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Research Article

Flawed foundation is the root cause of failure of medicine and precludes cures for chronic diseases

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Abstract

Modern (science-based) medicine adopted four presumptions when it evolved from ancient experienced-based mind-body medicine. To understand its failure in finding cures for chronic diseases, we examined four presumptions and found that statistical population of health properties does not exist for most research purposes, mathematical models are misused to model intensive properties, synthetic drugs are inherently more dangerous than nature-made medicines under their respective application conditions, and reductionist treatments are inferior and inherently dangerous. We found that clinical trials are valid only for research where the treatment effect is much stronger than the total effects of all interfering or co-causal factors or errors introduced by misused mathematical models can be tolerated. In all other situations, clinical trials introduce excessive errors and fail to detect treatment effects or produce biased, incorrect, or wrong results. We further found that chronic diseases are the manifestation of small departures in multiple processes attributes in distinctive personal biological pathways networks, that modern medicine lacks the required accuracy for accurately characterizing chronic diseases, and that reductionist treatments are good at controlling symptoms and safe for short-term uses. For all stated reasons, as long as modern medicine continues relying on flawed presumptions, it can never find predictable cures for chronic diseases. By implication, predictable cures to chronic diseases are adjustments to lifestyle, dietary, emotional, and environmental factors to slowly correct departures in process attributes responsible for chronic diseases.

Introduction

The systematic failure of medicine in chronic diseases was extensively discussed as early as 1875 [1] and is often the subject of critique by the media [2-4]. As of today, most chronic diseases have no predictable cure in medicine [5]. Population-based treatments have failed in cancer, heart diseases, mental disease, etc. [6-8]. Chronic diseases are the biggest economic burden in the U.S. [7] and are predicted to consume about $3.5 trillion by 2050 [8]. From medical performance, we see two distinct patterns: treatments for acute diseases are successful, but treatments for chronic diseases and cancer consistently fail. Thus, we suspect that the failure in chronic diseases must be of a systematic nature that might have precluded cures for chronic diseases.

In our prior study, we found that controlled trials are improper methods for studying weak health factors when many interfering factors (equivalent to covariates in statistics) normally exist in clinical trials [9]. Our findings support the conclusion that all controlled clinical trials are biased [10]. Our prior model study shows a common scenario where each weak treatment or factor cannot be resolved or accurately determined if it is interfered with by at least one to thousands of other factors that have similar degrees of effects. If a weak factor is studied in a clinical trial, it is improperly rejected as an experimental error. Most assumptions used in clinical trials and statistical analysis have not been considered [9].

To understand how weak factors affect disease outcomes, we need to examine biological pathways and disease-controlling mechanisms. We have shown that randomized controlled trials do not have the power to overcome sensitivity limits [9]. This insufficient-accuracy problem cannot be seen

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from the outcomes of clinical trials. When the validity of the research model is challenged, such a challenge cannot be resolved by examining the outcomes of research using the model. Moreover, due to the complexity of health problems and the massive number of interfering factors that exist in clinical trials, it is impossible to find problems by examining the data of clinical trials. To find research model flaws we are required to consider all kinds of evidence other than clinical trial outcomes.

Presumptions are part of the foundation of medicine and are taken as truth so that their validity has never been questioned or examined. When medicine evolved from ancient medicines into modern medicine, it changed natural medicines into synthetic drugs, changed populations into statistical populations, introduced mathematical models as universal tools for medical research, and used the binary scale to model health properties. To find the cause of the systematic failure in chronic diseases, we will examine all presumptions and assumptions. The oldest presumption was that "medicine can cure disease". While this presumption existed in early history, a medicine used in the Yellow River Civilization is not the same as "medicine" prescribed in doctor offices today. We will consider what is wrong with using a population to study chronic diseases and what problems mathematical models can create. In addition, we will examine each of the assumptions used in clinical trials and statistical analysis to show additional flaws from biological points of view.

Materials and methods

We collect from medical literature published data and research findings that tend to support or refute challenged presumptions and assumptions. We rely on data from four sources: one of the sources is research findings that establish the existence of interfering factors and their degrees of effects. Due to an extremely large set of study findings, we will cite only selected references, and treat others as common knowledge. We must use this unique approach because no single set of data or any particular findings can ever resolve this challenge. This is why conducting one or more experiments is meaningless because the data of each study is like a drop of water in a bucket. The second source of data we rely on is media stories, reports from health care providers, personal stories, and observations. When the validity of controlled trials is under challenge, we give more weight to those sources of evidence. Based on our prior studies [9], we ignore negative findings from controlled trials directed to weak factors.

Other data considered include biochemical pathways, cellular or structural data, disease mechanisms, host responses to stressors, immune responses, factor-factor interactions, organ-organ interactions, rational explanations based on body structural compartment, rate balance among different biological pathways, and balance between disease process and healing process. Due to the large scope, we do not cite all contributors directly. The third source of data is data from simple mathematical models to refute or support concepts or mechanisms. Such a method is used only to show that clinical trials with current data analysis can produce inaccurate, biased, or wrong results, but not used to establish that the use of the mathematical method is right. As we show, the use of mathematical models is often improper if the research purpose is assessing treatment benefits and finding cures. If the use of the mathematical models is refuted, clinical trials, as a research method, fall for this reason without regard for the propriety of mathematical models. The fourth source of data is the performance data in treating diseases. However, since most performance studies are based on clinical trials by various degrees, we must read them to offset potential inaccuracies. In general, the treatment benefits of weak factors are underestimated based on our prior study [9,10] and obvious logic.

Failure of clinical trials in chronic diseases

To show why clinical trials are invalid for most research purposes, we studied its development history provided in the medical literature [11]. To understand mathematical models, we study biological pathways and their interactions, the multiple interactive disease mechanisms, factor-factor interactions, and the structural effects of tissues and organs, etc. In addition, we will show that the treatment unit additivity assumption and an implied random error assumption fail to hold in nearly all clinical trials for studying chronic diseases.

A. Errors reflected in the development history of clinical trials

The development history of clinical trials reveals that clinical trials were developed by adding components piece by piece by different contributors over several centuries [11]. When the clinical trial was first used, there was no need to examine the statistical population because statistical analysis was not a part of the analysis method for clinical trials. "Population" used in early human history just means a collection of members, and early medical researchers naturally used population to study diseases because it always created a false impression that a treatment capable of curing more persons must be better than one that does not. This is still a reason for convincing researchers today. In the early days, there was never a need to examine the population of biological properties or health and disease properties. The controlled trial on scurvy conducted by James Lind in 1747 contained most elements. By 1946, all components of randomized controlled trials had been added. It is fair to infer that the clinical trials had gained general acceptance before the 60's [11] without using statistical analysis. Before about 1980s, medical researchers did not know the massive biological properties concerning disease initiation, development, and reversal, the complex human immune system, and the role of the Central Nervous System. They did not have a vantage to see how personal genomes, environmental factors, emotional states, etc. affect health and disease properties. It was natural to presume that any health property in different people is similar so that the values of the property from different people can be treated as a statistical population.

Decades after clinical trials gained general acceptance, researchers started looking into the human genome,

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biochemical pathways, environmental factors, lifestyle factors, emotional problems, etc. The effects of a large number of primitive factors on diseases have been established by tens of thousands of studies mainly after 1980 [See some references in Section E]. Even though a good portion of studies is conducted by using a population approach, affirmative findings in those studies suffer inaccuracy by various degrees. Nevertheless, those positive findings have firmly established that differences in health and disease properties cannot be treated as random errors, and there is no statistical population as far as health and disease properties are concerned. Unfortunately, massive discoveries have not prompted medical researchers to revisit the presumption of a statistical population in the last few decades. We have shown that the effects of massive interfering factors are responsible for trial outcome uncertainty. When the nature of interfering factors was not understood, it was natural to attribute trial outcome uncertainty and conflicting findings to experimental errors. It is natural to try to solve this problem by using misapplied statistical analysis.

Misuse of statistical analysis in clinical trials is clearly reflected in the development history of statistics. Statistical analysis was added to clinical trails as one of the few last components. The origins of statistical theory lie in the 18th century, but improved experimental design, hypothesis testing methods, etc. were developed in the 1910s and 20s by William Sealy Gosset and Ronald Fisher, and further refinements were made in the 1930s [12]. Hypothesis tests are used to determine whether positive outcomes in clinical trials are caused by the treatment effect or due to uncontrollable experimental error. The use of hypothesis tests in clinical trials started centuries after the initial use of clinical trials and more than a decade after the formation of modern clinical trials. Statistical analysis was added as an additional analysis step to clinical trials from the 30s to about 60s. When the statistical analysis was added, the traditional concept *population* was changed into a *statistical population*. No published study has seriously discussed whether the health properties of human beings can be treated as a statistical population and their numbers can be added and divided like fungible properties.

