Proactive Body Temperature Management Protocol and Lifestyle Interventions as Predictable Cures for COVID-19 Disease

Curative Protocols Discovered from a Century of Medical Discoveries

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ABSTRACT

Based on a century of medical discoveries, we propose a methodology of using lifestyle interventions and proactive body temperature management protocol as prevention and cure for COVID-19 disease. We produce robust evidence to show that lifestyle interventions have a 100% “expected response rate”, with a curative power being one to three orders of magnitude larger than that of a single lifestyle factor determined by clinical trials and can deliver immediate benefits to long-term curative benefits. On basis of a large number of studies, we propose that the local blood flow along the inner surface of the respiratory track works like an anti-viral shield, which is capable of robustly prevent and terminate viral and other infections. Breathing cold temperature from 26 °C to a frigid temperature can dramatically reduce local temperatures along the track and thus cripples the protective shield by reducing local blood flow to as little as 3-10%. A proactive body temperature management protocol (PBTM or PRTPM), which comprises pre-exposure, during-exposure, and post-exposure measures, are capable of boosting innate immune functions, anti-viral defenses, and vital organ functions. We estimate that pre-exposure and during-exposure measures can reduce temperature drops along the tract by 5°C to 20 °C, and that a series of post-exposure measures can increase local blood flow rates along the track by 2 to 20 times. The proposed measures can completely restore the anti-viral shield. All kinds epidemiological data support our estimated curative power that the protocol can prevent 90% to 97% infection incidences and deaths. We show that the protocol is even more powerful than vaccine, and maintaining a reasonable local temperature along the respiratory track is a required condition for delivering and boosting vaccine’s protection.

Current medical researches have excluded temperature and air as treatments in all on-going clinical trials. This misplaced priority is an inevitable result of the financial arrangement of all parties in medicine. Such financial arrangement provides too much incentive for medicalization, the key elements of which include finding revenue-making treatments, producing good data for promoting the treatments, and finding more patients for using treatments. Since lifestyle interventions and proactive body temperature management protocol cannot be studied by flawed research model and cannot be patented for monopoly, no entity has incentives to explore their extraordinary benefits. We also found that the reason of failure to contain the COVID-19 pandemic is same as failure to find cures for cancer and AIDS. Several studies imply that best solutions for cancer, AIDS and all chronic diseases are not revenue-generating medical treatments, but things that cannot sold for revenues and things that are born and carried in human genome. Based on a century of medical discoveries in disease causes, we propose for the federal government that the most cost-effective measures are finding and eliminating a large number of disease causes hidden in food production lines, family kitchens, cooking culture, personal cooking habits, home appliances, etc. This is the only way to root out causes for more than 90% chronic diseases incidences.

INTRODUCTION

In our last article, we extensively studied secondary effects of pandemic measures on global health [1] and we predicted that incoming cold temperatures and the secondary effects of the pandemic measures will be responsible for the worst global health crisis. That prediction was based on our prior works concerning effects of mask wearing [2], transmission routes [3], the roles of thoracic free volume on disease outcome [4], and personalize lifestyle interventions [5-6]. The current situation is serious because no existing antiviral drug has been found to deliver real benefits [7]. Recently, it is reported that efficacy of the Pfizer vaccine is 95%, and the medical world hopes that vaccines will contain the pandemic. In September 24, 2020, we posted our second article on the flaws in the clinical trials and reductionist treatment models [8-9]. Even though COVID-19 disease is NOT a chronic disease and our findings of clinical trial limitations appear to irrelevant. However, we found that personal resistance to the virus and ability to withstand viral damages are health properties that are amendable in response to lifestyle interventions like chronic diseases [1, 5-6]. Infection risk and disease severity highly depend on body structure and personal whole body health which can be altered by lifestyle interventions. Temperature, humidity, pressure, nutrition, etc. have immediate impacts on the disease process [10-11]. The U.S. incidence rates have rapidly risen in the coming winter, reflecting almost a ten-fold increase [12]. Based on the real time data, overall incidence rate in U.S. is 38 times of that in Japan, and the overall death risk in the U.S. for the entire pandemic is 53 times of that in Japan. The death rate among infected persons in U.S. is almost 200% (the data may change) of those in Japan and South Korean. In light of our findings of flaws in clinical trials [8-9] and epidemiological models [6], we attribute the huge differences in incidence rate to differences in lifestyle, environment, and health culture. Infection risks and particularly death risks are much higher among the elderly, obese and chronically ill people [13-15]. Old people at the age of ninety might have lost about 30% of organ's functional reserve [16-18]. Obesity and chronic diseases are largely results of fault lifestyles. Those facts imply that ultimate influencing factors are temperature, lifestyle factors and environmental factors [1,

5-6, 19]. We will explore how temperature intervention and lifestyle intervention can be used to prevent and cure COVID-19 disease, and their relative effectiveness as compared with antiviral drugs and vaccines.

LIFESTYLE INTERVENTIONS

A. The Concept of Using a Map To Formulate Lifestyle Interventions For Curing Future COVID-19 Disease

The concept of curing future infection is using a map below to examine personal lifestyle factors in light of five classes of health properties, identify offending lifestyle factors and correct them. Based on our prior study [1, 5-6], we tentatively identify 15 classes of measures for improving five viral defense mechanisms (“health properties”).

Table 1. A List of Lifestyle Factors and Their Combined Effects on Each of the Complex Health Properties.

Lifestyle and Other Factors	Exposure S1	Viral Entries S2	Innate Immunity S2	Adaptive Immunity S3	Resist Damages S5
1. Temperature	N/A	+ to +++	+ to +++	+ to +++	+ to +++
2. Humidity and pressure	N/A	N/A	Indirect	Indirect	+ to ++
3. Emotion, stress, depression	N/A	+ to +++	+ to +++	+ to +++	+ to +++
4. Nutrition balance	N/A	(may be)	+ to +++	+ to +++	+ to +++
5. Mineral balance (Na-K etc.)	N/A	Unknown	+ to +++	+ to +++	+ to +++
6. Avoid toxic matters/waves	N/A	(may be)	+ to +++	+ to +++	+ to +++
7. Avoid flu and infections	++	+ to +++	+ to +++	+ to +++	+ to +++
8. Exercise and inactivity	N/A	+ to +++	+ to +++	+ to +++	+ to +++
9. Sleep and circadian timing	N/A	+ to +++	+ to +++	+ to +++	+ to +++
10. Food and drink safety	+++	N/A	N/A	N/A	N/A
11. Food form, texture, structure	N/A	(may be)	(may be)	(may be)	(may be)
12. Personal hygiene	++	- to +++	- to +++	- to +++	- to +++
13. Mask wearing and devices	++++	-	-	-	-

14. Post-exposure measures	NA	+ to ++	N/A	N/A	N/A
15. Shear, vibration, etc	N/A	+ to ++	-	-	+
16. Deep breathing exercise	N/A	+ to +++++	+ to +++++	+ to +++++	+ to +++++
Total Index Score (%)	100	>90	>90	>90	>90

The number of “+” for each measure denotes potential impact degree and will be adjusted based on future research findings. Many factors can have both negative and positive effects, but only beneficial effects are shown because we will use them only to deliver their benefits. The number is indicative of maximum benefit, but the real value for a person would depend on whether it is relevant, how the lifestyle factor is used, how long it is used, and whether it is correctly used. Percent index score is a ballpark indicator of the total effects of all lifestyle factors in the column, which is relative to the maximum achievable.

B. Clinical Trials Are a Flawed Method

The massive findings show that any of the lifestyle factors could have beneficial effects on disease outcome, but medicine does not use lifestyle interventions as the first-line treatment options in clinics. We have proved that clinical trials are not a suitable method for studying weak factors among a large number of similarly-weak factors [8-9]. We will briefly discuss the problems below.

1. Each lifestyle factor exists among many weak and/or random lifestyle factors

As we have discovered and shown in the map, a health property is influenced by hundreds to thousands of lifestyle factors, the true effect of each of such factors cannot be determined by direct measurement of the health property [8-9]. This can be seen in the model $H_i = f(F_1, F_2, \dots, F_n)_i$, where the health property H_i can be measured by an experimental method, depends on $N-1$ interfering factors, each of which affects H_i by small degrees and many of which are random variables. The effect of $(F_2, \dots, F_n)_i$ can be ignored only if the total effect of $(F_2, \dots, F_n)_i$ on H_i can be ignored so that $H_i = f(F_1, F_2, \dots, F_n)_i$ becomes $H_i = f(F_1)_i$. However, vast most lifestyle factors have similar-degree effects and similar randomness. So, there is no conceivable possibility that a weak lifestyle factor can be resolved against a large number of other lifestyle factors unless the factor to be determined is a relatively strong factor.

Claimed validity of clinical trials is attributed to the intuition that comparing a treatment with a control must produce correct results. Most comparisons were made between a weak factor with the combined effects of other uncontrollable weak factors [9]. Contrary to the belief in variable control, the effects of lifestyle factors cannot be controlled. Besides unique personal genome [409-412], each person's life histories and living environments [29-94] have turned the person into a distinctive phenotype with distinctive biological pathways networks and structure [20-27]. Controlling present lifestyle factors during a clinical trial cannot undo past effects. Thus, dependent variables $(F_1, F_2, \dots, F_n)_1, (F_1, F_2, \dots, F_n)_2, \dots, (F_1, F_2, \dots, F_n)_m$ in different persons are always different. No person can be treated as same as another person. Hypothesis tests actually compare the effect of the treatment against thousands of other factors and always result in inaccurate, biased and

even wrong results [8-9]. Each lifestyle factor is defeated by a large number of other lifestyle factors.

We also show there are overwhelming other flaws in clinical trials by examining statistical theories, mathematical models, biological pathways, and H₀ health significance levels [8-9]. Even mathematical models were misused to sum up data from different persons because health properties are not the kind of properties that can be added up. No-zero variances observed for clinical data imply that a treatment or a factor has different effects on different persons. When massive lifestyle factors cannot be controlled, a null finding does not mean that treatment has no effect on all persons. By tracing the bias logic, we found that the response rate of using a correct lifestyle factor can never be null. Even air, water, cookware, house products, clothing, thinking, etc. (anything one can imagine) have different health effects on different persons [29-94]. For all those reasons, we found that clinical trials may not be used to disprove the benefits of lifestyle interventions. Epidemiological models do not address lifestyle factors, but use twenty to hundreds of imagined, abstract, and poorly-defined parameters [95-97]. The models can make good prediction of pandemic outcome only if human lifestyle, culture, environments, etc. are not changed.

2. Same combination pattern of lifestyle factors does not exist different persons.

For the reason stated above, valid evidence proving benefits of single or a few lifestyle factors cannot be acquired by clinical trials. Since our purpose is to correct all offending lifestyle factors as lifestyle interventions, we naturally consider whether we can evaluate a set of lifestyle factors at once. Lifestyle factors affecting personal vulnerability to the COVID-19 disease are different among different persons, and thus there is no population, all members of which share the same combination pattern of lifestyle factors $(F_1, F_2, \dots, F_n)_i$. Therefore, clinical trials are not a suitable method for studying collective effects of a combination of lifestyle factors. It may be possible that some members share a similar lifestyle factor for a short time, but its accumulative effects in their lifetimes must be different. Different lifestyle factors affect different persons by different degrees, and prior exposures to different lifestyle factors have turned each person into a unique phenotype. Lifestyle factors such as nutrients [98-107], exercise histories [108-109], exposures to heavy metals [72-75, 79-84], prescription drugs [110-113], etc. must have different effects on health properties on different persons. Uncontrollable lifestyle factors can distort measured results, rendering clinical trial conclusions meaningless. The effects of weak effects were never studied before [399-408].

3. Lifestyle interventions can be evaluated only for a specific person

Only data that can directly represent a person is data that is acquired from the same person. If personal data is unavailable, we cannot find an accurate reference for the person. The purpose of medicine is to cure diseases, save lives, and end the pandemic. That mission can be achieved without using population data or as reference. Evaluation of lifestyle interventions must be based on experience. Uniqueness personal genome [409-412], unique process attributes of the biological pathways networks [20-25], and unique exposures to lifestyle factors [29-94] determine that objective evidence is illusory. Even data that are acquired from the same person cannot always be trusted because process attributes in the biological pathways networks change with age, living history, and health conditions. Data acquired from a population may be used as a rough reference only after they are adjusted; and the ways of adjustments would depend on experiences or empirical

protocols. While medicine demands that treatments be developed by using objective evidence, it allows doctors routinely prescribe different drugs to “test” which drug works in personal drug trials.

4. Benefits of curing future diseases require new evaluation methods

Accurate evaluation of benefits of lifestyle interventions on COVID-19 cannot be conducted by using clinical trials and experimental methods. The ballpark benefits of lifestyle factors on COVID-19 can be seen by examining the association between lifestyles factors and death risks. For example, the benefits of lifestyle factors can be seen by noting great differences in infection and death risks between U.S. and Japan [12]. Finding offending lifestyle factors is difficult. The map embodies hundreds to thousands of potential lifestyle factors. Each of the factors $(F_1, F_2, \dots, F_n)_i$ is unique in each person, and their combination is also distinctive. Thus, H_i for a person is associated with a distinctive set of $(F_1, F_2, \dots, F_n)$. The contribution of a target factor F_i to H_i cannot be determined by using any experimental method. A constant value does not exist because the value depends on the values of thousands of other factors [29-94]. Net contribution of a target lifestyle factor F_i cannot be resolved by summing and averaging data H_i from different persons because their $(\dots F_1, F_2, \dots, F_n)_i$ are completely different. Offending lifestyle factors may be hidden in personal life habits and can harm the person on a continuous basis. What is important is to abate offending lifestyle factors but not try to find an objective value that simply does not exist and has little utility.

