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Plasma-Induced Enhanced Coagulation and Complement Activation of Blood Streams by Platinum Nanoparticles

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ABSTRACT

Catalytic converters have now been largely employed to significantly reduce the levels of carbon-based particles into the atmosphere, however, this approach generates nanoparticles (NPs) that are often released as fine airborne particles into the atmosphere, having abilities to remain suspended in the atmosphere for long durations and find their way into the human lung cells, and eventually into the blood stream. This could result in triggering the body's innate immune system. In this study, we exposed blood samples from healthy individuals to Platinum nanoparticles and compared the results to the effects induced by the thrombogenic TiO_2, to investigate the response mechanisms of the blood cells and innate immune system to these particles. Results showed a clear activation of coagulation system in samples treated with both NPs, compared with untreated blood samples. TiO_2 NPs had significantly higher coagulation effect (84% platelet consumption) compared to the platinum NPs (38% platelet consumption), while blood samples without NPs showed only a 14% platelet consumption. Also, TiO_2 NPs and Pt NPs induced slightly similar complement activation in blood samples as measured from the generated C3a (921±16.70 µg/L and 826±27.50 µg/L respectively) and sC5b-9 (136±3.46 µg/L and 138±6.49 µg/L respectively) components. However, blood samples without NPs exhibited significantly lower C3a and sC5b-9 components (522±22.50 µg/L and 101±4.70 µg/L respectively). The latter demonstrated the potential risks exposed to by urban dwellers, such as cascading inflammatory and thrombotic responses, there is need for more investigation on the patho-serological events that can be triggered by other airborne fine particles.

***Keywords*:** Platinum nanoparticles, Whole blood model, Contact system, Innate immunity and Hematology.

Introduction

Catalytic converters have now been widely used to significantly reduce the levels of carbon-based particles into the atmosphere due to the automobile industry's continuous growth. However, this hasn't entirely solved the problem of air pollution because these catalytic converters typically result in the emission of high numbers of NP materials into the atmosphere.[1,2] Inhaled airborne nanoparticles (NPs) easily make their way into the alveolar, where they can cause severe damage. [3] Typically, cells involved in immune system such as the macrophages are triggered in response to these materials, especially in cases where there are high levels of air pollution with this particles.[3] Multiple lines of evidence have shown that the concentrations of these air-borne NPs (generally referred to as platinum-group elements (PGE)) have over time reached their upper safe limits.[4,5] However, very few research have looked at the possible harm that these particles could cause to the circulatory system's components and to inhalers. These NPs frequently go to the blood circulation after entering the lungs. [6, 7]

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Once the particles reach the circulatory system, absorption from the blood capillaries sets off the lymphatic system to remove them; this process includes immunity since it sets off a cascade system to remove foreign particles and cells from the system. It's interesting to note that these defense mechanisms might also recognize airborne particulates as foreign substances, which could set off several blood cascade mechanisms and perhaps cause thrombotic and inflammatory reactions.[8,9] Filipova (2022) opined that this response is only of importance before the inflammatory response begins as secreted molecular markers may react with these particles and modify the immune response at the onset of inflammatory response[10]. Previous studies have reported that foreign materials are known triggers of the contact system, typically initiated by coagulation factor (FXII).[10 -12] Other reports have demonstrated that the levels of Pt NPs in air directly correlates with the number of neutrophils and eosinophils in human nasal cavities, indicating upper airway inflammation and allergies respectively.[12]

Standard metal NPs such as silver, titanium oxide, cerium oxide, and zinc oxide have been reported to trigger pro-inflammatory behaviors in neutrophils[13,14]. Neutrophils, which are the major mediator for innate and adaptive immune responses, are known to release cytokines and chemokines as triggers to escalate an inflammatory response in the presence of foreign materials, while also engaging in communication with other immune cells such as monocytes, macrophages, and lymphocytes.[15,16]