B. Flaws in past statistical studies

Past studies including those done by Altman, Senn, Zhao, and Berger [13-18] have made a presumption that any health properties such as survival times, process attributes such as conversion rate and intermediate concentrations, etc. in human bodies can be treated as a statistical population [13-18]. They did so without exploring the effects of all interfering and co-causal factors that normally exist in clinical trials. This presumption had been accepted for several decades before. It had been beyond challenges. By using this presumption, even extremely complex health and disease properties such as survival time and emotional health can be studied like statistical population, where outcome uncertainty can be attributed to random processes like rolling a dice or blowing colored balls from a lottery machine. After examining disease mechanisms and existing risk-disease data, we found that no disease happens like flipping a coin and blowing colored balls.

Due to historical development reasons, early researchers could not pay attention to biological properties and their effects on health properties. Flaws in those studies can be summarized as follows: First, they made a presumption that disease and health properties can be studied like drawing events and that the health properties of human beings in a treatment group can be treated as a statistical population. They then made an assumption that disease or health properties can be mathematically added up and divided to yield a mean for the presumed population. In doing so, they made another assumption that health properties are fungible and exchangeable, and all uncontrollable interfering factors do not exist or can be neglected as random errors, and failed to examine whether treatments have different effects on different persons, how interfering factors affect health properties, and how their plus and minus effects distort analysis outcomes.

In the early years, they did not have the vantage to see the irrefutable evidence that most so-called errors are not truly random errors that are seen in statistical trials, but a combined effect of hundreds to thousands of interfering or co-casual factors. They did not consider abundant evidence that treatments often have different levels of effects and different-sign effects on different persons, that the magnitude of measurement errors due to interfering factors can be larger than treatment effects; that the interaction between a treatment and any of potential interfering factors is distinctive in each person; that interfering factors can distort treatment effects by their positive and negative effects, with sufficient magnitudes to distort trial outcomes, and that personal biological properties are distinctive. Without considering external evidence, they were not in a position to compare the effects of treatment with the effects of interfering factors and naturally attributed all differences among individual persons to experimental errors.

Past studies by Altman, Senn, Zha, and Burger [13-18] share several common errors: They treated the health and disease properties of human beings as a population. They assumed that the differences among individual persons happen like those in statistical sampling, but never discussed external evidence about health properties such as process attributes [19]. By failing to look into the nature of all interfering factors, they bundle all contributions caused by different process attributes in the biological pathway networks into experimental errors. They concluded that there is no need to be concerned about the baseline balance. They never proved that the health properties of people can be treated as statistical populations. If statistical analysis can fix the overwhelming problems, we could reach absurd conclusions that controlled trials have the power to resolve contributory effects of any weak factors; valid scientific research does not depend on separation method and detection technologies; and research sensitivity limits can be overcome by running bigger clinical trials followed by doing statistical analysis. Each of those conclusions must fall automatically.

What is wrong is that the "statistical population" has been taken for granted for any research purpose. This is reflected nearly in all medical studies that never even attempt

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to determine whether a statistical population of a health property exists for intended research purposes. When a clinical trial is used to study a chronic disease, it is required that all persons must be similar in their chances of getting or resisting the same disease. Due to the massive interfering factors in clinical trials, clinical trials tend to produce different outcomes. Early researchers could not understand the sources of uncertainty and naturally assumed that trial uncertainty is caused by experimental errors beyond human control. Naturally, statistical analysis was used to solve this problem. When statistical analysis was added, the *population* was silently changed into a *statistical population*. Medical researchers have made a presumption that a statistical population exists for any health property and any research purpose. This is evidenced by the widespread abuse of statistical analysis in medical research publications.

While hypothesis tests are not wrong for all research purposes, they can address only experimental uncertainties that are truly caused by uncontrollable random errors that happen like flipping a coin, blowing colored balls out of a lottery machine, or rolling a dice. The massive medical findings have firmly refuted that trial outcome uncertainty is caused by uncontrollable random processes. Implied requirements for classical statistical trials are that the coin must have identical weights on two sides to have the unbiased chance to produce each outcome, all numbered balls in a lottery chamber must have the same weight, same shape, same size, and uniform internal density, and the dice must be a cubic with the same area on all six faces, and has a same density at every inner locality within the dice. If the rim or density near two surfaces of a coin is altered, it will introduce systematic errors that cannot be treated as random errors. A coin with an altered feature may produce an outcome ratio other than 1:1. The ball sizes and densities among different balls can be changed to result in different outcome probabilities. In clinical trials, systematic errors cannot be determined from trial results. Systematic biases cannot be corrected without understanding the nature of the biases. The systematic biases can be established in reality by external evidence other than trial results. All interfering factors in clinical trials can have systematical impacts on trial outcomes. The inability to control interfering factors is not the reason to ignore their existence.

A vast number of primitive factors such as nutrition, toxins, heavy metals, exercise, emotional issues, etc. are not really uncontrollable. Each of those factors is weak and hidden among the rest of the factors. It is like a situation where the effect of each factor cannot be determined but the collective effects of all factors are responsible for diseases. Even intermediate factors such as glucose or triglyceride levels in the blood can be altered by adjustment to lifestyle. None of those factors work like an uncontrollable driving force that makes a spinning coin take one particular outcome.

Misuse of statistical analysis could not remove the trial outcome uncertainty. Great uncertainty in trial outcomes provides great room for the manipulation of experiments. Instead of investigating the inherent flaws, medicine has tried to address this uncertainty problem by controlling selection biases and conflict interests as remedies. Thus, we see massive ethical regulations established after 1946 [11]. While selection biases can cure uncertainty caused by identifiable factors such as age, sex, overall health, disease stages, etc., they cannot do away with outcome uncertainty caused by a large number of other uncontrolled interfering factors. Conflict-of-interest measures can never do away with outcome uncertainty except that it has become a scapegoat for the flaws of clinical trials. Such measures create massive administrative burdens which are rarely seen in other fields such as bridge design, aviation, automobile, etc.

C. Statistical populations of health properties do not exist for most research purposes

While the population concept can be used for various purposes, the population, as used in statistical analysis in clinical trials for diseases, can be refuted by relying on observed health properties and known analytical data. Boys, girls, men, women, healthy persons, persons with unidentified diseases, etc., are expected to have different baselines. For example, a healthy young person may have a baseline survival time of five thousand days while an old patient may have a baseline survival time of fifty days. Among the persons in a trial, besides the term "person", they are different in biological age, physical strength, shape and look size and weight, etc. They differ in physical check-up data and laboratory analysis data [20,21]. Differences in local concentrations of intermediate compounds of some biological pathways in tissue cells between different persons could be more striking even though few studies were done to understand such differences at the cellular level. Even if assuming that diseases were realized in a manner like blowing human physical entities out of a lottery machine, some persons might be "drawn" at much higher probabilities. No population would meet statistical distribution except by approximation in studies concerning body weight and head count. In most clinical trials, the baseline health property for each person cannot be accurately measured and determined. This present inability is not a valid basis for treating differences in health properties as random errors.

As a general rule, when a treatment in a trial is sufficiently strong while experimental errors are relatively small, two experiments with two measurements in each would be enough without using statistical analysis. Statistical analysis is never required in most experiments in analytic chemistry. In a drug trial with the endpoint being survival time, real experimental errors are small because survival time, treatment dates, and drug doses can be determined and recorded accurately. However, for the interfering or co-causal factors, clinical trials repeated in the same condition are expected to produce consistent results without the need to use statistical analysis. In a trial involving a poorly defined treatment such as a stress-relieving method, part of the outcome uncertainty is caused by the uncertainty in treatment definition; and part of the outcome uncertainty is caused by interfering factors. Statistics is not a suitable method for taking care of interfering factors and definition uncertainty of treatments.

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D. Several model problems defeat the population presumption

We will discuss several model problems that make population presumptions fail.