C. Alternative Proof of Curative Benefits of Lifestyle Interventions

We will prove the curative benefits of lifestyle interventions by an alternative method that does not depend on any presumption and specific way of interactions.

1. Real Benefits of Lifestyle Interventions Are Backed Up by Positive Findings in Tens of Thousands of Published Studies.

Support for the lifestyle interventions listed in the map is massive researching findings concerning the effects of lifestyle factors on the immune system, the vascular system, personal infection risks, and structural features influencing personal disease severity.

(1) Temperature [12, 19, 114-115]. Temperature affects blood circulation and blood pressure [116-120], blood vessel constriction [121], peripheral blood flow [122-126], and low temperature is expected to affect the macrophage's patrolling functions [127], innate response and adaptive immune response [114]. T cell, B cells, macrophages, etc. must squeeze through smaller capillary pores [4], but low tissue temperature reduces pore sizes and raise blood viscosity and tissue rigidity and thus affects all S2-S5 functions.

(2) Humidity and pressure [19]. Humidity and pressure affects oxygen pickup [128].

(3) Emotion, stress and depression. It is well known that emotional stress, shock and unhappy mental state and depression can suppress the immune system [129-141].

(4) Nutritional balance [98-107, 218-224]. Nutritional imbalance and malnutrition (e.g., lack or imbalanced vitamins) are known to cause immune suppression and poor whole person health.

(5) Mineral balance [141-147]. Good minerals compete with heavy metals in absorption and secretion [45]. Sodium intake affects the balance of other minerals.

(6) Avoid toxic matters and waves. Smoking, heavy metals, pollutants, toxic by-products, organic compounds, waves, prescription drugs. etc. may suppress the immune system, damage the vascular system, and affect viral replication [29-94, 148-171, 233].

(7) Void cold, flu and bacterial infection. Flu may promote ACE2 expression [174] and enhance viral entries per collective infection theories [175-179].

(8) Exercise and inactivity. Exercise slowly improves organ function, improves lung ability to pick up oxygen, and cures obesity, high blood pressure, and diabetes [108-109, 180-191].

(9) Sleep and circadian timing. Sleep and activities timings affect the immune system and the ability to resist viral infection [193-194].

(10) Food and drink safety. ACE2 receptors are predicted to exist in the digestive track, potentially in the gut, intestines, kidneys, liver, etc. even though exact mechanism are not clear [194-207].

(11) Food forms. Processing contaminants, foreign matters, food ingredient structure, molecular conformation changes, etc. [72-88] affect nutrition absorption and balance, etc.

(12) Drugs, natural compounds, and vaccines. Drugs and natural compounds may inhibit viral activities [7], but also cause side effects.

(13) Personal hygiene. Microbiota affects the immune system [208-211]; and bacteria may either promote or inhibit virus [212]. Toxins from bacteria on the body skin surface may affect health.

(14) Mask and protective devices [2]. They are recognized as effective measures for preventing severe infection. A mask can filter out most viral copies from inhaled air and raise local temperatures along the respiratory track, and thus dramatically reduce risk of infection.

(15) Post-exposure measures. Viral entries require time because the virus must form a complex configuration [194]. The conformation-formation process may be disturbed by viscous mucus movement [implied by findings in 213-216]. Some measures are predicted to inhibit viral entries by promoting WBC migration and surveillance [127, 225].

(16) Mechanic vibrations and fluid shear. Mechanical motion and fluid shear can disrupt cell division [213-216], and viral infection and spreading are more permissive in region with low shear stress [215-216]. Flow properties may affect viral entries and viral attachment process required for making entries. Mechanical vibrations may facilitate WBCs' migration through capillaries [4].

(17) Deep breathing exercise. It affects whole body health by many mechanisms. Deep breath exercise can cause relaxation, raise body's temperature, induce calmness, lower blood pressure, improve vascular system, and boost immune system [226-232].

A cure for future COVID-19 diseases does not require all of them. It is possible that some people may require correction of a few lifestyle factors while others may require correction of many more.

2. Feed the abstract function with difference values

Abstract function $H_i=(F_1, F_2, \dots, F_n)_1, (F_1, F_2, \dots, F_n)_2, \dots, (F_1, F_2, \dots, F_n)_m$ is not susceptible to challenge because it does not use any assumption or specific kinds of interactions. We

will feed the function's independent variables with lifestyle factors to see what we can arrive at. We will use F_1 =temperature, F_2 =emotional state, F_3 =calories balance, F_4 =microbiota, F_5 =vitamins intakes, F_6 =arsenic exposure, F_7 =cadmium exposure, F_8 =chromium exposure, F_9 =nickel exposure, F_{10} =lead exposure, F_{11} =pesticides exposure, F_{12} =organic compounds exposure, F_{13} =foreign matter exposures. Many of those factors can be divided into a large number of sub-level factors. Temperature alone can be responsible for most infection incidences as this is revealed in incidence rates in U.S. [12, 115] Temperature affects blood vessel constriction and peripheral blood circulation, blood viscosity, and immune cell mobility (lung resident macrophage mobility). Emotional distress, chronic stress, depression, etc. affect the immune system. Vitamins exist at different levels in different persons. High blood levels of arsenic, cadmium, chromium, nickel, and lead can cause systematic damages, but each of which causes distinctive damages. Those, who eat rice, drink well water, and eat contaminated food, may be damaged by arsenic; those who keep contacting lead paints and breathing lead-containing air may be poisoned by lead; those who love to cook acid sauce in stainless pans may be impaired by nickel and chromium. Different diets used by different persons may have fostered different gut flora profiles and thus resulted in different kinds and amounts of metabolic substances, which have distinctive harmful effects on biological processes, cellular functions, and immune functions. Some people may be affected by bad sleep, co-infection, malnutrition, prescription drugs, etc. Some do regular exercise while others do not; some smoke and others ingest food colorants and artificial flavors or are exposed to harmful waves. All lifestyle factors affect health properties by their historical exposures. Thus, comparing health properties between any two persons is like comparing Apple with Orange.

3. Additive benefits by correcting multiple offending lifestyle factors

What makes COVID-19 a deadly disease are a large number of offending lifestyle factors. Our approach is correcting as many offending lifestyle factors as possible. Assuming that if the map enables a patient to identify one hundred lifestyle factors, the chance to get at least N factors is the sum of a large number of possible combinations. The combinations for $N=1$ will be 100, the combinations for $N=2$ include all combinations (1,2; 1,3;...; 1,100; 2,3; 2,4;...; 2,100; 3,4; 3,2;...; 3,100;...; 99,100, excluding duplicates). By using random drawing model, the total number of combinations for getting N factors out of $M=100$ factors can be determined by using known equations. Combinations, respectively, for $N=1$, $N=2$,..., $N=100$, can be computed. The chance of hitting at least some offending lifestyle factors is nearly certainty. However, some offending factors such as lack of exercise, calorie imbalance, ingestion of excessive heavy metals, lack of fibers, emotional stress, etc. are very common. Given the massive harmful substances in the food chain and modern lifestyles, expected response rate for a population would be near 100% as long as each person makes a reasonable attempt. The curative power would depend on how many of the identified offending factors are corrected in each person. We confidently predict that this map can help achieve benefits at one to two orders of magnitude larger than the benefits of correcting an offending factor or using a synthetic drug. This curative power does not include additional benefits from factor-factor interactions and whole health property optimization.

4. Additional curative powers are achieved by factor-factor interactions.

This map allows for determining any kind of factor-factor interactions under any of the five classes of health properties, as shown in the following examples. The function of each of the whole health properties is influenced by heavy metals, organic compounds,

nutrition, emotion, hormonal actions, thinking and working habits, etc. The performance of the interventions can be improved by correctly adjusting more of existing offending lifestyle factors. Interventions intended to correct multiple lifestyle factors can achieve more benefits than the mathematical sum of the interventions, each of which is directed to correcting a single lifestyle factor. The interventions can achieve additional gain from factor-factor interactions. Each lifestyle factor can affect different health properties within a row; different lifestyle factors can interact with other factors under each health property, and any lifestyle factor may interact with other factors under different health properties. For example, exercise can improve micro-vascular networks and thus enhance interventions intended to remove heavy metals, metabolic by-products, cell discharges, etc.

Wearing masks is an effective method for reducing exposure to the virus; however wearing masks has an effect like restrictive breathing [2]. Thus, long-term wearing mask is predicted to have adverse effects on health. A best method of neutralizing the side effect is using deep breathing exercise, which is most powerful remedy for improving blood oxygen level and improving lung functions [226-232]. Lifestyle factors have immediate benefits, progressively increased benefits, combination benefits, and long-term benefits. For example, temperature, post-exposure clean-up, air humidity, food and nutrition, emotional intervention, etc. affect infection and death risks by affecting blood circulation, peripheral blood circulation, immune cell mobility, etc. Reduction in daily exposure to heavy metals help to improve immune system functions; and exercise and calories balance may slowly improve micro-vascular networks; and reducing heavy metals and exercise collectively improve all of three key health properties. Any lifestyle factor in the map may interact with any of other factors under any of the health properties. There are thousands of ways of interactions that can be used beneficially to cure a future infection. Nutritional balance, reduction in heavy metal intake, excises, and stress management can jointly affect innate immunity, acquired immunity, organ functions and the ability to withstand lung damages.

5. Additional synergistic curative effects are achieved by optimizing whole health functions

Infection and death risks depend on a series of whole health properties such as human ability to prevent the virus from making entries, innate immune function, adaptive immune function, ability to withstand damages, etc. [4, 237-240]. Most lifestyle factors do not have a FIXED unit effect on a health property or disease outcome. This can be seen by focusing on a “whole function” rather than a single parameter. In one example, viral load that a person gets in each exposure or time window may depend on air ventilation, wind scale/direction, relative position between an infected person and a healthy person, and duration of each incremental exposure. Since viral particles can stay in the air for more than 3 hours [249], keeping six feet distance alone is not enough. If a healthy person walks after an infected person at 6 feet distance, the healthy person can walk into the viral-polluted zone within a few seconds, and thus breathe in viral particles discharged from the front infected person [1]. For this reason, we must consider all relevant factors. Human immune system may be damaged or influenced by many lifestyle factors including heavy metals, natural compounds, nutritional imbalance, emotional distress, etc. The immune function includes WBCs migration to infected tissue, killing infected cells or engulfing infected cells, and bringing digested cell content to outside the body [237-242]. The performance depends on WBC count, WBC cell function, and WBC mobility in tissues (like a cat passing through a keyhole), etc. If all other influencing factors are fixed, the immune function may be limited to some degrees by white blood cell count, cell structure health,

and micro-vascular networks. This mechanism implies that a suppressed immune system cannot be fully restored by altering only one parameter. Those lifestyle factors must interact among themselves. If the immune function is improved by X in response to a 5% increment in the WBC count at a high arsenic level, the improvement could become 5X if arsenic level is reduced by half. This example implies that simple linear mathematical models are flawed.

PROACTIVE BODY TEMPERATURE MANAGEMENT

In our prior research, we found for various reasons that temperature is the most important factor in treating COVID-19 disease. Here, we will explore the mystery of low temperature in depth.

A. Low Temperature Raises COVID-19 Incidences By Ten or More Folds

When cold air enters the respiratory track, the air is heated by components of the upper respiratory tract walls. When air reaches the lungs, the air is fully saturated with water vapor at about 37 °C [250]. Cold air temperature caused by low temperatures can cause many health problems [251]. Inhalation of cold air induces activation of the epithelium to generate proinflammatory substances and that epithelial injury, determines activation of any exposed peripheral nerves. Vasomotor control in the airways is mediated by parasympathetic and sympathetic nerves through the release of neuropeptides such as Substance P and Calcitonin Gene Related Peptide (CGRP) [250], which can induce powerful vasodilation [251]. General exposure to cold causes pulmonary vasoconstriction and promotes acute pulmonary oedema in subjects with congestive heart failure. Exposure to cold air can increase the number of granulocytes and macrophages in the lower airways [252].

The adverse effects of cold temperature on influenza are well known [19]. The role of cold temperature is clearly reflected in COVID-19 incidence data such as U.S. incidence data [12]. On September 7, 2020, 25,906 new cases were reported in the U.S., but 204,179 new cases were reported on November 20, 2020. This happened long before the arrival of coldest winter. We predict the low temperature will raise incidence rate by more than 10 folds. Among climatic variables, the average temperature showed a strong correlation with both death and case rates [115]. Even though this study does not pay attention to health culture and lifestyle, it rates temperature as the second or first influencing factor or next to age. Temperature is stronger than a delay in government first response, staying at home, population density, etc. Thus, we must regard temperature as the most powerful intervention factor. We note that the population data do not reflect potential benefit of proactively managing body temperature, but reflect an outcome of a population in an existing lifestyle, environmental and cultural condition. We predict that temperature can be used to reduce incident rate to less than one tenth.

B. The Magnitude of Effects of Cold Temperatures On Blood Flow Rate, Energy Metabolism, Signal Transmission, etc.

We note there are two kinds of cold stress. One is the cold effect caused by lowering the body's core temperature below 37 °C or the normal value of the person. The most common cold stress is from exposure to cold ambient air. The respiratory system inhales and exhales air constantly. The cold air is inhaled through the nose, passing the bronchi

and reaching deep bronchus, where the inhaled air is heated up while moving into alveoli by diffusion. The inhaled air is warmed up and later exhaled, bring out a certain amount of heat. Thus, the respiratory system is an efficient device of dissipating heat. If the core temperature is lower, or if the ambient temperature is sufficiently low and exposure is sufficiently long, the breathing cycles will decrease local temperatures by different degrees among the respiratory track to reach a dynamic equilibrium. It is expected that local temperatures at the membrane near the nostrils are the lowest while those at deep lungs are highest.