Although many medical professionals have not actively investigated the use of platinum-based nanoparticles in medical applications, such as drug administration, their airborne prevalence, particularly in metropolitan settings, exposes commuters and residents to potentially large dosages of these materials. As can be seen from the above, there

is growing evidence that the unique physicochemical characteristics of nanoparticles may be harmful to human health. Therefore, it is imperative to investigate the precise mechanisms underlying these cells' responses to nanomaterials as well as how they react to them. This study used a human whole blood loop model to investigate the particles' impact on the blood's cascade systems because to the limitations of in vivo models, in part due to ethical considerations. This approach has been successfully tested by recent studies.[11]

Materials and Methods

Particle generation

Platinum nanoparticles (Pt NPs) were generated using platinum electrodes in a spark discharge particle generator (DNP 3000, Palas GmbH, Karlsruhe, Germany) and collected on polycarbonate filters (Nucleopore, 0.8 μm, 37 mm) for testing on whole blood systems. Stock suspensions of Pt NPs and TiO_2 (21 nm, Sigma Aldrich, Germany) NPs (1 mg/mL) were prepared in sterile normal saline solution and diluted appropriately for the experiments.[11]

Ethical considerations

Ethical approval for the study was obtained from the hospital management board on health issues in accordance with the code of conduct for biomedical research involving human subjects (Ethical clearance no:058).

Study population

This was a hospital-based cross-sectional study in which 200 consenting HIV positive patients on Highly Active Anti-retroviral Therapy (HAART) at the Grimard Hospital and Maria Goretti Hospital between January and April, 2017 were recruited using a non-probability convenient sampling technique. These hospitals run a weekly HIV/AIDS clinic and are the most utilized health facilities in the study area with a record of approximately 2000 HIV patients per year. Trained medical personnel in each hospital clearly explained the objectives/bene□ts of the study to the patients and only those who gave consent by completing and endorsing □lled-in questionnaires were consecutively recruited. Consenting attendees, male or female, aged 5 years and above who provided written informed consent were eligible for participation in the study. Ethical approval for the study was obtained from the hospital management board on health issues in accordance with the code of conduct for biomedical research involving human subjects (Ethical clearance no:058).

Study population

This was a cross-sectional study in which 30 healthy consenting adults were recruited. Volunteers were issued questionnaires to obtain their medical history, and only healthy volunteers that had not been exposed to substances that could influence the study results, at least 2 weeks to blood collection were recruited for the study.

Blood sampling

Trained medical personnel in Prince Abubakar Audu University Teaching hospital with a clear understanding of the study objectives of the study were recruited for sample collection. Peripheral venous blood was obtained from medically fit fasted volunteers,[17] into bottles devoid of anticoagulant substances. All containers and materials to be in contact with blood were pre-coated using Corline heparin surface (CHS) (Corline Biomedical AB, Sweden) to prevent material-induced blood activation.

Whole blood model

A slightly modified whole blood model was adopted to examine the effects of Pt NPs in contact with blood. [18] Commercially available tubings (2 mL) (Medtronic Inc., USA) sealed with a plastic cap at either ends were used in this study. Briefly, the 2 mL tubes were filled with 1.5 mL of freshly collected human whole blood. Suspensions of the Pt and TiO_2 NPs were prepared in 150 mM NaCl and exposed to ultra sound treatment for 5 min immediately before adding to the blood to ensure that nanoparticles came in contact with blood as single particles. Ten microliter (10 μL) aliquots of the particle suspensions were added to the tubes resulting in a final concentration of 10 μg/mL of each particle type. The same volume of NaCl was added to separate blood samples from the same donor devoid of any NPs to demonstrate the effects of these particles on blood parameters. Inoculated samples were left under constant rotation at 30 rpm for 1 hour at 37ºC. To halt the effect of the test particles and prevent further activation of blood cascade system, EDTA (10 mM final concentration) was added to the samples. Plasma was prepared by centrifugation the tubes at 2500 xg for 15 min and thereafter stored at −70 ◦C until further analysis. The experiments were repeated three times with different blood donors.

