Since in cases of using blood from a suddenly died patient, in addition to serological tests, the autopsy was also performed, that provided a thorough study of all organs for syphilis, thereby most possibly minimizing the risk of transmission. The research group headed by Doctor S.S.Yudin actively worked at improving the laboratory screening for syphilis and

managed to reduce the time necessary to obtain Wasserman Reaction results from 24 to 4 hours [15].

By the end of XX century, transplantation had been started as a new, actively developed field in a clinical medicine. So, the issue of infectious safety of donor organs and tissues became even more crucial. The screening of organ and tissue donors for syphilis was supplemented with tests for HIV infection, viral hepatitis, and herpes virus infection [16]. The inclusion of tests for these infections in donor screening procedure was of great medical value, since while making the decision on transplantation, it was essential to eliminate the risk of a donor-derived infection in a recipient via transplanted organs or tissues.

The very essence of the treatment process is to treat rather than to infect, so getting infected is absolutely unacceptable.

Today there are many methods to diagnose BBVIs, the enzyme immunoassays (EIA) being the most commonly used. Serologic diagnostic techniques can detect HIV infection at 2-3 weeks after getting infected, HBV, and HCV infections at 6, and 9 weeks, respectively [17, 18]. The implementation of nucleic acid amplification technologies (NAT) shortened the diagnostic "window period" of HIV, HBV, and HCV infections to 9, 20, and 7 days, respectively [18]. However, mandatory screening for BBVIs by means of PCR does not guarantee a 100% protection from transmission. This is primarily due to the fact that the screening of donated blood by NAT is often performed in mini-pools. With a low viral load, the sample dilution in the process of the mini-pool formation can lead to false-negative results. Thus, the viral load in the occult HBV infection rarely exceeds 200 copies/mL and averages from 32 to 62 copies/mL [19], the viral load of HCV infection ranges from 10 to 200 copies/mL [12]; all that may hinder

the virus detection by a number of commercially available PCR test-systems. A case report published in Germany in 2009 described the fact of HIV infection transmission from the serologically and NAT negative donor to the recipient as a result of transfusing the washed red blood cells. A further epidemiological investigation found the sensitivity of automated PCR system for HIV RNA detection in mini-pools appeared inadequate to detect the viral RNA [10].

The causes of obtaining false negative results for BBVI markers can be associated with the presence of mutant or recombinant BBVI forms [20-23]. Most commercially available test-systems have been designed to identify specific genotypes and subtypes of "wild-type" virus, but the efficacy of detecting mutant forms may vary. For example, a large number of mutants and variants (escape mutants) of HBV infection have been described, their distinguished feature being the expression of HBsAg with atypical serological properties. The surface antigen with atypical serological properties can not be detected reliably by standard commercially available EIA (immune chemiluminescence) test-systems [22, 24, 25].

The Laboratory of Clinical Immunology of the N.V.Sklifosovsky Research Institute for Emergency Medicine developed an algorithm to identify/search for serologically relevant mutants of HBV infection and comparatively assessed the diagnostic potential of commercially available test-systems [24]. A number of test-systems seemed unable to confirm/ reproduce the specification-stated sensitivity characteristics and the ability to detect HBsAg mutant forms while testing the native blood serum samples containing HBsAg escape mutants [21].

Highly sensitive EIA test-systems allow HBsAg detection in blood serum in a concentration of 0.01 ng/mL. The use of such test-systems allows revealing the incidence of latent HBV infection [23].

The most common causes of the infection taking a latent form include the low levels of the viral replication, the expression of viral proteins, and also the specific features of human immune system functioning [12, 23].

Latent HBV infection is most common in the individuals who previously suffered from acute hepatitis B or who have a chronic form of the disease and lost HBsAg. The presence of latent HBV infection in organ donors frequently leads to virus reactivation and the occurrence of new *(de novo)* infection in the recipient after transplantation. According to literature reports, from 17 to 94% HBsAg-negative/anti-HBc-positive donors can transmit HBV infection to recipients in orthotopic liver transplantation [26]. In 2008, the experts from the European Association for the Study of Liver Diseases (EASL) defined *the occult or latent hepatitis B virus (HBV) infection* as "the presence of HBV DNA in the liver with HBV DNA detectable or not in the serum, without detectable HBsAg by available methods" [27].

Published in 2014 data on the high prevalence of latent HBV infection (anti-HBc^+/$HBV\ DNA^-$ in blood, and HBV DNA detected in the biopsy) in liver donors in Russia dictate the necessity to modify the currently used algorithm of laboratory testing for hepatitis B in potential organ donors [28, 29].