Effects of Continuous Exposures to Low Temperature. Barcroft et al. describes an experiment to determine peripheral blood flow in a forearm while the forearm is submerged into a cold water [126] maintained by a water bath. Water temperatures for various tests were maintained, respectively, at 13, 20, 25, 30, 32, 35, 38, 40, 42.5, and 45 °C. Measurements were made after about 10 minutes and lasted two hours. The estimated blood flow for the forearm was about 6 cc/100 cc forearm/min when water temperature was maintained at 38 °C as a reference. If the water temperature is reduced to 30 °C, the blood flow rate was reduced to about 1.8 or 30%, and further reduced to about 0.5 (8%) if water temperatures are maintained respectively at 13, 20 and 25 °C. When water temperature is raised to 42.5 °C, the blood flow rate shows an up and down curve, with highest values reaching about 18.5. The data show that blood flow rates could be about 0.5 and 14, respectively, for 13 °C and 42.5 °C, reflecting 20-30 times difference in local blood flow. The observed huge differences in local blood flow rate were consistent with the pattern established by six internally cited studies. The time for showing full effect of high temperature is less than 20 minutes with the maximum at about one hour, and the time for showing the effect of low temperatures is less than 20 minutes.

Local effects and systemic effect of temperature. Experiments show that whole body's response to exposure to low temperature is very different. Upon continuous exposure at 4 °C for 60 min in low temperature in a micro-climate chamber, it was found a high blood flow was observed in leg. Higher values of systolic blood pressure (SBP) after exposure in relation to the values before exposure were reported in most subjects (70%) [255]. This 4 mm Hg increase in blood pressure implies an elevated blood resistance caused by lower temperature. Compared to the findings of Barcroft, it actually raises local blood flow in legs. In this experiment, the subjects received a set of clothing with identical thermal insulation and only the subjects' faces were exposed to the cold, but measures were taken for legs. Since the faces are exposed to low temperature, the cold triggers the body to raise blood pressure [116-120] as attempt to improve blood circulation. The raise blood pressure caused some increase in local blood flow in localities in the body. The measured blood flow is not where low temperature directly hit. We expect that the local temperatures along the respiratory track are entirely different.

Effects of intermittent exposures to low temperature. Blood flow in a forearm is reduced when a prolonged intermittent cold application on forearm by ice pack is used as compared to a single cold application [122]. The influence of ambient temperature on the effect of segment skin temperature has been summarized by Montgomery [254]. At a given skin temperature, the blood flow through a body segment tends to be higher with increasing ambient temperature. The absolute effect of ambient temperature on hand blood flow is less pronounced at lower skin temperatures than at a skin temperature above 32°C. Above 35°C, the effect of ambient temperature on the forearm blood flow, at a given skin temperature, tends to decrease. The rate in segmental blood flow with skin temperature

above 32°C is higher in a warm environment than a cold one. Very short contact (<180 seconds) does not show impact on the blood flow [125]. This finding implies that brief exposure to low temperature is safe provided temperature is restored to normal or warmer temperature immediately after exposure.

Vasodilatation and vasoconstriction cycle. Temperature fluctuation cycles are very important to management of the body temperature. It is common experience that doing exercise will raise body temperature and causing vasodilatation, which will result in excessive heat loss and thus result in vasoconstriction. Studies have shown that local vasodilatation may follow initial vasoconstriction as a result of prolonged cold application [56-58, 321]. Following local cooling, the temperature of the skin and subcutaneous tissue decreases sharply, then more gradually, and finally plateaus [122]. However, Barcroft experiment supports this pattern only in high temperatures but not in low temperature. It is important to note that vasodilatation is not entirely overcome by vasoconstriction. Within 2 hours time window, blood flows for different low temperatures still differ by huge amounts. We suspect that exposure to low temperature causes vasoconstriction first and followed by some vasodilatation as the body is expected to make compensation. However, recovery is limited, and thus we cannot count on it in managing body temperature.

Low temperature's effects on energy metabolism, etc. Diminished blood flow implies a proportional reduction in oxygen and glucose which could be available for use by local tissues. The heat that can be generated from one unit of oxygen (α) depends on the substrate [259]. When the substrate is carbohydrates, the energy generated from 1 ml of oxygen is 21.13 J, and is 19.69 J when the substrate is fat [260]. If blood flow is reduced to 1/8 at low temperature, the ability to generate energy at local tissue must be limited by the available oxygen and glucose. Cold also decreases the rate of impulse transmission along motor and sensory peripheral nerve fibers [261].

Temperature gradient in the respiratory track. If the ambient temperature is anything between 26 °C or a freezing temperature, breathing cycles depresses the inner surface temperature by different degrees. For example, Cole in 1954 [262, 263] performed experiments in which a small thermistor in the tip of a hypodermic needle was pushed into the epithelium, and reported that on breathing room air (presumably at 20°C) the submucosal temperature was several degrees lower than the surface temperature, and remained well below body temperature throughout the respiratory cycle. This experiment indicates that local temperature at tissues would be different. McFadden et al. [320] studied airstream temperatures at glottis, carina, orifice of right lower lobe bronchus, orifice at anterior segmental bronchus, orifice of subsegmental bronchus, and a position of 5.8 cm beyond orifice of subsegmental bronchus, correspondent to distances from tip of nose to six locations from 18.2 to 47 cm. Measurements were acquired at minute volumes from 15 to 100 liter/minute. When breathing at room temperature of 26.7 °C, inhaled air is warmed up from the room temperature to 32 °C at the glottis and reaches nearly 35 °C at the distal position. A large breathing minute volume shows lower airstream temperatures along all locations, indicating that the body has a limited ability to warm up inhaled air. Large minute volume at 100 liter/minute show 4 °C lower in the glottis and about 1 to 2 °C lower in the orifice of subsegmental bronchus, as compared 15 minute volume. All measured temperatures for an inhaling cycle is slightly lower than the counterparts at an exhaling cycle. At the most distal location, the temperature is 35.5 °C. When breathing frigid cold air at -18.6 °C in an inhaling cycle, the temperature at glottis is about 8-9 °C lower than the readings acquired in the test with a room temperature, while the temperature at the most

distal location is 35.4 °C. Large minute volume at 100 results in 3 to 8 °C drops in respective temperature readings as compared with breathing at 15 minute volume. From the data, we expect that at nose and nasal cavities are much closer to air temperature. While no test was done in that study, we expect that all temperatures from nasal cavities to orifice of subsegmental bronchus (0 to 47 cm) would be raised by various degrees by breathing warm air, the temperature of which is higher than body core temperature.

The temperature of the air passing from nostrils to 9 cm distance within was measured by Webb et al. [322]. They found that with an inhaling air temperature of 6°C, the anterior 9 cm of the nasal respiratory epithelium is exposed to temperatures between 6 and 28°C and the epithelium near a nostril is exposed to temperature lower than 10 °C. We predict that exposure to a frigid air (-18 °C) can cause great cold stress on nasal cavities.

Core temperature vs. local tissue temperature. Those cited studies imply that the core temperature of a person affect blood flow. If local temperature of a segment along the respiratory track is significantly deviated from the normal 37 °C, it would result in reduced blood circulation in the segment. Second, even if the core temperature is not depressed, it is still possible that the local temperature within the respiratory track can be significantly lower than the normal values. Even room temperature at 26 °C can bring down temperatures along the respiratory track.

This would depend on exposure time and air temperature. In near zero degrees, a long-time exposure can significantly reduce local temperature inside the respiratory track. The depressing effect of cold air is expected to be less than what could be brought by circulating cold water on a forearm as in Bercroft, it is expected that temperatures near nose are significantly lower than those in bronchi. Running nose is the first sign of getting a cold.

C. Host Antiviral and Innate Immune Functions Work as a Viral Shield

Although not all studies agree, most studies suggest that inhaled cold air, cooling of the body surface and cold stress induced by lowering the core body temperature cause pathophysiological responses such as vasoconstriction in the respiratory tract mucosa and suppression of immune responses, which are responsible for increased susceptibility to infections [253]. To see the magnitude of effects of low temperature, we will review all potentially antiviral mechanisms which are sensitive to temperature. We will focus on local blood flow, capillaries pore sizes, blood viscosity, metabolic rate, and neuro signal transmission for all stages. Considering the limitation in research and potential role of co-infection and collective infections in COVID-19, we include all potential antiviral mechanisms in concept.

Mucociliary clearance or cilia beat frequency. The first line of defense is mechanical mechanism comprising a protective mucous layer, the airway surface liquid layer, and the cilia on the surface of ciliated cells. The cilia are specialized organelles that beat in metachronal waves to propel pathogens and inhaled particles trapped in the mucous layer out of the airways. Cilia beat frequency is temperature dependent [265-266]; because there is an optimal temperature for the enzymatic hydrolysis of ATP by dynein, low temperatures, as well as pH and smoking decrease the cilia beat frequency. A linear increase in cilia beat frequency of nasal cilia was found between 19 °C and 32 °C, reaches a plateau between 32 °C and 40 °C, and is slower below 32 °C. The nasal tissue normally operates between 32 °C and 40 °C [267]. When surface temperature is very low, this defense mechanism is impaired or disabled.

Neutrophils patrolling functions. Neutrophils are patrolling in blood in search of potential injuries and stimuli, e.g., pathogen- and damage-associated molecular pattern molecules, chemokines, cytokines, and lipid mediators, which induce their rapid accumulation in peripheral sites of inflammation. The primary role of neutrophils is pathogen killing and removal. About 40% of total body neutrophils are found in lung along [268]. Key protective mechanisms have been attributed to the neutrophil in the lungs. Additionally, it is believed that lung vasculature is involved in neutrophil “de-priming” via its ability to filter and inactivate primed cells before they are re-released in the blood stream [269]. However, this mechanism of neutrophil retention is impaired in acute respiratory distress syndrome patients, resulting in the exposure of peripheral organs to primed systemic neutrophils, leading to severe complications [270].

Cytokine-induced NK and Cytotoxic T lymphocyte (CTL) activation. As cytokines released by cells upon viral infection, they serve to signal to the NK cell the presence of viral pathogens in the affected area. Cytokines for NK activation include IL-12, IL-15, IL-18, IL-2, and CCL5. NK cells are activated in response to interferons or macrophage-derived cytokines. They serve to contain viral infections while the adaptive immune response generates antigen-specific cytotoxic T cells that can clear the infection. NK cells work to control viral infections by secreting IFN γ and TNF α . IFN γ activates macrophages for phagocytosis and lysis, and TNF α acts to promote direct NK tumor cell killing. NK cells are also important in resistance to mouse and human cytomegalovirus, and possibly to HIV, influenza virus, and Ebola viruses. A distinct NK cell population, NKT cells, may provide some antigen-specific innate immune protection against certain viruses. Many other leukocytes are involved in innate defense, including macrophages, DC, and neutrophils.

NET TLR Receptors. The nucleic acid-sensing TLR (TLR3, TLR7, and TLR9) and the RLR RIG-I and MDA-5 can recognize replicating RNA viruses in infected cells in nasal epithelium [271]. These receptors stimulated with artificial TLR and RLR agonists generate robust IL-6, IL-8, and interferon (IFN)- β responses and act as a first line of defense against viruses invading the respiratory tract. NET have been associated with numerous pathologies including autoimmune disorders and infectious diseases.

Mucosal-Associated Invariant T Cells. Utilizing an in vitro coculture system of influenza-infected airway epithelial cells (A549) with human peripheral blood mononuclear cells, an MR1-independent, CD14⁺ cell- and IL-18-dependent activation of MAIT cells was observed, featuring increased intracellular IFN- γ and granzyme B levels [272]. These results were later confirmed in another study in which MAIT cells were found to be activated in an MR1-independent but IL-18-, IL-12-, and IL-15-dependent manner in response to various viral infections, including dengue, hepatitis C, and influenza viruses [273].

Natural antibody defense. Natural antibody may play a role in defense against some virus infections. It was found that strong highly localized activation of B-1 cells in the draining lymph nodes of the respiratory tract after influenza infection and CD5-expressing B-1a cells respond to and contribute to the protection [274]. By using a murine model of influenza virus infection, it was found that the B cells that produce natural antiviral IgM neither increase their IgM production nor undergo isotype switching to IgG2a in response to the infection [275]. Because natural anti-bodies are present at the time of infection, they provide an immediate means for binding antigen, activating complement, and trapping of antigen-antibody complexes on follicular dendritic cells [276]. Virus-induced IgM must be

secreted in the presence of natural IgM for efficient induction of specific IgG and for immune protection, identifying B-1 and B-2 cell–derived IgM antibodies as nonredundant components of the antiviral response [275]. Their large size gives them excellent binding avidity, and can pick up trace amounts of infection to mark for recognition by phagocytes.

Phagocytic cells: The professional phagocytes include many types of white blood cells (such as neutrophils, monocytes, macrophages, mast cells, and dendritic cells). Some viruses may be directly inactivated by complement activation or be destroyed by phagocytic cells that bind and ingest complement-bound virions. Cytokines and chemokines induced by virus infection include the cytokines TNF- α , IFN- γ , IL-12, IL-6, and chemokines such as MIP-1 α . IL-12 is a potent inducer of IFN- γ from NK cells. Inflammatory chemokines may orchestrate macrophage, neutrophil, DC, and NK responses at the site of infection. Not only are these components of innate immunity involved in mediating initial protection against viruses, several components (such as the TLRs and type I IFN and IL-12) serve to shape the nature and effectiveness of the subsequent adaptive response to viral antigens.