Platelet count

The platelet titer were examined using a Sysmex XP-300 Haematology Analyzer (Sysmex Inc. USA) after incubation and recorded accordingly.

Thrombin-Antithrombin complexes ELISA

The levels of Thrombin-Antithrombin (TAT) complexes in the plasma collected from the whole blood experiments were analyzed using the sandwich ELISA (Thermo Fisher Scientific, UK). The TAT complexes were sequestered with a sheep anti-human thrombin antibody (Enzyme Research Laboratories, USA) and detected using horseradish peroxidase (HRP)-conjugated anti-human antithrombin antibody (Enzyme Research Laboratories, USA). Pooled human serum diluted in phosphate buffer with 1% BSA, 0.05% Tween and 10 mM EDTA was used as a standard. Equally, the buffer was used for dilution of the samples and for blocking of the microtiter plates.[11]

C3a and sC5b-9 ELISA

Sandwich ELISA (Thermo Fisher Scientific, UK) was done to measure the levels of the NPs-induced complement activation markers C3a and soluble sC5b-9 as described in previous studies[19]. C3a ELISA was carried out using mouse monoclonal anti-C3a SD17.3 for capture and a biotinylated rabbit polyclonal anti-C3a antibody followed by Streptavidin (SA)-HRP for detection. Also, sC5b-9 ELISA was carried out using the anti-neoC9 monoclonal antibody aE11 for capture, and biotinylated polyclonal anti-C5 antibody and SA-HRP for detection. For a standard, diluted Zymosan activated serum was used in both assays.

Kallikrein-C1inhibitor complexes

To measure the levels of formed kallikrein-C1-inhibitor complexes (KK-C1INH) ELISA was performed (Thermo Fisher Scientific, UK), a polyclonal goat anti-human KK antibody was used and a biotinylated rabbit anti-human C1INH pAb followed by an SA-HRP for detection. Standards were prepared from complexes with purified KK-C1INH (using a molar excess of C1INH) diluted in freshly drawn lepirudin plasma[11].

Data analysis

Graphpad Prism software was used for statistical analysis. Data are presented as the mean standard error of the mean (SEM). Similarities were tested on a two-way ANOVA using Tukey's multiple comparison test, with mean differences considered significant at *P < 0.5, **P < 0.01, ***P < 0.001 and ****P < 0.0001. Differences between means were further elucidated using the confidence interval plots.

Results and Discussion

The platelet numbers decreased after the addition of Pt NPs to human whole blood for 1 hour compared to the initial levels before incubation, indicating an activation of the platelets (Figure 1a). The average decrease in platelets among the different blood samples was about 38% after incubation with Pt NPs. This is significantly lower compared to the 84% platelet consumption measured in the blood samples incubated with the positive control TiO_2 NPs. In the negative control tubes incubated with blood, a minor decrease in platelet number of 14% was detected (Figure 1a). To investigate if the Pt and TiO_2 surfaces activate FXII directly upon contact, adsorption model of FXII to these NP

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materials were studied using the QCM-D. Results of this investigation is displayed in Figure 1c; Our results showed that FXII bound to both NPs, with more FXII on the TiO_2 surface (760 ng/cm2) compared to that of Pt (450 ng/cm2). We also observed that only FXII adsorbed to TiO2 could bind C1INH (300 ng/cm2), while no C1INH bounded to FXII at the Pt surface. Results showed that Pt NPs induced slightly higher C3a generation compared to the control samples, however, there was a significantly higher C3a levels in blood samples incubated with TiO_2 NPs (Figure 2a). The levels of sC5b-9 in the samples were also investigated and results showed a similar pattern where there were only slight differences among the blank samples and the samples incubated with Pt and TiO_2 NPs, which were all significantly different from those of the initial samples. (Figure 2b).