1. **The averaging of positive and negative effects of a treatment:** The first problem is that a factor or treatment can have a positive effect or negative effect on different persons. For example, to improve vitamin D supply, its levels in the blood for a sample of a population can be determined together with the mean and a standard deviation. This mean may be used to determine the total amount of Vitamin D required for correcting vitamin deficiency in the population. Since vitamin levels actually vary among persons, the amounts of supplement intakes cannot be determined on the basis of the population mean but on the actual vitamin level in each person. If the same amount of vitamin supplement is indiscriminately used by all persons, the amount is insufficient for those with low vitamin levels but may intoxicate those with high vitamin levels. This treatment will have both positive effects on some persons and negative effects on others. If we assume that 50% of persons need to increase vitamin D while the other 50% of persons do not, vitamin supply may happen to show a net zero. An overwhelming number of factors can have both positive effects, no effects, and negative effects on different persons for any health problem. Each of all nutrients, physical exercises, measures to reduce toxic pollutants, etc. is expected to have positive effects, no effects, and negative effects. The averaging operation used in clinical trials always produces meaningless results. A lack of effect is false because it is an improper average; a negative mean is wrong because at least some persons need the vitamin; and a positive mean may be underestimated because the values have been brought down by those who exhibit toxic reactions. Thus findings based on clinical trials are meaningless and cannot be used as treatment guidance.

2. **The treatment effect is distorted by the positive and negative effects of each of a large number of interfering factors:** Even if the treatment or the treatment factor has a fixed positive effect on the health properties of all subjects, this constant number cannot be accurately determined. This constant-effect assumption must be false, but we use it to show that a large number of interfering factors can distort the treatment effect. All interfering factors have positive or negative effects on different persons. Assuming that treatment T has a fixed treatment effect on all persons, the positive and negative effects of an interfering fact can distort its effect so that it may produce a false result. This problem is caused by the inability to resolve the contribution of the treatment and the contribution of the interfering factor on each specific person. This can be shown in the following table.

In Table 1, the treatment has a fixed effect of 1 on all persons. One interfering factor in row 2 has positive or negative effects and raises the variances of the observed data in row 3. The net interfering factor in row 2 could be viewed as a control. If no interfering factor, all values in row 2 would be near zero, all measured values would be 1, and the mean could be determined without any uncertainty. The interfering factor dramatically raises the variances of the treatment in row 3, and thus raises the threshold of rejecting the null hypothesis. The trial most probably fails to find the true benefit of the treatment. When hundreds of interfering factors exist, the variances seen for the treatment must be larger even if the interfering factors follow complex or unknown distributions.

In Table 2, a single strong interfering factor dramatically increases the variances of the observed data. The massive variations of the interfering factor find their way into the values of the treatment group relative to a control. Due to the massive variances between individual persons within the treatment group, the true treatment effect in row 1 may be completely hidden in the interfering effect. Although the treatment's mean is detected as unbiased, the enlarged variances will result in a much higher threshold for rejecting the null hypothesis. Based on other observational data, we must say that the variances from different persons are very high and result in failure to reject the null hypothesis. We suspect that strong interfering factors are very common in studies intended to study weak and slow-delivery environmental and lifestyle factors. In such situations, clinical trials always produce false negative findings.

In Table 3, a single strong interfering factor has a biased effect on the measured health properties of both treatment and control. Those kinds of interfering factors include fears, development stage, aging, seasonable effects, exposure to bad news, etc., that strike all subjects in both the treatment and control groups. They can dramatically increase the variances

Table 1: How An Interfering Factor Affects the Treatment Effects of a Treatment of Similar Strength.

	Person ID	1	2	3	4	5	6	7	8	9	10	Mean
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+1	-1	+1	-1	+1	-1	+1	-1	+1	-1	0
3	TX Obs.	2	0	2	0	2	0	2	0	2	0	1

Table 2: How a Strong Interfering Factor Distorts the True Effect of a Weak Treatment.

No	Person ID	1	2	3	4	5	6	7	8	9	10	Mean
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+10	-10	+10	-10	+10	-10	+10	-10	+10	-10	0
3	TX Obs.	11	-9	11	-9	11	-9	11	-9	11	-9	1

Table 3: Strong Biased Interfering Factor Overrides a Weak Treatment.

	Person ID	1	2	3	4	5	6	7	8	9	10	"Mean"
1	TX	1	1	1	1	1	1	1	1	1	1	1
2	IF (Ctl)	+10	-10	-10	+10	-10	-10	+10	-10	-10	-10	-4.0
3	TX obs.	11	-9	-9	11	-9	-9	11	-9	-9	-9	-3

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of the observed data. In addition, they also move the measured values as well as the mean to the negative side. Even though the treatment has a net effect of 1 on each person, the observed data may be still negative. In addition, aging, development stage, seasonal factors, or exposure to bad news may interact with the treatment. A treatment may have curative benefits, but negative news may make all subjects so sad that the news might have suppressed the immune system or the whole body's health. Due to the massive variances and negative interactions, true treatment effects are most probably rejected as errors.

In clinical trials, there are hundreds to thousands of interfering factors. Their variances can be added up for well-known distributions [9]. For unknown distributions, the final variances depend on the number of interfering factors and their effect on variances within the treatment group. This results in the systematic rejection of weak treatment effects.

3. **Treatment effects are distorted by interactions between the treatment and interfering factors:** The impact of interfering factors in clinical trials cannot be corrected by achieving a baseline balance between the treatment group and the control group. This can be shown by the interactions between the treatment and interfering factors. Assuming that treatment T is under the influences of uncontrollable interfering factors (H_1, H_2..., H_n), the detectable treatment value for a person is $AT_i=\Sigma(T_i+T_i-H_{j=1}+T_i-H_{j=2}+..., T_i-H_{j=n})$. Each interfering factor H_j causes plus and minus effects ($T-H_j$) over an imagined treatment T_i. Some interfering factors may raise treatment effects by various degrees while other interfering factors may depress treatment effects by various degrees. The net effect of the treatment on a person depends on the treatment and all interaction effects. Thus, the net treatment effect on a particular person must be different from the net treatment on another person. In the control, the correspondent term is zero. We ignore each of the interfering factors. All interaction terms ($T_i-H_{j=1}+T_i-H_{j=2}+..., T_i-H_{j=n}$) would depend on the treatment. It is possible that a treatment is predicted to have beneficial effects on a disease, but the interactions with other factors might have brought the predicted effect down to nothing or negative value. Because the number and impact degree of interfering factors are unique in each person, the effect of treatment will be altered by different degrees in different persons. This might be the reason many drugs do not deliver their intended benefits.

The total treatment's effect for the treatment group is the sum of all treatment effects on all persons (Ignoring the problem in additivity for the time being). A large number of interfering factors interact with the treatment. If they interact with the treatment in an unpredictable way, the average treatment effect is meaningless. The nature of interactions is determined by the treatment OR interfering factors. For example, a calcium supplement is predicted to benefit bone health, but high sodium daily intake promotes calcium loss. The sodium's effect on calcium balance depends on persons who have different sodium intakes. Similarly, exercise can beneficially affect innate immunity, acquired immunity, etc., and people vary in doing exercises. Exercise can dramatically raise the beneficial role of other treatments such as nutrition and detoxification of heavy metals intended to improve the immune system. Upper and downshifts of baselines cannot be determined for a specific person. Thus, the knowledge of baseline upper or downshifts by interfering factors can provide a better strategy for formulating treatments.

In the above example, a simple mathematical model is used to characterize the treatment effect and its interactions with interfering factors. However, accurate interactions cannot be characterized accurately due to multiple layers of complex healing and disease mechanisms.

4. **Treatment effect is realized at a very slow speed:** One unique problem with human health is that many lifestyle factors affect health and diseases slowly. This problem is an additional reason for the failure of clinical trials. Even if a treatment is relatively strong, it cannot be detected in a short trial. The treatment may be unable to trump the effects of random and uncontrolled interfering factors. Exercise is a very weak factor if it is examined in a short-term trial. No benefits can be detected for a short time trial. If exercise is examined in a long-term trial, its true benefit is interfered with by certain factors that also have systematic impacts. Those factors include age, aging, development stage, menopause stage, hospital isolation, etc. For people at advanced ages, part of the long-term treatment effects are interfered with by those factors.

E. A massive number of interfering factors and their nature

Each person is a unique being by genome [22]. The typical difference between the genomes of two individuals was estimated at 20 million base pairs (or 0.6% of the total of 3.2 billion base pairs) [22]. Moreover, even identical twins can become different beings by epigenetic changes that have an effect of turning on or off gene expressions [23,24]. Each disease like cancer is a distinctive product of personal genome, diet, living environment, etc. [25,26].