The phagocyte is the most powerful and most important part of the host defences against the invading viruses once they have penetrated the nasal mucus and breached the epithelial surface [277-278]. In animal experiments the macrophages were sampled from the peritoneal cavity and although the average decrease in body temperature observed during cold exposure was only 1.5°C, exposure to this degree of body cooling was sufficient to alter phagocytic activity. This super sensitivity can be explained by vasoconstriction which can dramatically reduce the mobility of phagocytic cells. In vitro exposure of peritoneal macrophages to temperatures of 4, 10, 24 and 37°C for 1 h showed a close inverse relationship between incubation temperature and the number of cells capable of phagocytosis [279]. Some of the respiratory viruses, such as the rhinoviruses, have been shown to replicate best at temperatures well below normal body temperature, i.e. 33°C, equivalent to the temperature of the nasal epithelium in healthy persons [280].

Alveolar macrophages (AM). Metabolically, AM exhibits a high basal glucose consumption and respiratory rate but a low respiratory burst activity [281-283]. By taking up inhaled particles including pollutants, allergens, and airborne microbes, AM serves as airway scavengers to keep the respiratory system clean and homeostatic. Another function related to their potent phagocytic capacity is the maintenance of surfactant homeostasis by engulfing and catabolizing local surrounding surfactant proteins, a functionality that is impaired in a severe disorder called pulmonary alveolar proteinosis [284-285].

Interferon-Stimulated Genes and antiviral proteins. There are a large number of interferons including IFN- α , IFN- β , IFN- ϵ , - κ , - τ , - δ and - ζ , IFN- ω , IFN- ν and Interferon- γ [290]. The longest-known and best-studied antiviral proteins are the α/β IFNs, which act by binding to the type I IFN receptor and result in the transcription of more than 100 IFN-stimulated genes. One consequence of this ‘antiviral state’ is the inhibition of cell protein synthesis and the prevention of viral replication. We will summarize some well known antiviral proteins in the following table.

Table 2. Anti viral protein expressed in the skin, their viral targets, and mechanisms of action

Antiviral peptide	Range of viruses	Viral target	Energy Required	Cells/ Reference
ADAP2	RNA	Clathrin-	Restricts the entry of viruses that enter	[291]

	viruses	mediated uptake	host cells using clathrin	
OAS proteins	RNA and DNA viruses	ssRNA	Form 2'5' oligomers which activate RNaseL to degrade viral RNA	[292]
MxA	RNA or DNA viruses	Ribonucleo proteins or nucleocapsids	Sequesters viral proteins into perinuclear complexes, prevents nuclear translocation of incoming viral ribonucleoprotein, and blocks viral transcription and replication within the cytoplasm	Peripheral blood cells [293]
MxB	Retrovirus/HIV	Pre-integration complex	Prevents the pre-integration complex from uncoating, importing into the nucleus, and integrating into host chromosome	[294-295]
GBP	Positive sense RNA viruses	Ubiquitinated replication complex	Promotes autophagy of ubiquitinated replication complexes	[296, 297]
IRG	Positive sense RNA viruses	Replication complex	Targets the replication complex using an ubiquitin-like LC3 conjugation system	[296, 297]
IFITM	Enveloped viruses	Fusion to late endosomes or lysosomes	Blocks viral fusion with cell membranes	[298]
IFIT	RNA viruses	Lack of 2'-O methylation or uncapped 5'ppp	IFIT1 detects viral RNA and then forms a complex with IFIT 2 and 3 to sequester the viral RNA from the replication pool	[299]
PKR	RNA viruses	ssRNA and dsRNA	Stops protein synthesis while promoting selective transactivation of stress response genes	[300]
ISG15	RNA and DNA viruses	Newly synthesized proteins	Uses ISGylation to prevent release of virus	[301]
OASL	RNA and DNA viruses		Newly synthesized proteins ISGylation of viral proteins	[302]

Abriviations: Oligoadenylate synthetase: OAS; Myxovirus resistance proteins: Mx; Guanylate-binding proteins: GBPs; Immunity-related GTPases: IRGs; Interferon-induced transmembrane proteins: IFITM; Double-stranded RNA-activated protein kinase: PKR; Interferon-stimulated gene 15: ISG15; ArfGAP with dual plekstrin homology (PH) domains 2: ADAP2 or centaurin- α 2 (CENTA2) is a member of the ADP-ribosylation factor (Arf) family of Ras-related proteins. Some proteins may be not expressed in the cells in the respiratory tracks. Our theory does not depend specific mechanisms. Even if a particular protein may be not relevant to the COVID-19 infection, the mechanism might be used by other proteins that have not be discovered yet.

Virus-infected cells are killed either because they deliver positive signals or because they lack adequate MHC-negative signals. Energy must be used for the transcription of the IFN-stimulated genes, Type I IFNs also activate natural killer (NK) cells and induce other cytokines such as interleukin (IL)-12 that promote NK responses. NK cells produce proinflammatory cytokines, they can kill infected cells and interact with DC, and are an important component of innate defense against viruses. NK cells are regulated by an array of activating and inhibitory receptors. It is obvious that when the energy metabolism is impaired at low temperature, all antiviral activities will be compromised due to reduced or unavailable energy.

Tissue repair and remodel. Macrophages can exist in a spectrum of species from M1 type to M2 type [286]. They play different roles in wound healing. M2 macrophages, which are present later in the healing process, antagonize the inflammatory response and allow initiation of healing. The M2-like macrophages produce anti-inflammatory cytokines, suppress anti-tumor immunity, and promote angiogenesis and matrix remodeling [287-288]. Tissue repair and remodeling must be part of any anti-viral mechanism because infected and dead cells must be replaced. Impaired communication between macrophages and epithelial cells, endothelial cells, fibroblasts, and stem or tissue progenitor cells all contribute to a state of persistent injury, which may lead to the development of pathological fibrosis [289]. As we will show that at low temperatures, macrophage mobility in local tissues must be impaired or crippled.

D. A United Theory on the Effects of Low Temperatures on Viral Infection and Proactive Body Temperature Management Protocol (PBTM or PRTTM)

Eccles proposed a hypothesis on the role of low temperatures on upper respiratory tract viral infections [264]. We now expand his hypothesis as a unified theory to cover all respiratory infectious diseases including COVID-19 and all potential antiviral mechanisms as shown in Figure 1. We will show the roles of temperature fluctuations and cold ambient air on human innate immunity and antiviral-defenses in initial viral infection, spreading within the respiratory track by internal reinfection process and damage repair. In our discussion, body temperature (BT) may narrowly mean respiratory track temperature (RTT).

1. Low temperature affects initial viral infection.

When air temperature is lower than body temperature, heat can be regained from the expired air, but around two-thirds of the heat transferred to the inspired air is lost on expiration [262]. When the body core temperature is reduced by as little as 1.5 °C, the body may cause the whole body to constrict blood vessels. A reduction in core temperature may happen due to a reduction in blood glucose from lack of food, inactivity or reduced physical activities, excessive heat loss from sweating, fatigue and stress, temperature decrease caused by circadian cycles, etc. This vasoconstriction could be caused by neurovascular

mechanisms [303]. Among certain people, a persistent toxic effect of polyvinyl chloride can contribute to the onset and pathogenesis of Ronauld disease [304]. Taking a nap in an air-conditioned room is a reliable way of catching cold or influenza. Decreases in mean skin and/or internal temperatures cause reflex activation of sympathetic vasoconstrictor nerves, resulting in cutaneous vasoconstriction and decreases in skin blood flow [305-306]. Sympathetic active vasodilator nerves, once activated during hyperthermia, are responsible for most (up to ~90%) of the substantial vasodilation that can occur [307-308]. A list of factors are known to affect cutaneous vasodilation and vasoconstriction [305, 309, 323]. Cutaneous vasoconstriction is a sign of lower core temperature and acts as a measure to preserve heat for maintaining heat for vital organ functions.

By reducing the pore size upon exposure to low temperature, local flow resistance increases and local blood flow in the respiratory track is reduced. The reduced blood flow reduces the amount of oxygen and glucose delivered to local tissues per unit time, and thus degrades energy production. The lower tissue temperature also impacts enzyme's activity for the energy metabolic pathways. If energy production is significantly impaired, cell signaling process is expected to be impaired [259]. Low air temperature may lower local temperature along the respiratory track even if the body's core temperature is not lowered or even if the person does not feel cold. In most cases, depressed core temperature and depressed local temperatures may happen at the same time, which is worse than any of the two situations. Their working mechanism are shown in the Figure 1.

(1) When cilia beat frequency is reduced, the respiratory system cannot perform the normal function to clean up the particles and foreign matter landed on the respiratory track.

(2) The innate functions by natural antibodies are impaired. The localized activation of B-1 cells in the draining lymph nodes of the respiratory tract require energy. The action also depends on recognition by phagocytes. It is implied that phagocytes must move around in the tissue to reach infected cells before they are able to clear antibody-bound virions or marked infected cells.

(3) Professional phagocytes (such as neutrophils, monocytes, macrophages, mast cells, and dendritic cells). Some viruses may be directly inactivated by complement activation or be destroyed by phagocytic cells that bind and ingest complement-bound virions. Since capillary pores in the respiratory track are much smaller than most of phagocytes, even a small constriction of capillary pores or increase in tissue rigidity can completely disrupt the normal balance, and thus restrain them from moving and performing phagocytic functions. Lack of energy may be a factor.

(4) Alveolar macrophages (AM). It is expected that local tissue temperature is lowered, AM has less energy for performing its function. Due to their excessive larger size relative to capillary pores, blood vessel constriction caused by low temperature cause worst impacts to AM mobility. Further, low temperature can increase blood viscosity and tissue rigidity, and thus reduces AM mobility. Thus, they could not engulf inhaled virus-carried particles, pollutants, allergens, and airborne microbes, and fail to engulf and catabolize local surrounding surfactant proteins.

(5) Antiviral functions by antiviral proteins are impaired. α/β IFNs act by binding to the type I IFN receptor and result in the transcription of IFN-stimulated genes. Creating this antiviral state requires energy. Also, virus-infected cells are killed either because they deliver positive signals or because they lack adequate MHC-negative signals. Type I IFNs also activate natural killer (NK) cells. NK cells can kill infected cells and interact with DC.

Gene transcription, NK cell regulation, and NK killing functions require energy supply. When energy supply is impaired, all antiviral functions are impaired by reduced or lack energy. Also, NK mobility can be severely impaired.

(6) Tissue repair and remodeling functions are impaired. Since macrophages play different roles in wound healing. M2 macrophages, which are present later in the healing process, antagonize the inflammatory response and allow initiation of healing. The M2-like macrophages produce anti-inflammatory cytokines, suppress anti-tumor immunity, and promote angiogenesis and matrix remodeling. When both energy supply is impaired and their mobility is dramatically reduced, their ability to repair viral damages are impaired.

Reduced energy availability cannot fully explain the roles of low temperatures on innate immune function because viral replication also requires energy. Lower availability of energy may be still possible if lack of energy can impair viral defense mechanisms more than it does on viral reproduction. However, most obvious effects of low temperature must be realized by its effects on the morbidity of all leuckcytes. In all antiviral mechanisms, killed cells must be cleared up and damaged tissues must be repaired. The repair process includes recruitment, proliferation, and activation of a variety of hematopoietic and non-hematopoietic cells including neutrophils, macrophages, innate lymphoid cells (ILCs), NK cells, B cells, T cells, fibroblasts, epithelial cells, endothelial cells, and stem cells that together make up the cellular response that orchestrates tissue repair [289, 310]. It implies that leuckcytes must move around, and interact with each other and host cells. The average diameter of pulmonary capillaries is about 5 μm while the diameters of macrophages are 15-20 μm [4], even slightest constriction would impair their mobility and thus impair anti-viral function and tissue repairing functions. The increase in tissue rigidity at low temperature may be much severer than the effect of reduced diameter of blood vessels. We found that when tissue temperature is slightly lowered, blood flow resistance at the local tissue would increase. This results in leuckcytes accumulation which in turn further raises local flow resistance. By such vicious cycles, lower temperature can severely impair antiviral activity and tissue repairing function.

2. Low temperatures promote viral spreading process within the respiratory track and lungs by speeding up viral reinfection

By acknowledging flaw of the binary approach, we proposed the reinfection concept [2-4], by which virus infected at one point in the respiratory track is discharged and spread to new locations through moving air inside the respiratory track, and is thus redistributed to uninfected cells within the respiratory track and lungs. We do not need to prove the validity of this concept by experimental data because viral particles that can be discharged outside of the body to infect other persons must be able to re-infect new cells within the respiratory track. The infection process is vitally important from kinetic point of view. Before more powerful acquired immune response starts working, the body depends on the innate immune functions within the 4-6 days time window or several weeks for those with immune system compromised [311-315]. In the reinfection time window, the respiratory system is intermittently or repeatedly exposed to low temperatures or the body core temperature has caused vasoconstriction, uninfected tissues within the respiratory system are infected rapidly by the virus distributed by the dead air in each breathing cycle [2-4]. When the innate immunity is suppressed, spreading the virus to the entire respiratory system or a large part of the lungs must lead to the worst outcome. We found that warm air protection of the respiratory system is important not only before the initial exposure to the virus, but at all times from the initial exposure to the resolution of the infection. Warm temperatures can

also prevent additional infection caused by subsequent exposure to external virus. If a person initially has one point infected, more external viruses may get into the respiratory track to cause more infections at different locations. Although viral particles originated from the internal track are expected to spread by cell-to-cell transmission and circulating blood, those spreading methods are kinetically disfavored. Virus spreading by air redistribution within the respiratory cycles is the fastest. We believe that crippled innate immunity caused by low temperature is primarily responsible for faster infection of the whole lungs. Temperature alters spreading timing which is everything for this disease.