Measuring the TAT complexes was also carried out to further examine the activation of the coagulation system after blood contact with Pt and TiO_2 NPs and in the control tubes (Figure 2c). Results showed that a relatively low level of TAT was generated by the Pt NPs (ca 3142 µg/L) when compared to the massive increase of TAT generated in the samples incubated with TiO_2 NPs (ca 10,260 µg/L). We also found that the TAT levels much lower in both the initial samples collected before incubation (ca 26 µg/L) and in the in the control samples, with no NPs addition (ca 85 µg/L). These variations were not so pronounced throughout this study, however, the ratio between the NPs incubated samples and the control was the same throughout our experiments, regardless of blood donor.

Measurement of the KK-C1INH complexes in the blood samples after incubation with the NPs showed that TiO_2 NPs induced the highest levels of KK activation, compared to Pt NPs that gave a significantly lower increase (Figure 3). The KK activation in the control sample was not significantly different from the initial blood sample, with the initial blood sample possessing a slightly higher KK activation than the control sample.

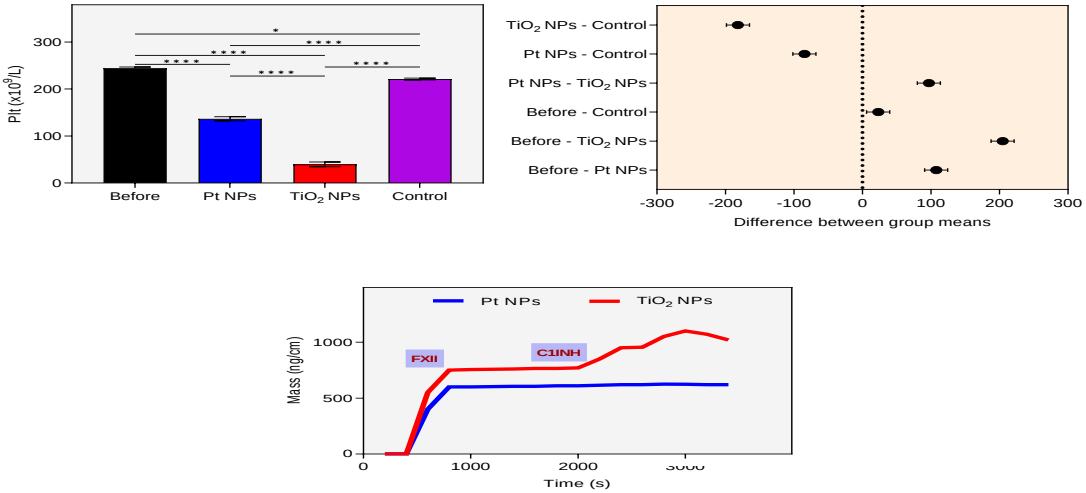

Figure 1: (a) Effect of Pt and TiO_2 NPs on blood platelet activation measured in platelet reduction number **(b)** Tukey simultaneous 95% confidence intervals plot **(c)** QCM-D analysis of FXII binding to Pd and TiO2 surfaces and the subsequent FXII activation monitored as its ability to bind C1INH. Values are represented as means and standard deviations. * $p < .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$, ns not significant ($p > .05$).