1. **Evidence showing the effects of interfering factors:** All factors a person is exposed to can affect the person's health. Emotional shock, chronic stress social isolation, etc. can affect inflammation [26-28], the immune system [29-33], influenza and respiratory infection [34-36], cancer development and metastasis [37-40], heart diseases [41,42] and drug metabolism [43]. Since the brain controls hormonal actions and biological processes, disorders in the brain must affect correspondent tissue ecosystems. This critical role was described in 1875 [1]. Nutrition affects immunity to viral infection [44-46], infection [47-49], viral pathogenicity [50], etc. Selenium affects viral mutations [51-53], and zinc affects the risk of pneumonia in the elderly [54]. Obesity affects immunity to infection, inflammation,

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and immune responses [55-62]. Excessive cell phone usage increases the risk of brain tumors [62-65].

Metals, including lead, cadmium, mercury, arsenic, chromium, copper, selenium, nickel, silver, and zinc, and other metallic contaminants including aluminum, cesium, cobalt, manganese, molybdenum, strontium, and uranium are found in living organism, plants, contaminated vegetables, industrial materials and polymers, soil and land resource, and air and water [66]. Most heavy metals such as aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel, and radium increase the risks of cancers including lung, kidney, liver, stomach, intestines, bladder, colon, gastric, nasopharyngeal, pancreatic, breast, gallbladder, esophagus, prostate, testes, gastrointestinal skin cancer and non-Hodgkin's lymphoma [67-69]. Exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular diseases and coronary heart disease [70,71]. Heavy metals can damage cells [74], disturb the Redox balance [72,74], and suppress the immune system often at very low concentrations [73,74]. Many heavy metals can damage the liver, kidneys, brain, and nerves [74]. Alteration of homeostasis of metals could cause the overproduction of reactive oxygen species and induce DNA damage, lipid peroxidation, and alteration of proteins, thus increasing the risks of developing brain tumors [75]. Metals such as lead, mercury, cadmium, and arsenic may be important contributors to neurodevelopmental disorders and disabilities [76]. The findings in those studies firmly establish that heavy metals can cause specific diseases, but they must be viewed as having global adverse health effects because they can interfere with enzymatic reactions that control reaction rates of all biological pathways.

Inorganic and organic substances can have adverse health effects. Sodium, the most common flavor is the number-one silent worldwide killer due to its role in raising blood pressure [77]. Habitual dietary salt intake is positively associated with the risk of gastric cancer [78]. Besides cardiovascular diseases, high salt intake increases risks of gastric and some other cancers, obesity, Meniere's disease, worsening of renal disease, triggering an asthma attack, osteoporosis, exacerbation of fluid retention, renal calculi, etc. [79]. High sodium intake is associated with obesity [80]. Moderately high salt intakes affect calcium metabolism and bone health [81]. Reduction of sodium intake can reduce both systolic and diastolic pressures [82]. Exposure to common quaternary ammonium disinfectants may decrease fertility based on animal models [83-85]. Hydrogen peroxide may cause poisoning [86]. Lack of exercise and physical inactivity are found to be the substantial causes of chronic diseases [87-88]. From the benefits of exercise on cancer survival [89-100], it is expected that reduced exercise and increased inactivity have adverse impacts on survival among cancer patients. People have different organ reserve capacities [101-103], which are presumed to be the most important factor that affects patients' ability to survive diseases.

Available spaces in the thoracic cages affect their ability to accommodate tissue swelling in the lungs [104]. Obesity is found to be a high-risk factor for COVID-19 disease [105,106]. Information stored on the CNS neurons is different, and it, like computer programs, affects emotional health and CNS regulatory functions in the body. The lack of medical findings is not a reason to deny its role and importance. Full details of those factors can be presented only in a searchable database. Even environmental factors such as oxygen [107], humidity [108], and temperature [109] affect immunity and pathological responses to infection. Massive organic compounds, industrial materials, industrial chemicals, pesticides, herbicides, fungicides, etc. will be discussed elsewhere.

Many factors exhibit non-linear complex effects and may interact with each other. The CNS interacts with bone, marrow, and the micro-environment [106,111]. Enteric microbiota and central and enteric nervous systems interact through the gut-brain axis [112,113]. Sodium also exhibits different effects under different use conditions. High salt (4% NaCl, as well as 1% NaCl, enriched tap water feed mice for 2 weeks) inhibits tumor growth by enhancing anti-tumor immunity [82] contrary to the long-term adverse effects. Like glucose level that has both good and bad roles, sodium's short-term effect may be realized by influencing blood viscosity and fluid ionic strength while its long-term effects are most probably realized by affecting blood pressure and the vascular system. Any factor affecting viral diseases could also depend on a large number of other factors that affect innate immunity, host responses, acquired immunity, micro-circulation, and structural features of target tissues. The cited findings provide irrefutable proof that none of the interfering factors can be ignored in the mission to find cures.

2. **Slow effects of weak factors:** *T*o understand the nature of interfering factors, it is important to understand event timing. Some treatments such as consuming glucose to raise blood glucose can show immediate benefits. Other treatments or factors will affect the biological pathways networks without immediately causing symptoms. It may take time to distort the biological networks. The distorted networks then slowly alter the structure of the body. This is similar to the development of chronic diseases. Altered biological networks and altered body structure also interact with the Central Nervous system by the mind-body interactions [114,115]. The mind-body interactions may be a mechanism for stabilizing the physical body. Most departures in biological networks in tissue cells cannot be directly determined in clinics because reference ranges of chemical analysis data for normal ranges are very large. Chronic diseases are often diagnosed by examining blood compositions, changes in cellular structures, and disease biomarkers. It is difficult to determine the effects of weak primitive factors by monitoring blood compositions, cellular structures, and disease biomarkers.

F. Flaws of using mathematical models

In modern medicine, another presumption is that every health problem can be represented by a mathematical model. Now, a supermajority of medical studies includes statistical analysis. We refute this presumption.

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1. **Flawed assumption of the linear effect of a treatment:** The assumption of the linear effect of treatment is widely used in medical research but fails in nearly all situations. Most interfering factors influence health properties in a complex manner. For example, nutritional intake, physical activities, sleep duration, thinking activities, and environmental factors such as temperature, atmospheric pressure, humidity, etc. affect personal health often by quadratic functions (if we do not resolve precise effects at a finer scale). A low nutrient intake has negative effects, its beneficial effect increases with intake amount, and hits an imagined optimal point; after this point, further increased intake causes a reduced beneficial effect, and results in progressively increasing toxic effects. The point of the optimal value for any factor is not static. The shape of the effect-concentration curve depends on the personal genome, health condition, age, physical activities, lifestyle, diet, emotional states, etc. This rough quadratic pattern is true even for physical activities. Too little sleep can hurt due to insufficient rest time and too much sleep time may result in excessive fat accumulation. It is even true for things like usage levels of body parts such as hands, feet, or joints. Long inactivity hurts, and overuse also hurts. Thus, the relationship between two variables is unique in each person. Regression cannot be done for a population.

Mathematical models cannot model complex interactions of health properties and primitive factors. Health properties such as glucose level, triglycerides levels, oxygen saturation, etc. may work as influencing factors for other health and disease properties. They also affect other high-level health properties such as disease risks, death rates, survival time, etc. Due to complex interactions, we found that most health properties must be multiple complex functions of a large number of primitive factors. There is no best nutritional profile, no best diet, no best copper intake, no best environment, etc. because the effect of each factor also depends on other factors and personal activities. There are no objective criteria for determining what is best. There is no best amount of exercise, and nor best kind of exercise for all people in a population. Even for a given person, there is no static best value. An imagined best value may exist only under certain conditions by using arbitrary evaluation criteria and must change with age, health condition, activity levels, emotional health, and other personal, environmental, and lifestyle factors. The notion of best value such as the best sleep duration for a population is flawed. The linear models used in statistics can model only simple properties like crop weights and production yields when the research purpose concerns a fungible property.

The unique nature of process attributes implies that health properties are not the types of properties for mathematical operations. Moreover, interactions between disease initiation and multiple layers of disease defense mechanisms also refute this assumption completely. Disease mechanisms are further influenced by a large number of primitive lifestyle and environmental factors. Clinical trials can produce unpredictable and inconsistent results due to the effects of influencing factors at different layers. A factor promoting diseases may be found to have no effect if a strong defensive mechanism in most human subjects can overcome initiated diseases; and in another trial, the same factor promoting disease initiation may be found to be a strong controlling factor if the defensive mechanism in most subjects is compromised.