3. An anti-viral shield: temperature-regulated peripheral blood flow

For obvious reasons, maintaining a normal core temperature and local temperatures along the entire respiratory track should be the primary focus. Blood flow on the entire respiratory track works like an anti-viral shield to ward off viral infection. The best prevention and cure are to keep this shield working well in the entire risk period. Rhinoviruses, which infect the upper airway and sinuses, replicate best between 33 °C and 35 °C, and inhaling air at about 45 °C for 20 minutes can greatly improve the symptoms of a common cold [316]. In contrast, treating the common cold with aspirin causes an increase in the rate of production of the virus [317]. Since temperature and aspirin treatments do not depend on molecular-binding specificity and their effects can be extended to COVID-19 virus. Based on Barcroft [126], 45 °C is the limit that humans can tolerate, but most people can tolerate 42.5 °C. In a study, the forearm was maintained 33 °C and was heated by an air blower at 40-42 °C for 50 min, laser-doppler imaging which is proportional to local skin blood flow rose from the baseline at about 200 to about 500 in about 5 minutes, then reaches a nadir and then climbs to reach a plateau maintained at nearly 500 [318]. This experiment indicates that skin heating by air of 7-9 °C higher skin temperature could double the local skin blood flow even though actual skin temperature cannot reach the air's temperature. This study confirms Barcroft's finding [126] that heating above body core temperature can dramatically raise local blood flow, thereby improving innate immunity and anti-viral defenses.

Due to the great sensitivity of the innate immunity to peripheral blood flow condition, the loss of the viral shielding function may happen with little or no warning. If a person feels cold, the person's core temperature must have been too low and a reflex adjustment [303-306] is made to cause vasoconstriction as a heat-preserving measure to restore the lowered core temperature to the normal value. However, this life-saving measure opens the door to viral attack. Thus, it is vitally important to restore the core temperature as soon as possible if COVID-19 virus exists in the surrounding. A brief body overheat caused by exercise or spike high room temperature may lead to the same result. Lack of covering or too low room temperature during night sleep is one obvious cause, but most people do not know its adverse impacts. Exercise causes the body to generate excessive heat and thus triggers vasodilatation to transfer more heat to the skin surface for dissipation. The vasodilatation may be accompanied by sweating as additional mean for enhancing heat dissipation. High skin temperature and sweating help the body to lower core temperature quickly. If, at this point time, heat flow from exercise or physical activities stops, the core temperature will decline rapidly. Thus, the person will feel cold from lost heat and have compromised innate immunity. If the vasoconstriction is not improved as soon as possible, the person will get the same result of losing viral shielding protection. Exposures to both temperature fluctuations and cold air generated by air-conditioners in the summer are responsible for summer incidences, while exposure to temperature fluctuations and exposure to freezing cold air are responsible for high incidences in winter.

4. A predictive cure for COVID-19 disease: proactive body temperature management protocol (PBTM or PRTTM)

The following temperature management protocol is based on our personal experience in preventing cold and influenza. It has been used for years before, but we have refined it based on knowledge acquired in the last century. The goals used in the protocol can be deduced by comparing differences in temperature exposures in a hot summer and a cold winter. In a summer without exposure to air-conditioned cold temperatures, body core temperature cannot go down below a value of feeling cold and people do not breathe air that is lower than 28 °C. Under those two conditions, no cold and influenza could happen except by accident. Thus, the preventive goal is to maintain the core temperature so that the person will not feel cold under any circumstance. Practical methods for maintaining core temperature would depend on persons while some lifestyle techniques may be shared. A number of things can be used to maintain body core temperature. They include controlling foods, doing moderate exercise, and using coffee, etc. In cold seasons, restricting total calories intake should be reasonable because a low blood sugar level can cause the body temperature to fall. If one has to control total calories for other reasons, he should be aware of its potential adverse effects on body core temperature. In a situation no viable method for adjusting body core temperature is available, one can always do exercise to raise core temperature as an emergency measure, if health permits. Exercise should be performed with just enough intensity and duration to generate enough heat to feel warm without causing sweat. Sweating can cause excessive heat loss and thus results in peripheral temperature drop, which will cripple innate immunity again.

The second preventive goal is to avoid breathing cold air. One goal is to avoid breathing in cold air that is below 26 °C as much as possible. In a winter, maintaining the body core temperature is not difficult, but avoid breathing cold air in winter is impossible. We explore ways to avoid exposure and means to neutralize adverse effects of exposing to cold air. First, breathing cold air happens normally when people go out to work or shop; and the time window can be reduced to the minimum. Exposure to cold air may happen often in a relative short time. Second, one may warm up the body before being exposed to the cold air. The warming up will slow down the temperature drop along the respiratory track. Cold air can bring down local temperatures along the respiratory track. The degrees of impacts depend on the temperature of air and the body ability to generate heat. Before being exposed to cold air, do a little bit in-house warm-up exercise so that the body warms up and is ready to generate heat for use during exposure. Third, protective measures may be used to warm up the temperature of head, nose, face, and mouth. Those parts should be covered by clothing to raise their local temperature. When more of those parts of the head is kept warmer, cold air can depress local temperatures along the respiratory track by a few degrees. In addition, wearing a thick cotton mask may help to raise inlet air temperature because the mask is warmed up by previous exhaled air, the exhaled air strikes the face surface to warm up nose, mouth and covered face. In the next inhaling cycle, the mask and the face serve as a heater to pre-heat cold air inhaled in the next cycle. Mask's roles are not just reducing viral amount by ten folds, but also dramatically improve innate functions. Thus, wearing a mask is the most powerful protection in the cold winter. Breathing volume is also an important factor. In a cold winter, deep and slow breath may be better but faster breathing at large minute volume will dissipate more heat [322]. During exposure to cold air, controlling minute volume (liter/min) to a lowest value, if it is possible. Avoid doing excessive wasteful, large volume and fast breathing cycles because this breathing mode can cause excessive heat loss. Use nose to inhale while exhaling also through nose to

reheat nasal cavities. In the entire exposure, make sure that the body is generating more heat to heat up the respiratory track. If it is necessary to do moderate exercise to warm up the body, it is important to control intensity and duration to avoid sweating. If sweating does happen, the body will lose excessive heat and inevitably results in vasoconstriction leading to crippled innate immunity. If sweating happened, it is minimum to wipe sweat off completely or better to take a warm bath.

After the exposure to cold air is over, do a few post-exposure measures to raise core temperature and local temperatures along the respiratory track as soon as possible. Post exposure measures must be valid based on viral infection kinetics notwithstanding the binary infection-and-no-infection notion. After the membranes along the respiratory track is constricted, degraded blood circulation in the membranes results in crippled innate immunity and invites the virus to take advantage of the temporarily crippled anti-viral shield. It still takes two hours to two days for landed viral gene copies to make entry into the membrane of the respiratory track and to replicate sufficient viral amounts to cause meaningful damages to the respiratory system. There is an ample time to neutralize existing damages or continuous damage in whole or in part. If local temperatures are quickly restored and local peripheral blood circulation is restored to the normal or above normal levels, innate immune function can be restored in a similar time scale. Such measures prevent viral particles landed on membrane from making entire, activate anti-viral host responses, turn infected cells/tissues into anti-viral state, and finally allow immune cells to clear viral copies that have been entered. While medicine never teaches such measures, raising temperature should be presumed as the most powerful post-exposure measure.

Post-exposure measures include avoiding cold food and cold beverage. It is preferable to eat food that is slightly warmer than the body. A large amount of cold beverage can depress the body core temperature and thus cause the body to constrict blood vessels. Also, increasing the amount of water helps eliminate metabolic by-products more efficiently. The amount of water intake should be reasonable for those having high blood pressure. For those having no high blood pressure, addition of a small amount of salt helps keep mineral balance.

Post-exposure measures should be comparable to exposure severity and duration. If exposure to cold air is severe and long, if exposed cold air is known to contain a higher concentration of viral particles, or if the exposure is in a pandemic season, or the person is highly susceptible to cold and influenza, stronger and more post-exposure protective measures should be taken. Post exposures should be taken as soon as possible after exposure to cold air, and should continue throughout the time window equivalent to the incubation time.

Making sure that the body is not exposed to cold temperatures within an incubation time window. Within this time window, body should not be in a state to feel cold. If one feels cold even slightly, the body has constricted blood vessels; and it is even possible the body might have constricted blood vessels without feeling cold. One needs to learn how sensitive personal temperature sensor is and should error in the side of keeping warm rather than repeating exposure to low temperature. One post-exposure protective measure is to breathe warm air of 42.5 °C for 20-40 minutes, and may repeat this measure several times on the first day. Warm air can raise local temperature by a few degrees and force blood vessels to dilate; and breathing warm air periodically is the best measure. Additional measures include taking a warm bath as soon as the initial exposure and taking more warm

baths afterwards. This can massively improve blood flow per Barcroft [126]. A warm bath can trigger the body to massively dilate blood vessels and is expected to restore innate immunity and improve heart, lung, and kidney functions. We have used this for years as the primary measure to stop or abate a coming cold and influenza. Japanese take warm bath as part of its culture and this may be one of the reasons for the low incidence and death risks. Another effective measure is to use heat-generating drink that can help the body warm up and thus dilate blood vessels. A cup of warm ginger tea is our classical favorite. A study found that the ginger enhances thermogenesis [319]. Cumin generates less intense heat that will warm the body up without causing sweat. Other choices include a cup of hot coffee, date soup, etc. as long as it does not cause allergic or toxic reactions to the user. There are a large number of thermogenesis foods and spices, not all are good. One can find the best options from personal experience and published studies. If those options are not available, doing moderate exercise is always mean to heat the body up to the warmest point before sweating. After those measures are taken, even if a cold, influenza, or COVID-19 eventually occurs, it will be much milder and most probably will resolve naturally.

If a second exposure to low temperature happens within a post-measure window of a first exposure, restart the post-measure time from the second exposure. If the first exposure has resulted in viral entries, it may trigger the acquired immune response and thus the risk from the second exposure is lower. However, to improve the acquired immune power, post-exposure measures are still necessary. It is possible that the first exposure has not resulted in the viral entries or entered virus has been quickly cleared without meaningfully triggering the acquired immune response, protective measures within the whole time window are important. Regardless, immediate measures after a latest exposure is necessary, and restarting the time window can err in the side of protection. If one can repeat this cycle several time, the chances are that the person will acquire some protection against the viral like vaccine.

For a health person, the post-exposure time window is the duration from suspected viral exposure to the time that symptom would appearance. The minimum time window is about 14 days for healthy persons. It should not shorter than 6 days. For those with immune compromised, the time window can be longer than 14 days. To track the time window, one may write down each exposure to cold temperature. For example, if on day 1 exposure to low core temperature, and on day five, exposure to 0 °C cold air for one hour, the widow time should restart from day five, and post-exposure measures are taken for the time window from day five. Warm temperature is a required element for acquired immune function. Thus, one should maintain reasonable body temperature for the entire season. Extreme cold exposure will cripple both innate immunity and acquired immunity. Like any influenza virus, it can cause infection.

This protocol can be used by all people due to extremely low risk. However, people with particular health issues should discuss with their doctors if there is any compelling reason to avoid, adjust, or add anything to this protocol. For those who are insensitive to temperature sensation, they need to learn when it is too cold and try to figure out best body temperature.

After the pandemic season is over, or the person has improved resistance to the virus and other viruses, or the risk of getting the disease is gone for whatever reason, there might be a need to retrain temperature regulation sensitivity. The purpose of retraining is increasing personal ability to adapt to cold environment and low temperature.

5. Deep breath exercises as the most powerful measures

We list deep breathing exercise as a separate measure. We discussed it elsewhere several years ago. Dr. Wu started using deep breathing exercise solely for managing cold and flu. He learned Qigong and then used deep breathing exercise as the main measure for preventing and mitigating cold and influenza. This art was used for thousands of years in all civilizations even though scientific mechanisms were not understood. Some physiological effects were established in studies published before 1980 [226-232]. One review concludes “the breathing pattern, as defined by respiratory rate, tidal volume, diaphragmatic activation, respiratory pauses and passive *versus* active expiration, has a profound effect not only on respiration efficiency but also extending to cardiovascular function and autonomic function, where the effects are bidirectional.” [226]. Most of functions are not directly investigated. Deep breathing exercises affect the body by raising body temperature, improving blood circulation, increasing oxygen pickup, harmonizing hormonal actions, etc. each of which can beneficially affect innate immunity, anti-viral responses and tissue repairing abilities. We consider it as the most powerful weapon for fighting cold and influenza including COVID-19 diseases. It may be used in any time after exposure, particularly in the post-exposure time window. It should be performed in a warm and well ventilated room or environment. Do not do the exercise in a cold environment.

There are all kinds of practical rituals, many of which can be found in public domain. Meditation, deep breathing and Qigong share similar elements. Despite conflicting and confusing instructions, all deep breathing exercises are intended to improve the lung's ability to pick up oxygen, relax the whole body, improve relative energy metabolism, improve blood circulation, and improve emotional state. They improve immune functions [227-228]. True effects may not be reflected in changes in absolute numbers. Even though the amount of increased oxygen pickup is not significant, overall oxygen supply is dramatically improved on a relative scale because this happens while the demand for oxygen is lowered during such exercise. Predictably, energy metabolism is improved while the body's demand for energy is reduced. Since deep breathing alters both inhaling and exhaling cycles, it is a custom exercise for the lungs; most beneficial effects are expected to confer on the lungs, which are also the main targets of the virus. Deep exercise is extensively studied in China from 1950 to 1960 [231-232]. The exercise can cause the body tissues and blood vessels to relax and thus raises the mobility of immune cells along capillaries and tissues. Deep breathing exercise may improve signaling efficiency as a result of improved energy metabolism. It can create favorable blood vasculature in support of innate function, anti-viral activities, and tissue repairs. To appreciate the immense benefits of deep breathing exercise, one needs to pay attention to the critical role of rate competition between conflicting biological processes. Health outcome is always lost imbalance between the overall viral damaging process and the overall repairing process. If viral replication is faster than the immune system can clear, or if the viral damage rate is faster than the tissue can repair, if more immune cells are caught in inflamed tissues than they could exist from the tissues, or if more wastes are generated than what kidneys can remove, the outcome must be the bad. Absolute rate of any of those processes is not controlling. As long as any of the processes are out balance, death is inevitable. Deep breathing exercise can alter process balances and can be used in any time and anywhere without any costs. Medicine ignores this most powerful healing art that has been used for thousands of years in nearly all civilizations.