The antibodies for capsid protein, i.e. anti-HBc antibodies provide an additional serological marker that indicates the presence of current or previous HBV infection. Anti-HBc is the HBV infection marker that is not ideal, as stated by the EASL Expert Group, but it is the recommended

marker to be used in case where testing for HBV DNA is not available, e.g. in case of organ donation [27]. According to RF Epidemiologic Surveillance Regulations SP3.1.1.2341-08 on "Viral hepatitis B prevention", the individuals with a past history of HBV, regardless of disease duration and etiology, and those positive for HBV serological markers (HBsAg, anti-HBc IgM, anti-HBc, anti-HBs, HBeAg, anti-HBe, and HBV DNA) are not allowed to donate.

Occult (seronegative) HCV infection can occur in chronic hepatitis of unspecified etiology, in the families where one of the spouses has a chronic HCV infection, and among apparently healthy population [30-32].

Raised normal ALT levels make one of the causes to reject blood donation on medical grounds and the main reason for discarding the donated blood [33]. According to WHO guidelines, ALT is a non-specific marker of infection, providing no identifiable benefits in terms of improving blood safety [34]. However, a number of authors, on the contrary, believe that the ALT activity testing has not lost its diagnostic relevance and does prevent post-transfusion infection cases after negative tests for BBVI laboratory markers, including the transfusion of non-quarantined blood components: red cells, platelets [35].

Considering the problem of organ donation infectious safety, it is necessary to address the issue of the donor population characteristics in blood donors and potential organ donors. Many published reports in Russia presented the studies of the medical and social portrait of a modern blood donor, his/her motivation, and factors influencing donor's activity [36-38]. The studies have demonstrated the vast majority of blood donors, being working people or students, have the main motivation of altruistic blood donation [39].

Existing Russian algorithm for the medical selection of blood donors that considers the health and social status of the donor, the presence of harmful habits (alcoholism, drug addiction), signs of antisocial behavior, the possibility of multiple screening, in terms of the current practice of quarantine and virus-inactivation of blood components may ensure a maximum infectious safety of blood donations.

Meanwhile, the algorithm for the selection of potential organ donors differs from the one for blood donors. Organ donation, as a rule, takes place as a result of a casual injury, a traffic accident, fall from a height in condition of alcohol intoxication, acts of violence or self-aggression, etc. Such injuries may frequently be considered a consequence of a certain social behavioral model of the individual that is assessed as deviant behavior not subjected to liability and not requiring a mental health specialist intervention [40]. Most often, such people are prone to antisocial and risky behavior, alcoholism, substance abuse, high-risk sports. [41]

Often, some mental disorders may underlie getting injuried. According to data from Rospotrebnadzor (*the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Well-being),* in the first quarter of 2015, 61.3% of all deaths from mental disorders occurred in alcoholic psychoses, mental and behavioral disorders due to alcohol abuse. [42]

The current RF legislation stipulates that the organ retrieval may be undertaken after the consent from the patient or his/her family has been obtained, or in accordance with the "presumed consent" [43]. In the latter case, the decision about organ retrieval shall be taken by medical personnel who may not possess a complete information on infectious diseases, mental and social status of the patient. The healthcare providers primarily consider

somatic rather than social characteristics of the individual. With the development of innovative medical technologies, transplantologists have gained the opportunity to use the pool of potential donors who were previously considered ineligible for donation, i.e. "extended criteria donors" (ECDs), including those with a marginal behavior [44] that, in turn, entails an increased risk of infectious agent transmission from the donor to a recipient. In opinion of some experts, a possible alternative to such donor population could be the patients with cerebrovascular diseases and stroke whose mortality is rather high outside the Resuscitation Wards and Intensive Care Units (ICUs) [3, 45].

Limitations existing in the preservation of donor organs pose two main tasks for a screening laboratory, specifically to make investigations in short terms and to get highly reliable results. Some authors consider a high number of identified BBVIs among potential organ donors to be the result of laboratory over-diagnosis [46]. As demonstrated, the causes of false-positive or questionable reactions for BBVIs could be non-specific interactions of EIA test-system components with free hemoglobin in terms of blood hemolysis [47]. However, more recent studies could verify neither the cases of laboratory over-diagnosis, nor the effect of hemolysis on the quality of the obtained result [48, 49].

Conclusion

Ensuring infectious safety of donor organs and tissues is a pressing global problem, and directly depends on a through medical selection of donors and the reliable laboratory testing of blood donations. Innovative technologies enabling to warrant the infectious safety of donated blood and blood components are actively implemented and used. Legal regulations on

the selection of potential organ donors and their laboratory screening for BBVIs need update and further revisions to meet the criteria of currently advanced clinical medicine, and follow the requirements for infectious safety of donations. An earlier solution of the above problems would reduce the risks of BBVI transmission and improve the infectious safety of transplanted organs and tissues in the short term.

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