2. **The mathematical average of health properties generally has no meaning:** The notion of equating the average of a population as the best value was formed from a false perception of comparative results in clinical trials. By using a comparison, clinical trials always produce a false impression that the positively determined treatment must be good for the population. Thus, treatments developed from clinical trials have been regarded as the best in practice for centuries. The validity of controlled trials has been presumed for centuries but has not been proven. The purpose of a clinical trial is to determine whether a treatment is better than a control often by using statistical analysis. In conducting statistical analysis, measurement values from all persons in the treatment group are added up to yield an average. There is no scientific proof that such health properties can be added and that a determined average can represent all persons in the treatment population. This presumption holds only if all persons in the population actually had a mean, and the averaging operation is merely to remove truly random experimental errors.

Most health properties are process attributes such as conversion rates, the concentrations of intermediates, or the matrix of those things. In the treatment group, a mean determined by mathematical averaging can represent none of the members in the treatment group. If a treatment is found to have positive effects over a control group, what is proved is that the treatment has sufficiently positive effects on the members of the treatment group over the control. Such a positive value can be detected if the treatment effect is stronger than the sum of all interfering factors in the treatment group, the treatment produces beneficial effects on more persons than it produces adverse effects of the same degrees on others within the treatment group, or the treatment has a net beneficial effect on the treatment group over the control for whatever reasons. It does not prove that the treatment is effective for the treatment group, is effective for treating the disease, or is the best for all persons with the disease.

The notion that "an average represents a population" is generally wrong unless a statistical population can be established by independent evidence. In politics, number-based representation is a principle imposed by will, but not natural law. In a statistical population, the members must share enough similarities so that the members can be used to investigate a treatment. This requirement is entirely relative to the investigation purpose. A computed average can represent a population only if a statistical population actually exists. The existence of a statistical population cannot be proved by the mathematical operation itself, reasonable data pattern, or a

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computed average value. Mathematics can be used to determine the average weight of a sesame seed and a fighter carrier or the average heart output of an elephant and a bird. Such averages can represent neither the weights of the sesame or the carrier nor the heart outputs of the elephant or the bird. While the values in those two examples are extreme, similar data values do not provide a basis for finding a statistical population. Similar reaction rates in certain tissue cells in tigers and turtles do not make the rates a statistical population (even though the turtle's mean may be used to estimate the tiger's mean in practice). It is possible that apple tree data might nicely fit into human data purely by accident.

The existence of a statistical population must be established by examining individual members and the purpose of the investigation. If an identical nutrient intake has a beneficial effect on one person but a toxic effect on another person, the average value, which has the same value, does not represent a beneficial effect for both, nor a toxic effect for both. On the contrary, apple, orange, and plum in a compartment mixture could be treated as a reasonable statistical population if the investigation purpose is to estimate packaging volume. Even abstract concepts may become a statistical population if their differences do not defeat the investigation purpose. Similarly, deformed coins, irregular balls, and non-cubic dice with varying inner local densities cannot be used in drawing sampling for classical statistical trials. In the vast medical research articles, research purposes and accuracy requirements have been ignored. This single error makes many study findings meaningless.

The permissible use of mathematical operations for population-based study depends mainly on the purpose of the research. Grain weights may be added and divided if the research purpose is to study grain supply and demand. In this situation, grain weight is fungible because mathematics does not differentiate sources just like market demand. However, if the research purpose is to increase individual seed weights by using a new treatment, grain weight is not a fungible property. We must consider if the treatment has the same effect on each seed. If the same treatment can have different effects on different seeds with different genetic compositions, a mathematical model that regards the treatment as having the same effect must fail. Lifespan is partially controlled by complex biological pathways, and thus is not fungible: extending 20 years for a boy is not the same as extending 20 years for an elderly person. However, survival time could meet the statistical population if the research purpose is to determine total community life spans for the purpose of getting a financial reward under a lifespan-based reward program. If a mathematical model treats positive and negative effects of influencing factors as experimental errors, the errors must be sufficiently smaller than the treatment effect so that study validity can be justified by approximation. Based on this rationale, mathematical operations cannot be used to find the best treatments for persons who have distinctive biological properties.

Mathematical averaging of process attributes is improper also because most process attributes have no standalone meaning. One class of properties is *in*tensive property which reflects the local physical property of a system. Examples of intensive properties include temperature, pressure, refractive index, and density. Extensive properties such as mass and volume are additive. Temperature is not additive because heat absorbed at different temperatures would be different, and temperature at different systems such as water and gas means completely different things. Process attributes and health properties are similar to intensive properties. A Civic uses fuel at the rate of 1 gal/time (where time is a suitable time unit) and an Accord consumes fuel at 2 gal/time. Their average would be 1.5 gal/time. This number may indicate the average usage of fuel from fuel supplies. However, this number cannot be used to study the performance of the cars because the performance of each car depends on a large number of other variables such as driving distance and weight of carried goods. The average, 1.5 gal/time, has no meaning if it is viewed out of context. Fuel injection rate can be evaluated only against criteria such as shipping weight and running distance. We can infer that all process attributes such as fuel injection rate, coolant flow rate, heat dissipating rate, etc. from individual cars or planes cannot be added and averaged across the different models, and then applied to any specific unit.

Direct mathematical average is proper only for fungible properties such as crop weight and production volume. For such properties, the significance of each unit of weight or volume does not depend on other variables. However, direct averaging without using weights is improper for computing the average for alcohol of 99% purity and alcohol of 30% purity. The net weight of alcohol depends on their purity which is an additional variable. For nearly all health properties, the significance of process attributes always depends on other variables. Mathematical operations used in classical probability trials do not violate the fungible requirement. In probability trials, events are defined accurately. The appearance of a numbered ball, a dice position, or a coin face is not subject to additional variables. Each outcome has the same significance as any of the other outcomes. That is the basis for adding them up to get a sum. Observing examples in statistical books, we found that an intensive property may be used as a statistical population only for the same system or similar systems. For example, the daily production rate of a machine can be added up and averaged for different days because all other variables are fixed and thus the number of product pieces is the only variable. Whether production rates from different machines can be summed and averaged depends on the purpose of mathematical operations.

Contrarily, process attributes are generally not the kind of properties that can be summed up and divided. The specific values of process attributes do not have standalone meanings. They are incapable of determining system performance like health or disease states. Glucose level, a process attribute, affects health by interacting with other factors or variables. When the glucose level is low, it is vital to survival. If it increases, its benefit reaches a plateau. Further, an increase in the glucose level will cause negative effects by damaging the vascular system. Thus, the 15 mg/liter on the low end and 15 mg/liter on the high end have different benefits even for the same

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person; and 10 mg/liter in diabetes patients and 10 mg/liter in hypoglycemia patients have different meanings. Averaging glucose levels for diabetes patients and hypoglycemia patients would result in a "healthy" mean, which is clearly contrary to reality. We can find that all process attributes share this same problem.

Any process attribute, as well as a unit change to an attribute such as glucose level (mg/liter), red blood cells (no/liter), white blood cells (no/liter), enzyme activity (in any units), etc., have no standalone meaning unless it is considered for a specific person under a set of specific conditions. Thus, a computed mean of any health property has no meaning. If the reaction rate of a specific biological pathway in a person is X while that for another person is 2X, the mathematical average can represent neither. Intermediate concentrations also have no meaning. A low glucose concentration would imply low conversion speed only if the rate constant for the biological process is the same. However, in reality, 110 mg/liter in an obese person may reflect an even lower conversion speed than 70 mg/liter in a young person. Similarly, the rate constant or activity level of an enzyme has no meaning unless it is considered in context. The high concentration in an obese person might be caused by an excessively slow conversion rate so that more of the absorbed glucose is backed up in the blood. In addition, the net conversion rate must be influenced by the physical structural features of the body.

Each process attribute in the biological networks [116-118] of a person is distinctive and this nature bars approximations. Given the long development time of chronic disease, departure in any process attribute in the biological network is very small. Thus, the computed mean cannot be imposed on any individual person because the mean must be different from the corresponding value for the person. Based on the above discussion, we find that all process attributes have non-linear, complex effects on personal health and that their effects on personal health depend on many other personal factors. Personal health values cannot be added up across different persons except in situations where research purposes can tolerate such errors.