Actual benefits of deep breathing exercise depend on personal skills: the achievable benefits depend on correct use of focus, actual ability to achieve relaxation, correct breathing method, and many other factors. For a given person, exercise benefits depend on body condition, exercise times, practice duration, etc. While some individuals can deliver powerful benefits, others may achieve limited benefits. Exercise can also deliver some benefits as long as the person makes reasonable effort to learn the exercise. Deep breathing exercise may be combined with regular exercises and sound-uttering exercises. Each exercise session may last 20 minutes to one hour, and be repeated several times a day. Based on related studies, one hour practice may confer great benefits on abating viral infection. Three hour exercise right after exposure to severe cold temperature may stop or greatly mitigate infection.

Practicing deep breathing exercise can slowly improve personal sensitivity to detect physiological state inside the body, particularly the lungs. It is well known that people with great experience can feel body internal existence. Some subtle life signs of lungs and heart beating can be detected internally by most people. In performing meditation or deep breathing exercise, the person's focus is directed to the inner body, and thus increase sensitivity to feel heart beats and mechanical movement inside the thoracic cage. If the person pays great attention to the lungs, one would sense changes caused by exposures to low temperature. In hot days, the person could feel that the content inside the cage is warm, which is often referred to as existence of life energy (Qi). If the person is exposed to cold air for more than a few minutes, the level of warm feeling in the lungs diminishes or completely disappear. If exposure to low temperature is severe and long, not only does the subjective sensation about the cage content decline, but also the temperatures of the chest. By self-training, many people could tell differences in subjective sensation about healthy lungs and cold-stressed lungs. Much obvious changes can be felt if the lungs are infected or are about to develop a respiratory or lung infection. This skill can be a powerful way to predict a coming cold, influenza or other viral infection.

The skill of sensing inner Qi can help patients to collect personal kinetic data for respiratory infection. Viral infection can start at anywhere in the respiratory track such as nasal cavities, sinuses, throat, bronchus, deep bronchus and lungs. It may take hours to more than one day to have an initial infection to reach other locations. For example, an infection that is originated in the left nasal cavity may move to the right nasal cavity. The time delay is about several hours to more than one day. Consensus incubation time for COVID-19 between an initial exposure and systemic symptom is one to several days. Based on our experience, viral spreading from one locality to new localities may take several hours. If multiple exposures take place independently, it may take similar ballpark time windows to develop each localized infection before systemic immunity is developed. Study findings, personal experience, and reported stories all show that there are reasonable windows within which post-exposure protective measures can be taken. The disease process is never like a binary infection or no infection event. Disease outcome depends on exposure viral load, initial locations, repeating exposures, immune system responses, and organ health. That is why the disease can manifest as nothing, a mild flu, severe lung infection, disability or death.

After the respiratory track has been exposed to cold air, the person will not be able to feel the same sensation about the lungs. After a viral infection has resolved, the person will not be able to feel the same sensation about the lungs for many days. Those observations suggest that lung physiology cannot be fully restored soon after exposure to

low temperature. Those observations are consistent with long-lasting lingering effects of influenza and COVID-19 that have been extensively reported. We believe that delays in regaining normal sensation may be caused by continuous tissue repair that may take much longer time to complete. Those observations should be considered in developing best preventive measures. A person in the process of recovering from a viral infection may be susceptible to other viral infections and should exercise due care.

6. Potential side effects of proactive temperature management

This proactive body temperature management protocol is for containing the pandemic, as a survival strategy. It is the safest among any drugs that might appear. However, everything including air, water, and thinking can have side effects. For example, excessive warm is not necessary for healthy children. Growing *Xenopus laevis* embryos at cold temperatures results in an increase in the number of spinal motor neurons in larvae [324]. Thus, warm temperature is not good for grow up. Another side effect is that warm temperature may cause male infertility [325]. These findings suggest that maintaining too warm for extended long term can have adverse effects. Those side effects are not relevant to the elderly people who are vulnerable to the COVID-19 disease. For young and healthy people, proactive temperature management should not last too long and measures should be reasonable. Warm air for inhalation should not be too high. If the body is maintained in a warm room, the temperature should not cause obvious discomfort and should not reach the fever level which could damage the brain.

RELATIVE BENEFITS OF PANDEMIC INTERVENTIONS

A. Predicted Effectiveness of Lifestyle Interventions

A body of evidence has shown that high infection and death risks are caused by the massive disease agents, which adversely affect humans through modern lifestyles. We note that COVID-19 death is nearly always associated with chronic diseases and diminished organ capacities. Lifestyle interventions are the best options because they have 100% potential to cure and prevent COVID-19 disease.

The virus can attack and kill immune cells [243-246]. This finding implies a grave risk. We hypothesize how the disease get into this situation: the fight between the virus and the immune system is like a military battle which is always controlled by the supremacy side. If viral concentration SARS-CoV-2 rises slowly, the virus does not have a decisive power to kill substantially all T and B cells in the bloodstream. If the immune response rapidly, it can produce enough antibodies to clear up the virus. However, if viral concentration rises rapidly while immune system is activated with a long delay or respond slowly, the virus might reach a concentration to kill substantially all T and B cells that are moving into the bloodstream. We suspect that viral infection of T and B cells may be not uncommon, and what is unique in this disease is that viral replication in some persons dominates the underdog immune response so that the immune system has no chance reverse their positions. Thus, what is important is how to prevent the virus to gain its supremacy to suppress the immune system. This hypothesis should be understood in light of the retention of white blood cells in the lungs, and effects of metabolic toxins and nutritional condition on immune cells. The death of immune cells in the lungs does not prove that the virus is particularly lethal to immunity cells. The outcome could be changed by altering this speed competition

in the earliest stage, but hardly in a later stage. If the virus is not cleared, it is possible the virus may induce AIDS like disease many years later. No one can bet whether it will happen. This new “AIDS” cannot be prevented because accurate testing is impossible [426-433] and can be transmitted by airborne particles [432].

B. Predicted Effectiveness of Proactive Body Temperature Management

Temperature is the most important factor affecting infection and death risks. All kinds of available epidemiological data reveal that proper management of temperature could reduce at least 90% infections and deaths. If we extrapolate the Japan’s baseline incidence rate to June, 2020, it has about 50 daily cases, while its November daily incidence rate could reach 2,585, low temperature is mainly responsible for 50 times increase. The US. Incidence rate rose from about 20,000 in June 2020 to 220,000 in the early winter, reflecting an 11 times increase. We also note that U.S. data reflects a peak centered in the end of July, which indicates the effect of air conditioner’s effects. If we estimate the incidence rate for highest in the U.S. in the early winter to the lowest incidence in Japan, we find they differ by $(244.724/328)/(50/126)=1,912$ times. This huge difference represents both cultural/lifestyle/health difference and cold temperature effects. The U.S. citizens are much more unhealthy, I will allocate half of contributions to cultural/lifestyle/health factors and the other half to temperature. Temperature is responsible for 44 times increase. Even many lifestyle factors in Japan are integrated with temperature management [441]. The people take hot bath typically between 40 and 43 °C in evenings. That is the temperature for raising local blood circulation by 20 to 30 times relative to cold temperature and powerfully boost innate immunity to contain the virus (see all kinds data we cited). If one understands the magnitude of temperature’s effects, he would have no trouble to find that proactive managing body temperature can reduce U.S. incidence rate to 1%. We note that U.S. incidence data reflect about 10 folds difference, this is because temperature fluctuations in summer raised its baseline. There is a further room to reduce the rate by another 90%. Thus, we estimate that it is very realistic to reduce daily case rate to 1%. We must find that the pandemic can be ended by using our protocol teaching sophisticated temperature management skills. As a fallback estimate, the protocol would easily reduce incidence rate to about 95% or less. It is suppressing to note that all temperature-related studies are conducted to advance basic research or marketable technologies [250-263, 267, 351-357], but no research is done to enable people to manage body temperature to avoid infection and death. We note that more than a thousand of clinical trials are being conducted to discover new anti-viral drugs for the disease [358], but none is attempted to enable people to master basic skills for proactively managing body temperature, which is much more powerful than any anti-viral drug targeted in a single mechanism.

C. Adjusted Effectiveness of Vaccines

Vaccines may reduce influenza chance by 40-60% and a full immunity cannot be developed due to a kinetic problem [4] and viral mutation [359]. The efficacy of Pfizer vaccine is reported to be 95%. The Pfizer study enrolled 43,538 participants started on July 27, 2020 and thus cannot predict long-term benefits. Per its Protocol C4591001 from <https://www.pfizer.com/science/coronavirus> [326], the study does NOT include people who did not want to be vaccinated. The trial specifically excluded volunteers with the following conditions: known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), hypertension, diabetes mellitus, chronic pulmonary disease, asthma, current vaping or smoking, history of chronic smoking within the prior year, chronic liver disease stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/

min/1.73 m²), resident in a long-term facility, BMI >30 kg/m², and anticipating the need for immunosuppressive treatment within the next 6 months. If we rank human infection vulnerability from the most vulnerable to the least vulnerable, the exclusionary criteria would exclude at least 20%, potentially 40%, of U.S. population. The death rate of the COVID-19 is about 4% in the U.S. (2% in some other countries) of infected persons, and deaths happen among elderly, obese and chronically-ill people [13-15].

For several reasons, vaccines alone cannot best address the pandemic. First, for those with immune system suppressed, vaccines do not work well and trial protocols have excluded the immune suppressed [326]. Vaccine trials have used volunteers who are willing to accept adverse reaction risks and used specific exclusionary criteria to exclude a variety of vulnerable people. As a result, old, fragile, obese, immune suppressed, and chronically ill persons are often excluded. Based on data on chronic ill population [348-349], we estimate about 40% of the population might have been excluded. If we make a ballpark adjustment, only about 40-60% general population would avail the benefit of vaccines. It was once reported that 48% deaths in Maryland happened in nursing homes [15]. Many of them could not be vaccinated. Also, vaccine trials are intended to run at least one to two years, available interim data reflect only short-term benefits. Since the virus, an RNA virus, mutate fast [359], long-term benefits of most vaccines are expected to be poor [360-362]. No COVID-19 vaccine currently in development has shown an ability to prevent infection through the nose. We attribute this to impaired immune cells mobility that are caused by extremely poor local blood circulation in the winter. In addition, lungs are not an organ that can be reliably protected by acquired immunity because the virus attacks the lungs from the path from the respiratory track to lung cells without traveling through blood [5-6]. This infection mode leaves the short time window, within which the virus could cause sufficient lung damages. Second infection and second serious infections have been reported [362]. Thus, the benefits of vaccines is limited and partial. A full protection must include temperature management and lifestyle interventions.

D. Benefits of Antiviral drugs

Good anti-viral drugs have not been found [7]. Most drugs target one step or a single biological pathway. The chance of success of anti-viral drugs are limited by several fundamental limitations. First, a synthetic entity has not been in the food chain in evolution and they tend to have side-effects that patients cannot tolerate. True side effects, as weak effects, cannot be accurately determined by clinical trials [8-9]. When a patient's biological pathways have been disturbed by hundreds to thousands of toxic substances, it is highly unlikely that a drug can cure the disease by intervening a target mechanism. The five health properties in the vulnerable persons are impaired by offending lifestyle factors. If a drug is used to intervene one step in a biological pathway, the drug is predicted to be very poor. By using a linear model, if a lifestyle factor (e.g., vitamin C) has 1 unit benefit, a drug for correcting this lifestyle factor can deliver only one unit. In contrast, simultaneous correction of 100 factors would have 100 units benefits. One big flaw in using a synthetic drug is focusing on possible benefits from the intervened step, but ignore adverse effects of massive offending lifestyle factors on the rest biological pathways. Each vulnerable person might have been damaged by any and many of thousands of substances in different concentration combinations. Some substances include arsenic, lead, nickel, toxins, accumulated fats, malnutrition, excessive calories, radiation, infectious agents, etc [78, 80, 93, 149-163]. They cause distinctive and systemic damages to the whole body. Some damage liver, some damage kidneys, some damage heart, some damage lungs, some

damage the immune system, some damage the Central Nervous System, and some damage any or all combinations. Thus, a drug intervening one single target mechanism cannot be a cure for the disease. The reductionist approach focusing on one single or few steps are consistently found to be poor [330-341]. After many organ functions have been impaired with the driving force to continue inflicting more damages to tissue, a cure cannot be a synthetic drug for altering one step in the immune system or viral replication process. Even if the immune system is strengthened by a drug, the by-products from immune response may exceed the capacities of the impaired heart and kidneys, and kill the patient. Drug efficacy is repeatedly found to be the minimum [111-113, 164-171, 342-344], but even such marginal ratings are under challenge because drug trials could not detect how much of organ functional reserve is diminished by the drug, how much of the adverse effect has been hidden by lifestyle factors [8-9] and how surrogate endpoints used in drug trials distort conclusions. Even the concept of using a drug to cure disease is never proved. This concept was extended from ancient nature-made products without any proof. Each synthetic drug inevitably distorts one or many of other unintended biological pathways. Adverse drug reactions (ADR) must be presumed, and cannot be tolerated by those with diminished organ functions.