In this study, we simulated the inflammatory responses that are likely to be induced by the exposure of while blood to Pt NPs. The Pt NPs were generated using a spark discharge particle generator [20] and experiments carried out to determine these NP's effects on the coagulation and humoral cascade systems in human blood samples. While researchers have majorly focused on dealing with the challenge of scaling up nanoparticle production to support contemporary medical applications, understanding the potential long-term effects of nanoparticles on the human body, especially the blood system, is crucial to checking inadvertent harm to exposed patients. Many studies have reported diverging results on the cytotoxic effects of Pt NPs on different cell lines, with many reports showing mild to critical cytotoxic effects;[21,22] even though earlier studies had shown no cytotoxic effects of these particles on tested cell lines.[23,24] To evaluate the immediate effect of Titanium NPs on human blood, we included TiO_2 NPs in the experiments as a positive control; they have been previously reported to induce strong coagulation activation in human whole blood.[25,26] In all the parameters tested upon exposure of human whole blood to both NP materials, our findings showed significantly high coagulation activation effects compared to the blood samples before exposure to the NP materials as well as the control samples. The response observed from the control samples could because of a weak contact system/KKS activation, which may occur on most surfaces over time.[11] However, the coagulation activation effects were considerably higher in blood samples exposed to TiO_2 NP compared to those exposed to Pt NPs. Other investigators have nonetheless reported contradictory observations, showing that administration of Pt NPs to human blood in vitro decreased inflammatory cytokine production in monocytes/macrophages, indicating that Pt NPs could circumvent the induction innate immune responses.[27] The authors described the anti-inflammatory inhibition as a possible consequence of Akt and extracellular signal regulated kinase-suppressed phosphorylation by pectin coated-PtNPs. These diverging findings may be because of the different physical and chemical properties of the specific NPs tested, which are critical factors that could influence the interaction of these materials with blood components.[18,28] The findings of this study indicate a higher risk of possible thrombosis and inflammation upon exposure to TiO_2 NPs, the significantly higher coagulation activations observed in Pt NPs treated blood samples compared to the controls indicates a potentially severe threat to continuous exposure to high doses of this common air-borne nanomaterials. The QCM-D analysis demonstrated clearly that the FXII, which was initially allowed to attach to the surfaces of both the Pt and TiO_2 NPs got activated only on the surface of the TiO_2 NPs with those on Pt NPs surface staying inactive. A very similar observation was made by Frommel and his colleagues,[11] where they also compared the same parameter using palladium nanoparticles; they posited that the reason why there was no activation in the QCM-D-measured system compared to the human whole blood is that there are other proteins in blood that can get attached to the surface of the Pt nanoparticle and induce activation,[29,30] the minor differences in C3a and sC5b-9 levels between the tested nanoparticles provide valuable insights into their interaction with the immune system. While the results suggest a generally consistent level of complement activation, understanding these nuances will be crucial for optimizing nanoparticle design for safe and effective use in various applications. These findings are in alliance with the report of other findings.[28] The findings of this study clearly highlight the potential risks involved with the exposure of

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blood to Platinum NPs i.e. inflammatory responses resulting from the high levels of coagulation and complement activation.

a less trigger compared to TiO_2 NPs, but of a potentially significant concern when observed from the outlook of results obtained with the control blood samples.

Conclusion

This study investigated the activation trigger effects of the Pt NPs and TiO_2 NPs on human whole blood. Our findings revealed that Pt NPs is