Many large-scale clinical trials such as the TAILORx trial [119] reveal misuse of the representation principle. It attempted to get better "representation" from people by running multiple national trials. Since findings from clinical trials always had some kind of average of personal numbers, they cannot represent a supermajority of the persons other than lucky persons whose numbers luckily fall on the average (which may happen by the chance of winning a lottery). The average is not the optimal value of any person in the trial subjects. Since the mean of a health property derived from a population cannot represent individual persons, a treatment based on such health property cannot be valid for any of the participant persons except the abstract person who does not exist. There is no basis to find that such a treatment is best for other patients outside the trial. The flawed logic is that the validity of the treatment for persons in the U.S. depends on how good the treatment is for persons in Brazil.

3. **Use of the binary scale and characterizing properties by categories:** Another problem arises from using the binary scale. Most health properties are continuous properties except for a few things like gender and death. Many health properties actually exhibit 0 and 1 states, with 1 state further comprising values in a non-linear continuous profile. One obvious example is exposure to a virus. Exposure can be classified as no and yes. Among exposures, infection risk would depend on the number of viral copies exposed. However, nearly all health properties or process attributes of biological pathways are continuous. They differ in amount or degree. Conversion of such properties into the binary scale introduces excessive errors. By common sense, digitizing a sound with a two-bit digital scheme can introduce great distortions. Conversion of data into the binary scale can introduce as much as 50% relative error. The 49.9% will become zero while 50.1% will become one, but each of the two numbers could get a different binary value. The binary scale has been widely used to characterize health conditions, disease definitions, blood pressure, selection of control groups, etc. The binary scale is not used in nature but is imposed by human will (e.g., normal blood pressure). The normal and abnormal marking system is widely used for chemical analysis data and thus introduces excessive errors relative to the required accuracy for correcting chronic diseases. Categories are also used in classifying side effects, cancer stages, etc. in an attempt to break continuous properties into categories by human wills. The binary scale does not provide the precision required to characterize chronic diseases.

4. **Other assumptions used in statistical models:** The unit treatment additivity assumption is used in regression and variance analysis. Most weak factors, if they are studied as treatments, defeat this assumption because they have positive and negative effects on different persons. n The human body always has several layers of disease-fighting mechanisms including innate, host response, acquired immune responses, resolution of inflammation, and recovery of damage. Whether a treatment shows its effects would depend on the roles of a mechanism targeted by a treatment relative to other mechanisms. A weak mechanism must be hidden within a strong mechanism. Exercise may have negative effects on some people whose blood vessels are severely damaged, but positive effects on others. Finally, even if the treatment effect is constant, interfering factors can distort their values; and a large number of nutrients, physical properties, environmental factors, etc. can distort treatment effects by interacting with the treatment, making this assumption fail.

G. Altering the Presumption That Medicines Can Cure Diseases

"Medicine can cure diseases" is the oldest presumption that everyone takes it for granted. The first synthetic drug, chloral hydrate, was discovered in 1832 by Justus von Liebig in Gießen

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and introduced as a sedative-hypnotic in 1869 [120]. Before the start of the new drug industry, all medicines, referred to in old medical literature, were natural products comprising a mixture of natural compounds, and most medicines are even formulations of natural products like herbs. After 1869, the medicine definition was changed without examining its validity to mean mainly active synthetic components [121]. There are several important changes to the original meaning. Old medicines work like multiple-component diets with much milder effects while synthetic drugs are used at higher concentrations. Second, early medicines are things that once worked as a selection pressure in evolution. For example, the compounds from herbs, plants, and natural products might have found their way to human bodies through the food chain. It is reasonable to infer that the human body can tolerate them in low concentrations. The fecundity phenotype will not be passed on to the next generation if the person cannot tolerate natural compounds at low concentrations, and dies before reaching reproductive age. In comparison, most human beings are not exposed to synthetic drugs, and thus selection will start upon ingesting such compounds. Those two things affect drug side effects and the ability to restore the biological pathway networks.

Failure of reductionist treatment model

The flaws in clinical trials and the failure of reductionist treatments are two different things but share some common elements. We have proved that treatments derived from clinical trials are deemed to be poor or inherently dangerous due to mismatched applications [9]. Besides the mismatch of treatment, the poor performance of population-based treatments can be attributed to the reductionist approach, which is found to be poor or unworkable in nutrition [122,123], lower back pain [124], n**euroscience and brain research** [125,126], diagnostics [127], exercise [128], patient care [129-140], public health programs [132], and holistic medicine [110,133-135]. The evidence, taken as a whole, has firmly established that reductionist treatments are inferior. Those findings in combination with our simulation study [9] prove that reductionism is a wrong approach to chronic diseases.

A. The Limitation of Reductionist Treatment Approach

Most medical treatments are developed according to reductionist thinking. The reductionist idea is that the human body is like a machine, and any fault can be fixed by targeting the fault part. This notion has been proved in some aspects such as organ transplant. However, we also see severe limitations. For example, after a person has died for some time, there is no way to revive the dead person like restarting a repaired car. The human ability to intervene brain is very limited. A reductionist treatment always has two components: a treatment is developed from a population and applied to the patient in the treatment of a disease. Both components are responsible for the failure of reductionist treatments.

1. **Population-based reductionist treatment cannot cure diseases:** It is generally believed that a treatment developed from a population must be good for persons A, B, C, etc. While this idea formed in old history, it can be summarily rejected by using a car repairing model. Automobiles made by Honda, Nissan, and Ford cannot be repaired by using a common method or common specification because they are distinctively designed. We now know that each human body is also distinctively designed. Second, even for cars, many process attributes cannot be altered without changing the whole car. For example, the cooling system and exhaustion system for each model of the car must be matched to the rest of the car. Even the wheels for a given model of car cannot be replaced by the average sizes of the wheels used in the auto industry. The average fuel consumption rates from a Civic and a Mercedes-Benz G550 cannot be imposed on either car. We can imagine that if auto repair and plane repair industries used a population approach, mechanical problems in automobiles and planes would be incurable. All planes will crash.

A treatment derived from clinical trials is mismatched to patients. For example, John Doe suffers from Vitamin A deficiency but Jack Doe suffers from Vitamin A poisoning. Both are sick even though their average is perfect. If a treatment is developed from such a population, the treatment reflects an impermissible transfer of process attributes in the biological networks. The treatment cannot be valid for both of them. This is not an isolated problem but a universal problem in treatments for chronic diseases. Most, if not all, of nutrients, pollutants, activity levels, etc. are expected to have both positive and negative effects. If a treatment is used to affect one of such factors, the treatment must be improper for a considerable portion of persons. Even if a treatment has a constant treatment effect, the interfering factors affect the treatment (Tables 1-3). Mathematics makes an impermissible average in finding treatments and such treatments cannot be good for anyone except by accident.

Treatments derived from population trials always make improper trade harmful to patients. In a mini-trial comprising a 90-year-old man, a 40-year-old man, a 40-year-old female, and a 10-year-old boy, their health and disease properties must vary greatly. We acquire data and find an average value of a health property for this population. The data does not form a statistical population. If we impose the averaged value onto all of them by imagined measure, we should anticipate that the measure most probably will kill all of them in the long run. Obviously, to develop a treatment by the population approach, attempts are made to balance age effects and sex effects. Treatment of the old man is balanced by the need to offer benefits to the young boy. Treatment for the man is balanced by the need to offer benefits to the female. This mathematical averaging violates our observed principle that health property cannot be altered arbitrarily and cannot be transferred from one person to another person. Any treatment based on the representation principle must be detrimental to all persons if the treatment is used for a long term. This flaw cannot be cured by increasing the number of participants in the trial.

Even the responsive rate used in medicine is a poor concept. Two treatments with 5% curative rates are considered

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in mathematics as same. However, they mean completely different things if one treatment cures only females while another cures only males. The population model makes an assumption that all persons are treated in the same way, but in reality, they cannot. What is really important is who will survive and who will die. Treatments determined by using a mathematical model are insensitive to personal differences and cannot be used to formulate the best treatments for all persons. Two treatments respectively with responsive rates of 50% and 40% lack comparison basis and cannot be compared. If they work with entirely different persons, they would treat 90% of the population if they are matched to the right persons. If their joint responsive rate is 20%, they would benefit 70% of the population.

2. **Reductionist treatments cannot correct departures in human biological pathways networks:** Each person has a unique biological pathway network [116-118], and chronic diseases are manifestations of a large number of departures in process attributes in the network. All attributes in one person's biological pathway network are different from those in another person's network. This distinctiveness is implied by well-known variations of chemical analysis data [136]. The distinctiveness of the physical check-up profile of each person is common knowledge. If a treatment is used on different persons, changes caused by the treatment in process attributes in one person's network must be different from changes in other persons' pathways networks. Even if the treatment is derived from a population, it cannot be matched to any person because the personal network is different from that of the average person. If a treatment is the best for one person, it cannot be best for another person.