E. Other Benefits and Risks of Lifestyle Interventions

1. Lifestyle interventions are the only real cures for future infection

Personal health conditions are shaped up by personal lifestyles, environments, diets, activity habits and emotional state. Similar levels of toxic substances or their profiles exist in the same water, same air, same environment, same food, some sources of food, food with same contaminants, same cookwares, same household products, same clothing, etc. Many offending lifestyle factors may be hidden in same life activities, same houses/buildings, same environments, same production lines, same working habits, same thinking habits, etc. Repetitive exposures are implied by habits in light of a large number of research findings [29-94]. They affect personal whole health by different factors in different degrees. The massive findings establish that most chronic diseases are in part or whole caused by offending factors which impair vital organs, CNS, the immune system, cellular and biological pathways, and cell and organ structures. When disease-driving forces are in personal lifestyles and activity habits, they not only keep aggravating existing diseases, but also create new diseases. To cure diseases that are rooted in lifestyles, environments and culture, drugs are wrong options except in limited situations. It is time to treat lifestyle interventions as the primary options for chronic diseases including COVID-19.

2. Lifestyle interventions are the best options for the vulnerable people

Lifestyle interventions are particularly suitable to the elderly, vulnerable, and chronically ill people because they have the lowest risks. Lifestyle interventions are most important to low-income families because the interventions are free and low-income families are more likely hurt by low quality foods, toxic substances, contaminated household products, emotional distress, lack of exercise, misuse of prescription drugs, lack of entertainment, etc. The interventions can help low income families reduce medical service costs and increase their ability to conquer other diseases. The interventions are best for retired people because they have time to learn self-care knowledge and develop basic skills for reducing infection and death risks.

3. Lifestyle interventions can prevent secondary health effects caused by COVID-19.

At present, society has relied on locked-down and home isolation as main measures for fighting the pandemic [1] and they cause secondary adverse health effects [413-423]. The map clearly predicts how movement-restriction practices affect human ability to resist the virus and surviving from infection. As a result of using movement-restrictive measures, most people do less exercise, eat more food, eat more fast food, eat more processed food, watch more TV, play more games, absorb more toxic disinfectants, inhale more toxic chemicals, worry about employment, are often in isolation, etc. Increased exposures to offending lifestyle factors are reflected in lifestyles, diets, environments, and daily activities. Secondary health effects caused by pandemic measures are realized through the same mechanisms shown in Table 1. As a result of influences of the secondary effects, the population becomes more and more susceptible to viral infection and severer lung damages. Secondary effects harm the vulnerable people more severely because their organ functions are closer to death thresholds. Financially disadvantaged people are more likely hurt because financial difficulties force them to buy low-quality diets, harmful hygiene products, defective protective devices, etc. In addition, they may lack time for exercise, entertainment, and sleep. In addition, inadequate education and lack of medical knowledge may put them at higher risks of getting infection, repetitive infections, and cross-infections. Worries about jobs and lack of income may cause emotional distress and depression. A person who would have survived by marginal organ functions may die if secondary effects have depressed their organ functions to closer to death thresholds. We noted that within half a year time window, secondary effects have resulted in weight gain, depression, degraded health, etc. among a good portion of population.

4. Obstacles to use of lifestyle interventions

Biggest obstacles to the acceptance of the lifestyle interventions and proactive temperature management are conflicting conclusions in a large number of clinical trial studies. While people believe in lifestyle benefits to some extent, they have been told that lifestyle interventions cannot cure diseases. Clinical trials have been regarded as the final arbiters of medical controversies. Before flaws in clinical trials are understood, public existing medical knowledge will continue influencing population's health wisdom and cause people to make wrong health care decisions. By believing in negative findings of clinical trials, patients may give up their efforts whenever they do not want to adhere to lifestyle disciplines. Moreover, many lifestyle factors work slowly, and patients may quickly find "no benefit" and resume their old life activities. Therefore, what is far more important is to correct public health wisdom.

IMPLICATION OF PUBLIC HEALTH POLICIES

A. Medicine Lacks Inherent Incentive to Find Cures For COVID-19

We conducted a search on Nov 28, 2020 using terms COVID-19 and drug on www.clinicaltrials.gov [358], and we got 2,165 clinical trials. Among those registered trials, a few are conducted to test vaccines or biological substances, most of them are intended to find drugs for treating COVID-19 disease or investigating related drug interactions. Only one trial concerns exercise and lifestyle intervention on clinical outcomes (NCT04396353); only one concerns digital service (NCT04453475); one concerns video-based exercise (NCT04346953); and one concern the effect of exercises on young adults (NCT04346966).

Not one single trial in this giant database is to investigate effects of temperature on COVID-19. We also found 126 government-sponsored clinical trials in the database.

Massive evidence has established that the flawed population approach is directly responsible for this disastrous pandemic landscape. The population medicine transfers death risk from a tiny small vulnerable population to the whole population, thus having an effect of imprisoning all people. After having grossly expanded the disease population, medicine takes off all potential cures that have passed down from evolution. The best treatments for the vulnerable population are lifestyle interventions including skillful body temperature management. Based on the extraordinary effects, temperature is the first thing that should be used as the weapon against the pandemic. However, medicine considers only a few things that can be commercialized.

Not a single trial in the trial registration site [358] explores use of body temperature obviously because temperature is not a revenue-generating object. Interest holders seize the pandemic as opportunities to make largest profits. They are willing to invest massive research fund on synthetic drugs because they can own drugs for monopoly. Even governments got into the business of promoting enterprise research activities and medical service revenues. Massive pandemic deaths, economical disruptions, dysfunctional social activities, and miserable human lives are inevitable result of such a medical system.

B. Challenge to the Tenet of Using Synthetic Drugs

We have witnessed on-going HIV epidemic [363-365], the cancer epidemic [366], and the COVID-19 pandemic. Each of those diseases has become a global health crisis. Medicine attributes AIDS to the HIV virus, cancers to genetic mutation, and the COVID-19 to the virus. Our analysis shows the real problem is impaired human immune system and whole body health. AIDS is clearly associated with heavy metals [364], chemical compounds [365] and a large number of systematic environmental, ecological, social and economical factors [363]. Human inability to eliminate HIV virus are in part caused by massive toxic substances in modern time. Similarly, the public has been told that cancer is caused by mutation [368], but massive discoveries and our observations show that cancer is a disease caused by pollutants, mental stress, and a fault lifestyle [366, 369-372]. In this study, a century of medical findings collectively show that COVID-19 disease is aggravated by loaded toxic substances in the human body.

1. The tenet of using drugs has never been vetted

The tenet of using synthetic drugs to cure disease were NEVER vetted but driven by human ability to synthesize drugs [164]. Using “medicine” to cure diseases was a concept proved by human experience in the entire human history. The validity can be shown by considering using orange juice to correct vitamin C deficiency or using natural products to kill insects, bacterial, etc. by impairing their biological pathways. After the man is able to synthesize drugs, old medicine suddenly was expanded to include synthetic drugs to intervene human biological pathways. Due to lack of knowledge at that time, the idea sounded so natural that there was no need to prove its validity. The term medicine was changed to mean synthetic drugs. In more than a hundred years, medicine fails to find cures for any of the major chronic diseases by using synthetic drugs [342-350]. One problem is that human biological pathways are integrated as a distinctive network. Using a single drug to intervene one pathway cannot speed up or slowly down its process according to human wishes. This is similar to a traffic network, the system performance of which cannot be improved by enlarging or narrowing one segment only. It is similar to a car,

performance of which cannot be improved by increasing fuel injection without improving heat dissipation speed and combustion waste removal capacity. Every physical models we can find suggest that use of single drugs cannot work.

The tenet is challenged even in field of using target drugs. In the last half century, immunological researches brought hope for conquering challenging diseases. The final verdict is still a general failure [342-345]. The disappointing results can be explained by several reasons. First, the accuracy of substantive medical knowledge should be questioned. Most of findings are expressed as possible mechanisms. Knowledge of cell signaling paths does not contain much details such as spatial features, relative process speeds among conflicting or competing signaling paths, effects of interfering factors, interactions with Central Nervous System (CNS), etc. [114, 290]. We believe that the whole cell signal paths system is so complex that there is no suitable method for accurately characterizing them. The truth may be far complex than what is shown in those studies. Even if those concepts were correct, they most probably reflect only a small part of reality. For example, gene expression of a large number of anti-viral proteins may be controlled or influenced by cell condition (a huge number of sub-factors), energy availability, other substances, CNS and hormones, fluid properties, chemical environment (nutrients, pH, minerals, ionic strength, viscosity, charges, etc.), and interfering substances including heavy metals, organic compounds, inorganic compounds. The final cell behavior relevant to personal health cannot be determined by focusing on one single path by any imagination. Thus, final response in a real person to a synthetic drug cannot be predicted by such overly simplified concept. At present and perhaps by end of civilization, humans are unable to study all cell signaling paths as a whole system. Thus, researchers not only lack a suitable method for addressing the whole system, but also ignore hundreds to thousands of interfering factors. Leaving cell conditions out, heavy metals, organic compounds, imbalanced nutrients, and CNS can cause enough problems. While benefits cannot be accurately predicted, their side effects are absolute and unpredictable [110-113, 165-171]. When human cells and blood are loaded with harmful substances, they can impair biological functions slowly by the mentioned mechanisms. Those problems cannot be denied simply because the matter is too complex to study.

2. Overwhelming evidence refutes the drug tenet.

The tenet of using single drug as a cure has been refuted for those reasons: (1) the reductionist model, as compared to holistic model can deliver only a tiny fraction of benefits [8-9] and it is clear that lifestyle interventions can cure diseases and drugs cannot; (2) drug research model fails to take into account up to 70% of organ reserve function [16-18] and thus often massively writes off true side effects; (3) most studies cannot detect long term side effects due to limited duration and due to interference by hundreds to thousands of other factors; (4) the drug independent action model cannot represent prevalent drug-drug and drug-compounds interactions in humans; and (5) the binary scale used in clinical trials can easily introduce 50% additional errors [2]. Due to those reasons, drug side effects are grossly underestimated. At the early time, it was not understood that vital organs have massive redundant functions and the existence of so many lifestyle factors. The flaw is also revealed in the reductionist treatment approach, which is found to be poor consistently [327-341]. Many of those problems have been found after 1980, medicine lacks any incentive and channel to correct them because interest holders promote medicalization. In light of the accuracy required in maintaining personal distinctive biological networks, there

is no basis to believe that drug-based treatment protocols can cure chronic diseases other than managing symptoms.

The tenet may be wrong for failure to include CNS. We proposed a theory on the CNS's role of regulating biological pathways like a computing program [28]. Per our theory, chronic diseases are like acquired skills similar to ones for performing a triple loop. The skills are stored in CNS memory. If our theory were proved to be correct, changes in health properties are determined in a main part by the CNS. CNS role was noted in 1875 [373] long before massive study findings were published. CNS role implies that even if a drug is used to speed up a particular biological pathway, the overall condition in the body may cause the CNS to send signals forcing the body to take contrary action. This theory explains the crucial role of the CNS in chronic diseases through influencing biological and cellular processes and immune system [28, 188, 369-377]. Medicine has produced massive evidence to show that CNS is part of diseases.

The tenet is refuted by the flaw of the toxicity independent action model, which is found to be wrong even for a two metal system in an animal model [434], but it still controls population health not because it is right but because it helps interest holders to generate profits. Now, thousands of toxic substances are present in air, water, environment, house products, buildings, and whatever we contact [29-94]. The actual harm is much worse than what could be revealed in animal model [434] because research models would not detect weak cumulative effects. Different toxic substances affect health by binding to the same enzymatic sites, impair different steps in the same pathways, and affect multiple points in the biological network. There are ample factual basis for toxic substances to work synergistically. Regardless of mechanisms, damages must be accumulated: a house stricken by thousands of bullets must be worse than an identical house with just one shot. The effect of each toxic substance in presence of a massive number of other toxic substances cannot be determined by clinical trials.

Due to those flaws, benefit-to-risk ratios for drugs are grossly exaggerated. Since medicine has never justified the tenet of using synthetic drugs, and all data we can find from literature show they have little benefit but overwhelming adverse effects. We thus officially reject synthetic drugs as cures for chronic diseases. Medicine cannot correct those obsolete and wrong theories and treatment options because they generate massive revenues.

C. Interest Holders Promote Medicalization

Medicine has gained its popularity by taking the advantage of success in treating acute diseases. Since medicine is a financial creature and a professional art, it is naturally driven by money [378-394]. Under the U.S. or other similar legal systems, interest holders naturally explore medicine for maximum profits and naturally take advantages of all flaws to achieve maximum benefits. They promote medicine as only science-based medicine by spending tens of billions dollars advertisements [378]. After the flawed science is promoted as best science, their adverse impacts are far-reaching, widespread, and devastating. They affect not only treatment of diseases, but the life and wellness of every person and every family in every nation. The flaws also affect all species in the world by adversely influencing our environment, ecosystem, and climate. They also affect political and social justice indirectly because they result in massive waste of medical spending and responsible for creating the incurable notion.

One adverse effect of the flaws is realized by legalized monopoly. Interest holders take advantage of the flaws as revenue-generating machinery. Since clinical trials and reductionist treatment models are most favorable to revenue-generating objects, interest holders have inherent incentive to promote their scientific merits [380-381, 391-394]. As a result of their concerted promotions, flawed medical models are promoted as final arbiters of medical controversies and injected into laws, regulations, funding policies, social policies, cultural beliefs, literature, textbooks, etc. Achieved legal protection for flawed research models work like perpetual patent protection for revenue-generating medical objects.