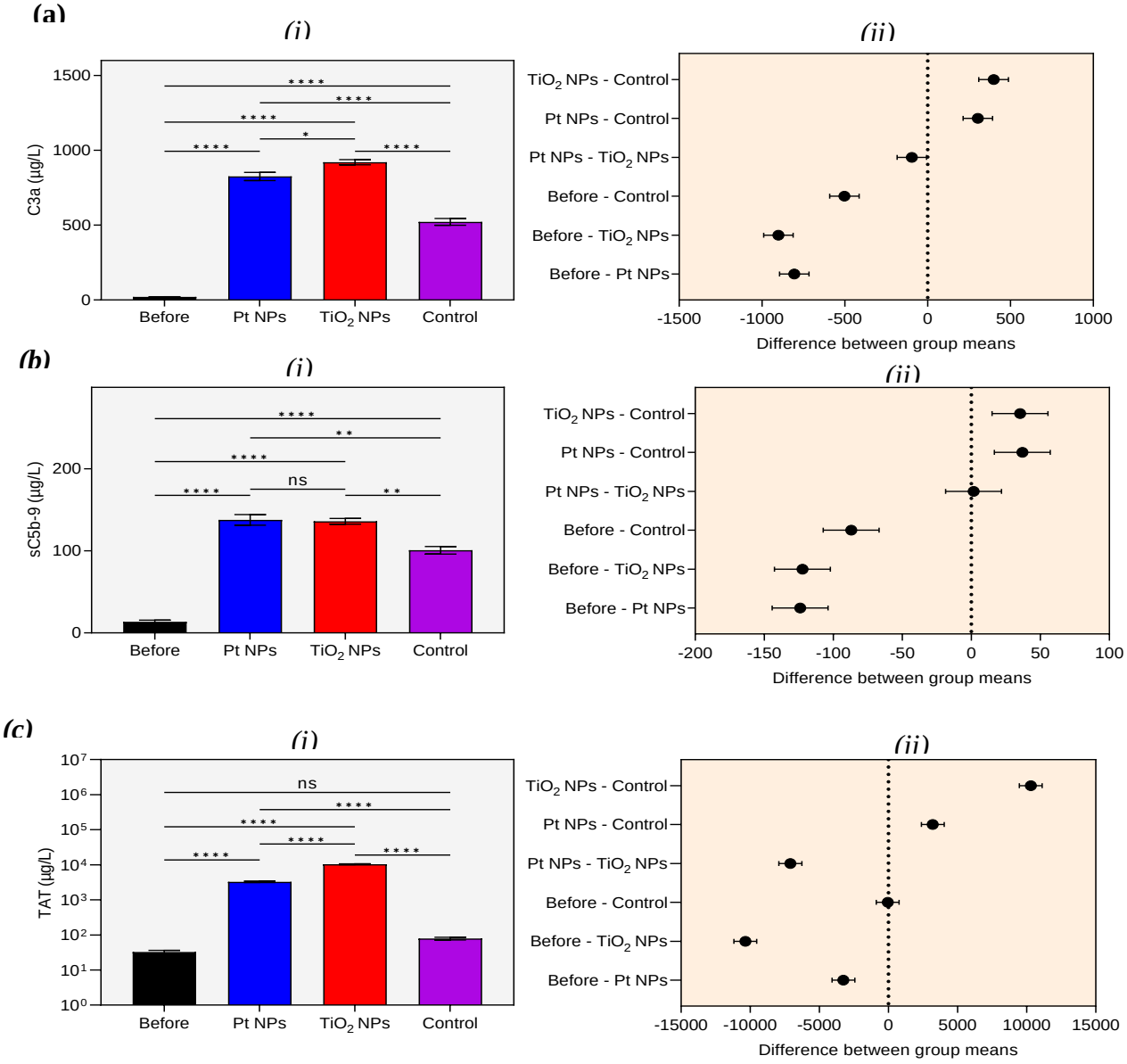

Figure 2: (a) Effect of Pt and TiO_2 NPs on complement activation maker C3a (i), and Tukey simultaneous confidence interval plots (ii) **(b)** Effect of Pt and TiO_2 NPs on complement activation maker sC5b-9 (i), and Tukey simultaneous confidence interval plots (ii) **(c)** Coagulation activation assessed using the levels of TAT formation (i), and Tukey simultaneous confidence interval plots. Values are represented as means and standard deviations. * $p < .05$, ** $p < .01$, *** $p < .001$, **** $p < .0001$, ns not significant ($p > .05$).

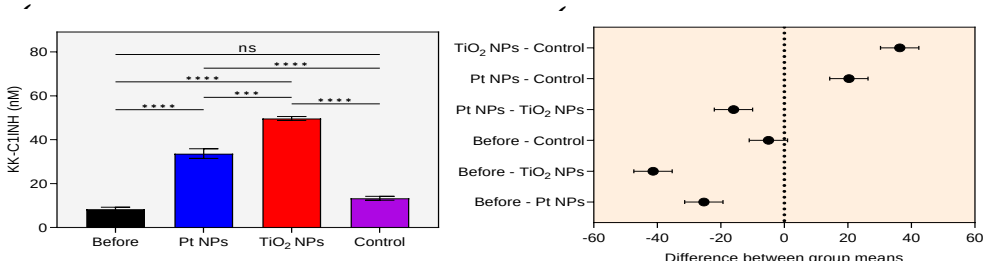

Figure 3: (a) Contact/ Kallikrin-kinin system activation evaluated from the level of generated KK-C1INH complexes **(b)** Tukey simultaneous confidence interval plots.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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