If a treatment is to alter a single process attribute in the biological network, such a treatment cannot correct all departures in the biological pathways network. One well-known example is the alteration of biochemical and cellular pathways in cancer patients: attributes of six categories of biological properties (growth signaling, cell apoptosis, anti-growth signaling, angiogenesis, tissue invasion and metastasis, and cell replication limits) are changed in cancer patients [118]. Those process attributes are shown in P1, P2.... Pn in Figure 1. The top diagram shows a plurality of process attributes. Fault environmental, dietary, emotional, and lifestyle factors slowly cause many process attributes to depart from healthy values. It is highly unlikely that the disturbed biological networks can be corrected by using one single synthetic drug. This may be the reason why drugs deliver results that are poorer than what is predicted in theory. It is anticipated that the application of several primitive factors can have better chances to correct the departures in process attributes responsible for chronic diseases.

3. **Reductionist treatment cannot correct problems in CNS:** The mathematical models cannot characterize interactions between the Central Nervous System and the body running biological pathways. The role of CNS was known even in 1875 [1]. It is well known that the

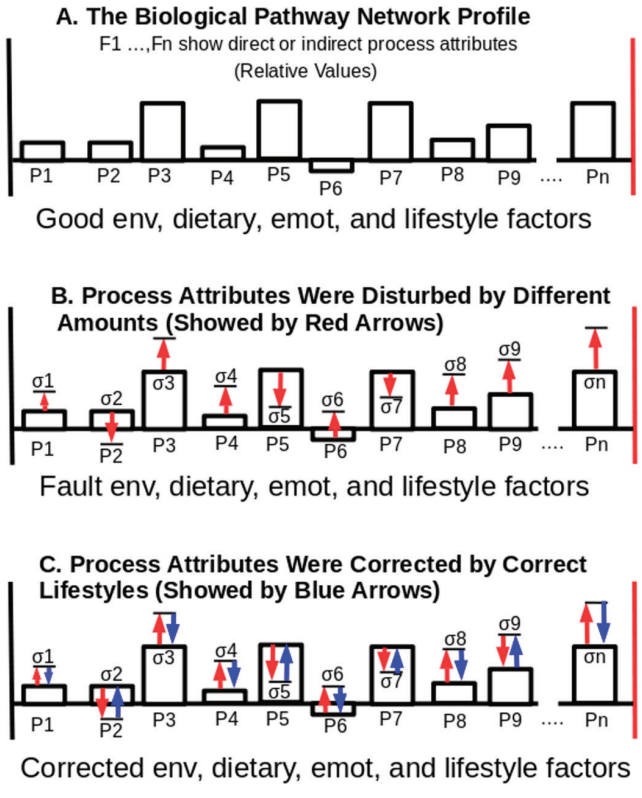

Figure 1: How the Process Attributes Profile of the Biological Pathway Networks Is Disturbed by Fault Environmental, Dietary, Emotional and Lifestyle Factors and How It Is Corrected by Adjustment to the Lifestyle.

CNS and the body constantly exchange neuronal signals but little about the signals is understood. It is expected that any changes caused by emotional interventions will invite the CNS to respond. We reasonably assume that the CNS-body interactions are to resist changes in the body. Mind and body interactions are like a gearbox containing two gears. One gear cannot be freely altered without making a corresponding adjustment to the other.

4. **Reductionist treatments lack the force to correct existing departures or further disturb process attributes in other attributes:** All process attributes in personal biological networks are influenced by a large number of interfering factors. Correction of problems in personal biological networks cannot be made by targeting only one or a few steps in the networks. This is shown in Figure 2. For example, the immune system can be suppressed by sad emotions and chronic stress, toxins and heavy metals, nutritional imbalance, poor vascular system attributed to lack of exercise, toxic micro-organic byproducts, etc. The actual causes may comprise a large number of primitive environmental, dietary, and lifestyle factors. Simultaneous correction of hundreds of fault factors is more powerful than doing one single thing that may completely miss the target.

A treatment targeted to one attribute such as P2 of one pathway lacks sufficient driving force. Such treatment cannot correct all departures in process attributes but most probably

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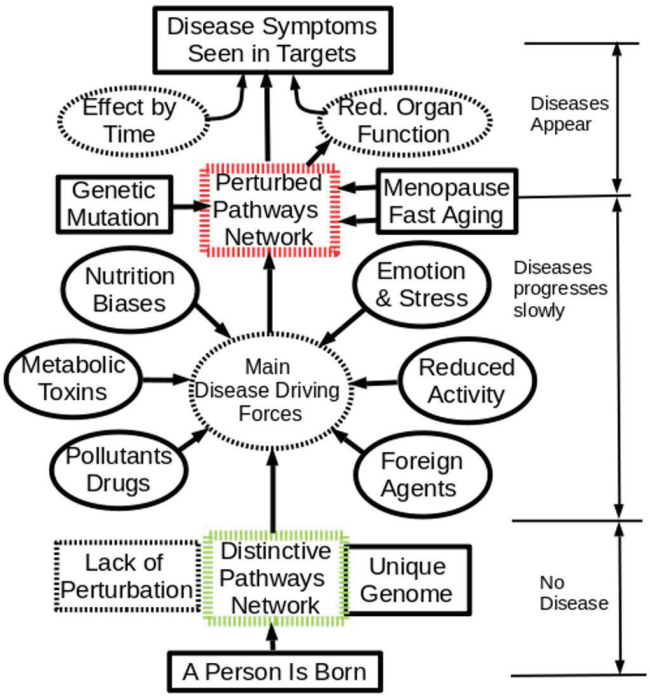

Figure 2: Environmental, Dietary, Emotional, and Lifestyle Factors Slowly Cause the Biological Pathways Networks to Depart from A Healthy State.

disturbs other process attributes. If a treatment is to alter the rate of one biological pathway, it is impossible to tell how the treatment might alter other pathways. Besides, responses in other pathways might depend on personal variations. Thus, one should find that diseases cannot be cured by correcting one seemingly faulty pathway. Some unexpected changes in other process attributes may make personal health or disease worse. This is one reason that synthetic drugs fail to work.

Figure 2 may be used to interpret the cancer treatment model. In this case, P1 to Pn could mean, respectively, genetic mutations, foreign matter, microbiota, pollutants, and toxins, nutrition, heavy metals, vascular condition, organ functional capacities, inflammation biomarkers, micro-circulation condition, innate immunity, CNS condition, nerve health, glucose level, emotional states, etc. Microbiota affects metabolic byproducts which may damage cells; foreign matter such as fiber grass and asbestos may affect tissue's local environment. P1 to Pn may denote process attributes (e.g., the glucose level) or anything that can directly or indirectly affect the process attributes of local biological pathway networks. Each of the P1 to Pn bars may mean a large number of primitive factors. Foreign matter may mean anything that could disturb the biological pathways with an effect to promote cancer. Toxins may mean one or more of potentially thousands of known and unknown compounds. With the massive variations in mind, Figure 1 may represent completely different process attributes for the same disease for two different persons. Two colon cancer patients may have completely different process attributes in Figure 1 and naturally require different lifestyle prescriptions. Considering their lifestyles, one may be caused by using a large amount of salty, hot, fried snacks while the other might be caused by excessive stress, distinctive microbiota, and lack of exercise. While they may share some common things, they must be treated differently to achieve better results.

5. **The reductionist approach could not address highly complex health problems:** We will consider how a mathematical model might perform when it is used to predict disease outcome of COVID-19 disease for a person. Infection diseases are mainly controlled by (1) exposures to the virus, (2) viral reproduction ability, (3) innate immune responses and host responses, (4) acquired immune response, and (5) the capacity to withstand tissue swelling [104,141-146]. Thus, disease severity such as the risk of death could be expressed as multiple functions of a large number of influencing factors under various conditions. If virus exposure is well controlled, the contribution from (2) to (5) will appear to have no role in the disease outcome. If the acquired immune response is fast and powerful, all of the effects from (1) to (3) and (5) may appear to have no role. From those mechanisms, we expect to establish a mathematical model having multiple component equations with various conditions as switches. Each of the component equations may include a linear equation, polynomial equation, power law, etc., which has tens to thousands of primitive lifestyle, personal, dietary, emotional, and environmental factors. Disease severity also depends on aging or development stage, information in neurons, hormonal regulation, epigenetic changes in cells, menopause status, personal activities, etc. Many of the factors (e.g., the independent variables) are random variables so some of the component equations are random variables. For a population, disease severity is just viewed as the sum of all functions for all individual persons. No solution could be found to such a complex function, there is no way to combine all personal functions for the population, and there is no way to solve a combined function for the population.