To achieve best financial goal, interest holders must find the largest number of patients and sell the largest number of treatments that can be monopolized. The U.S. patent law favorably protects man-made inventions; and the U.S. Supreme Court favors man-made drugs [395-396] which are known to harm long term health and may cause cancer. Due to such patent protection preference, interest holders cannot invest their money to promote anything made by nature or from nature. If an entity can own temperature, influenza and COVID-19 cannot be even an issue in the public media. Promoting synthetic drugs is the best mean to realize medicalization [378, 380]. Synthetic drugs can turn chronically ill patients into lifetime revenue feeds because none of synthetic drugs can cure cancer, heart diseases, mental diseases, COVID-19 infection, infertility, increasingly popular mental disorders, etc, but cause more chronic diseases [109, 345, 348-350]. Despite repeated failure, medicine clings to synthetic drugs because they can generate revenues. They are succeeding in turning the medical industry to a \$6 trillion industry in the U.S. [349]. Globally, medicine has become a revenue generating system comprising three components: causing people to get diseases by increased chances by various ways, dissuading patients them from using safe and non-medical methods, and treating them by drugs for revenues, which make them more ill, and thus repeat new cycle.

A massive number of studies done in the last half century produced irrefutable evidence showing the preventive and curative effects of lifestyle factors. To limit their effects, medicine separates prevention from treating disease, a concept has limited merit. By using this creative approach, medicine refuses to recognize the curative benefits of lifestyle interventions and anything other those revenue-generating objects mainly by relying on conclusions from flawed clinical trials using reductionist treatments. To justify the failure of finding cures, medical literature uses “treatable” as a reason for using drugs. Interest groups promote drug monopoly by disseminating information that anything not approved by FDA cannot cure or treat diseases [397-398]. By relying on flawed research conclusions, medicine disproves lifestyle interventions for lack of evidence. Medicine appears to do well in preventing deaths in AIDS. The flaw in this assessment is same as the assessment for cancer treatments. After medicine has excluded lifestyle interventions and everything else under the Sun, it does not know whether temperature, air, moisture, pressure, laughter, thinking, etc. would be much better cures. Indeed, cancer self-resolution triggered by changes in lifestyles is much better than cancer drugs.

Medicine does the worst by misleading the population that lifestyle interventions cannot cure diseases. As a result of influence of such propaganda, cancer patients, COVID-19 patients and chronically ill patients are willing to ingest toxic and even carcinogenic drugs for achieving health that cannot be realized. It systematically excludes experienced-based medicine, folk remedies, lifestyle interventions, personalized

treatments, all by flawed conclusions from clinical trials [397-398]. The incurable notion is the worst aggravating factor for cancer patients.

Flaws in medicine is responsible for creating and maintaining the medical treatment culture of promoting narrow treatment options for medicalization. If true beneficial effects are accurately rated and long-term adverse effects are correctly rated, the real benefit-to-risk ratio of drugs is much lower than the nominal values that are presented to the public. However, much bigger errors are caused by excluding the curative benefits of lifestyle interventions and all non-medical treatments. The benefit-to-risk ratios of lifestyle interventions are much higher than those for drugs. The population relies on exaggerated treatments claims to their detriments.

Medicine lacks channels for correcting flaws due to influences of money [378-390, 392]. Medical literature is filled with obsolete, flawed or incorrect knowledge including drug-side study model, cancer theories and treatments [343, 368], use of binary disease system [9], epidemiological models [5-6, 97], toxicity independent action model [8-9].... When each of those models was first used, its accuracy was not a problem [424-425]. After they have gained general acceptance, they are incorporated in laws and regulations and are relied on by the business of interest holders. Some problems are caused by changes in the world or revealed by later research findings. When the world environment is clean, researchers could naturally assume that each toxic substance affects a person independently and had no reason to think that hundreds to thousands toxic substances attack each person.

Clinical trials become the magic shield for all flawed theories, models and practices. Influenced the toxicity independent action model, the population is misled into a belief that a person can protect himself by limiting each substance intake. This fundamental flaw cannot be corrected because it has been in laws, regulations, agency practices, and is relied on by businesses. By relying on flawed models and misleading findings, people are willingly to ingest toxic substances daily from a variety of sources. We believe that most toxic substances such as artificial colorants, food additives, text modifiers, flavors, etc. could be avoided by choices; some substances could be avoided or dramatically reduced by making reasonable efforts; some toxic substances can be massively reduced by urging governments to impose stricter environmental and product regulations. Unfortunately, people keep ingesting toxic substances because they have been taught to look at each substance independently. By considering each single substance, they believe that each substance is below daily limit and thus safe. Flawed medical knowledge causes people to ingest too much toxic substances, avoid using lifestyle interventions as real cures, and rely on drugs. Misled by flawed medical knowledge, modern humans have turned their biological networks into abnormal networks. When their body cells and blood are loaded with hundreds to thousands of toxic substances, cancer is a reflection of disturbed biological networks, AIDS is the natural consequence of impaired immune system, and severe COVID-19 outcome is an inevitable disease of crippled immune system. Adverse effects of the flaws find their ways to fish in polluted water, pets, and wide animals in polluted environments.

D. Who Can Fix It, When Medicine Has No Fix

All aspects of medical activities are controlled and influenced by revenues. Medical research subjects are naturally driven by research funds [386-387] which are often provided to promote revenue-generating objects. Since most medical treatments and treatment protocols are developed by using clinical trials, medicine must defend clinical

trials. In the last year, we have proved that clinical trials produce inaccurate, false, and wrong results [8]. We have proved that epidemiological models may not be used to preclude personalized remedies, and lifestyle interventions are the most powerful cure [5-6]. Medicine ignores our findings even though we have proved its invalidity beyond reasonable doubt and even through our proof is backed up by convincing evidence produced by tens of thousands of post-1980 studies. Since medical knowledge and treatment options are selected by their potential for generating revenues, medicine clings to the independent toxicity model and clinical trials. As reflected in current trials registration, medicine does not explore a method of using temperature to achieve >90% reduction in COVID-19 incidence.

Even NIH funding policies are deeply flawed as NIH historically devoted disproportional funds to drug-discoveries, and funded drug discovery enterprise researches that have failed time and again. Similarly, we also found that public interest organizations routinely solicit donation from patients but use donated funds to promote drug research, most of which will not deliver immediate public health benefits. Funding agencies, non-profitable organizations, and research foundations use flawed peer review system [393-394] to suppress disruptive discoveries, and use the general acceptance standard to keep revenue-promoting obsolete knowledge, profitable practices, and wasteful research activities for promoting research revenues. As we have shown from the current clinical trials, the private funding priority is to finding a drug or device to make a fortune. NIH funding priority include “foster innovation by setting NIH priorities to enhance nimbleness, consider burden of disease and value of permanently eradicating a disease, and advance research opportunities presented by rare diseases....” [437] Its details include precision medicine, vaccine, drugs, drug screening, FDA-approved therapies, mobile health, wearable biosensor, alcohol-related injury, technologies to reverse paralysis, artificial pancreas, and biomedical research. It mentions “tailored behavioral and social interventions,” but does not go far enough to cover personal lifestyle. Despite its statutory mission for finding cures for the public [436-437], its funding announcement and funding policies miss written conditions on finding cures [438-439]. NIH lacks funding priority to support research which can help tax payers to correct and avoid massive disease agents from food production lines, family’s kitchens, grocery stores, and polluted air, water, house products, buildings, etc. We see a latest mystery illness in India [440]. The massive toxic substances are substantial causes of cancer, AIDS and COVID-19 [363, 366]. While environmental pollution is a matter for EPA, more than half of exposures can be avoided or mitigated by changing behaviors. Thus, personal health knowledge and health wisdom play a crucial role in preventing and curing the disease. NIH automatically excludes research for understanding temperature, humidity, air, pressure, lifestyle interventions, etc. to cure the disease and contain the pandemic [438-439]. In this article, we have proved the cheapest and most powerful cures for COVID-19 disease are temperature and air (the way of breathing). Just three hours of deep breath may spare half of the deaths, and proactive body temperature management protocol could reduce death rate to one tenth. Temperature role can be seen from incidence patterns for U.S. and Japan. The impacts of different lifestyles are revealed in differences in daily case rates and death rates. Temperature’s role is reflected in epidemiological data for nearly all nations. NIH did not allocate research funds for extracting knowledge that can help people save life immediately.

E. Only Governments Can Fix Medical Infrastructure

We have shown that interest holders in medicine share a common interest to promote flawed medical science because they are controlled by money; but medicine lacks any interest to correct flaws and mistakes. Medicine is a profession having no organizational structure, no leadership, no controlling persons. If we want to hold it accountable, we cannot find its existence. We cannot bring medicine to court to force it address the massive foundational flaws. Medicine is controlled by existing knowledge, research methods and models, and practicing conventions. If something is wrong, it will keep hurting mankind and civilization. When we have found foundational flaws, it has no channel to discuss. It is no one's business. Our thousands of email got no response. We note that no body has power to do something, no body has time to do something, and no body can get paid for doing what we are doing. Concerning correcting flaws, medicine lacks a common financial interest, but becomes a disjointed, disorganized, and a non-existing thing. Medicine lacks incentive and means for promoting public interest.

As demonstrated by a century of research findings, modern humans are attacked by an overwhelming number of harmful and toxic substances. When human blood and body cells are loaded with harmful substances, ingesting more harmful drugs will not solve health crisis. Massive problems are caused by food production lines, family kitchens, personal cooking habits, and cooking culture. Just one bad cooking pan can generate 2,800 times more of lead than California's Maximum Allowable Dose Level [80]. A bottled water contains potentially 24,520 chemicals [35]. We do not know human culprits we are ingest each day. When a family is diagnosed with multiple cancers or multiple chronic diseases, the first thing to look into is foods they eat and family's cooking habits. If a person has developed a habit of wining a lottery of ingesting the largest amount of poisons, he will ingest it every day. We can see unlimited scenarios to have a whole family members poisoned and killed. Cited references represent only a small number of health risks. Real problems are much more pervasive and severer than what we can show. People may poison themselves without slightest ideas and most health problems can be prevented if medicine teaches science. Those problems cannot be addressed by federal agencies.

In the U.S., the biggest burden of the national health crisis like this is the U.S. government. Widespread diseases can cripple national economy, and incur more medical spending for treatments of diseases. The health crisis has resulted in the loss of trillions dollars of tax revenue, and will add trillions more to future medical spending. It infected persons will develop AIDS several years later, it will the time for the whole mankind to regret for failure to take care of disease causes. None of the current federal spending can really solve massive health crises from cancer, AIDS, heart diseases, COVID-19 pandemic, mental diseases, population infertility, future pandemics, etc. We urge the U.S. government to see the extreme seriousness of the current national health condition and change its role from promoting medicalization to cultivating health culture because this is the cheapest and fastest approach to mitigating national heath crisis.

One global measure is to build a national database for pubic use. The database enables ordinary users to search and seek information about toxic substance exposure. For example, a person can search the database to determine the amount of leached heavy metals from a particular brand of pan, pesticide residue amounts in a water system, the best way of cooking a particular food, the identities of substances from home appliances, etc. This database is intended to help people to determine what might damage their human health. In addition, the federal government should appropriate funds for establishing and/or subsidizing toxic substance test facilities for the population. By using this program, anyone

can have their food samples, air samples, water samples, etc. tested at low or no costs. Test results are entered into the searchable database so that test results can be shared by those who might have the same problems. Sparing tens to hundreds of cancer cases from one test report is a huge saving to the government. Since all test results are shared, people do not need to send samples for testing the same pans, same heaters, same furniture, or same appliances. We estimate those two measures can help the population to get rid of 80% to 90% toxic and harmful substances, prevent most cancer, dramatically reduce lung infection, and solve most challenging diseases and prevent future pandemics. We trust that most people can understand the brutal reality: natural law does not respect for science that are found on flawed foundation. To solve overwhelming health problems, medicine must correct all flaws before research funds will yield predictable cures. Fixing the flawed medical system is not what medical scientists can do.

One more thing the U.S. government and all statement governments must do is to fund and support public education on health and good medicine. U.S. citizens are bombarded with endless drug advertisements and medicalization messages, but no public educational messages about lifestyles, environment, and known risks in medicine. The biggest beneficiary for achieving national health is the U.S. government and state governments. If the governments do not want to invest on population health, no body else will. U.S. government and state governments are clearly on the track to lose \$10 trillion from national health crises. The governments can solve their future budget crises at tiny fractions of costs.

FINAL REMARK

Medicine, as defined by its current infrastructure, lacks real incentive for finding cures for diseases. It cannot save millions of lives from the COVID-19 pandemic, just as it cannot save about 30 million premature global annual deaths from chronic disease. It will consume \$6 trillion medical spending in the U.S. by 2027, assuming that the pandemic will not create AIDS-like global crisis. If this pandemic becomes an air-transmittable AIDS in five or more years, that will be a nightmare. The lack of accuracy in medical research are root cause for uncontrollable pandemics, future pandemics, climate changes, population infertility, the AIDS epidemic, cold-like cancer epidemic, widespread mental diseases, etc. Clearly, solving the overwhelming health problems is not a medical science problem, but a badly needed restructuring financial interest balance in the medical industry, systematic improvement in standard of science, and method of knowledge dissemination.

CONFLICT OF INTERESTS

None.

ADDITIONAL INFORMATION

Additional information is provided in a supplemental document and some information will be stored in igoosa.com online database. Ping contribution is limited Part lifestyle inter-

vention and proactive body temperature management protocol. The policies implications are opinions of Dr. Wu only.

FIGURES

Figure 1. Temperature affects all antiviral mechanisms that have been studied and all those that might have not been discovered. Its biggest impacts are through immune cells mobility and tissue repairing functions. Not all mechanisms are shown in this figure.

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(The scope of the proposed research is very broad because it actually covers everything known, therefore, citations to side issues are not provided due to practical impossibility. Cited references are exemplary.)

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