A mathematical model developed for a person cannot be used to predict disease severity for other persons unless they are close to the person. The model may tell how to change dependent variables to achieve a better outcome. We must find that current epidemiological models [141-150] are irrelevant to the disease and human health. An articulation like "temperature or oxygen can cure the disease" has far more science than a mathematical model. Epidemiological models contain almost none of the biological factors. Manipulation of the twenties to a hundred factors, most of which are conceived out of imagination, will not help solve the pandemic. Medicine needs to pay more attention to human disease biology and personal health, rather than things like coins, dice, lotteries, etc. It is a wrong strategy to jump onto population health while forgetting basic disease biology.

Strong treatment that is not matched to the patient's condition must produce drug side effects if the treatment is used for a long time [137-140,151-155].

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Discussion

1. Flawed presumptions in the foundation of medicine

When medicine evolved from experienced-based ancient mind-body personalized medicine to drug-based reductionist modern medicine, medicine silently changed multi-component natural mild medicines into highly concentrated synthetic drugs, changed the holistic mind-body medicine into reductionist treatments, turned health properties of human beings into statistical populations, and started using mathematical models for most research subjects. Those four presumptions have been accepted as the foundation of medicine, without ever being validated. Our analysis using massive data produced by tens of thousands of medical studies firmly refutes the presumptions. The biggest flaw in modern medicine is the use of mathematical models to add up process attributes, which are intensive properties, across individual persons. While this presumption is not always wrong for all research purposes, it is always wrong in a trial to study chronic diseases. Chronic diseases are a manifestation of distinctive biological pathway networks in humans often with very small departures in multiple process attributes, the addition of intensive properties across different persons produces meaningless results except for a strong treatment. Without overhauling the foundation, modern medicine lacks the required accuracy for accurately characterizing chronic diseases and will never find predictable cures for chronic diseases.

2. Limitations in clinical trials

In assessing treatment effect, (1) a clinical trial is useful in a study when a strong treatment T is against N interfering factors Fi, where T is much and much stronger than the sum of all interfering factors Fi. In this situation, the statistical population exits by approximation while all interfering factors can be viewed as experimental errors, and if the treatment is not intended to disturb the biological networks, the treatment is only for short-term use; (2) clinical trial may be able to detect the effect of treatment T among N interfering factors Fi if the accumulated effect of the treatment in a sufficiently long period can stand out accumulated interfering factors Fi. This is why some long-term trials can result in useful estimates; (3) clinical trials cannot produce the right result if a treatment T in the study is used only for a brief time so that its treatment effects are hidden among N interfering factors Fi. A brief exercise, brief diet, and brief emotional invention show no detectable benefit; and (4) a clinical trial produces a false result if treatment T in a study does not have the same or similar effects on all subjects, or if all interfering factors have different impacts on different subjects, or both. In those situations, the positive effects of the treatment T on some subjects are nullified by negative effects on other subjects, or distorted by randomly interfering factors. Moreover, treatment effects on all subjects must be compared with differences attributable to different subjects in light of the accuracy requirement of investigation purposes.

Clinical trials are invalid for studying drug side effects that are realized slowly while the measured health properties are interfered with by a large number of interfering factors. Among the massive medical studies, only one class of studies directed to strong treatment effects is correct by approximation as far as treatment effects are concerned. However, those studies may still fail to produce correct results for the side effects of treatments.

Root flaws in clinical trials include (1) misuse of statistical populations as presumption without considering research purposes and required accuracy; (2) failure to study the massive interfering factors and co-causal factors; (3) misuse of mathematical models with attempts to change process attributes as if they were fungible properties; (4) use of a mathematical model that is remote from reality; (5) misuse of representative principle when there is no statistical population and no approximation is allowed; (6) failure to determine required accuracy relative to interfering factors; and (7) failure to address one-way biases caused by interfering factors. Each of those problems can make study findings inaccurate, biased, or even completely meaningless.

Due to the widespread use of clinical trials, all studies involving weak environmental, dietary, emotional, and lifestyle factors are most probably wrong if the findings are negative. This flawed method in the studies poses the worst risk to civilization. Each of the potentially thousands of harmful and toxic substances is found to be harmless because it is interfered with by a large number of other interfering factors. Those harmful substances strike human health slowly. We regard the misused clinical trials as well as population-based studies as the main reasons for human inability to protect the ecosystem and provide lame excuses for the abusive use of avoidable toxic substances such as food additives, synthetic flavors, texture modifiers, etc. Now, cancer, infertility, mental diseases, infectious diseases, etc. are striking mankind with unprecedented impacts. The risk of getting cancer in a person's lifetime rises from 0.04 to 0.4 and will soon reach unity. Stories like six cancer patients in a family and three cancer deaths in a year will become more frequent. There is no way to find causes, and nothing could be attempted to arrest many bad trends. Problems like infertility will become a civilization crisis.

3. Problems in reductionist treatments

Reductionist treatments cannot cure chronic diseases for all of the following reasons: The treatment (1) is based on clinical trials that attempt to make impermissible trades in health properties between different persons; (2) is mismatched to individual persons' biological networks; (3) fails to address the interlocking role of CNS; (4) lacks the force to alter departures of process attributes in the biological networks; (5) cannot deal with multiple layers of mechanisms concerning disease initiation, progression, innate immune response, adaptive immune response, resolution of inflammation, and resolution of damages; and (6) has a too strong force to distort intervened biological networks and thus causes drug side effects by further distorting the biological networks. This proves why medicine has failed for centuries.

Population-derived treatments should be presumed to be dangerous if they are used to directly affect a step in the

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biological pathways networks for the long term. Biological pathways in each person must be maintained as a distinctive pattern in terms of intermediate species concentrations and conversion rates. Each person's values cannot be changed into the population averages or the values of another person because the person's values are constrained by upper-stream, coupled, and downstream biological pathways in the pathways networks. It is impossible to alter just one single or a few steps in the networks without altering others. Intervention by using a strong drug must distort other process attributes and thus cause new diseases. This distinctive nature implies that the mathematical averages of the values have no meaning and that chronic diseases cannot be cured by intervening in one single or a few steps in the networks.

Immediate cures for chronic diseases lie in the use of primitive factors to slowly alter personal biological networks. The use of evolution-compatible lifestyle factors is presumed to be the safest cure. Most biological properties (except genes and age) can be altered by using lifestyles, foods, exercise, emotion management, and avoidance of toxic substances. Even certain genetic properties can be altered to a limited extent by changing epigenetics. The effects of many primitive factors have been found in studies; and the effects of weak factors such as activity habits, cellular phone use, etc. cannot be determined under current research models but may be established by studying disease mechanisms or disease risks. The adverse effects of lack of exercise and inactivity can be seen in elevated disease risks among obese people, people having vascular diseases, and people who are sedentary. However, negative findings in clinical trials should not be read to preclude the potential benefits of weak factors on specific persons.

Most diseases progress from altering primitive factors, altering the biological networks, altering the structure, and altering the CNS function. The severity of chronic diseases is almost always manifested in functional impairment caused by structural changes. Changes in each of those phases may take considerable time, and disease development and disease reversal would take considerable time. Preventive measures may be used in any of those phases, and there is no difference in mechanism between curative measures and preventive measures except that reversing diseases is more difficult.

The democratic representation principle used in research harms minorities. Treatments developed in clinical trials can have severe adverse impacts on minorities. Genetics are more similar between persons within a race than between members of different races. The computed average of health property for a population of a majority race is expected to be different from that for a population of a minority race. If a treatment is developed by a clinical trial containing persons of both races according to their population ratio, the average will be closer to the average of the majority race. This implies that the treatment for the minority race is poorer or more dangerous than it is for the majority race.

The problems in clinical trials are found by studying its theory, basic assumptions, biological pathways, disease initiation and defense mechanisms, factor-factor interactions, body structure, etc. Treatments developed by using the population approach are inherently invalid except by accident and inherently dangerous if they are used in the long term. All four presumptions -- treating health property as a population, using synthetic drugs, using mathematical and statistical methods, and using reductionist treatments -- are refuted. The flawed foundation precludes finding predictable cures for chronic diseases and cancer.

4. Impacts of this study

The findings of this study will affect the lives of tens of millions of people who are dying from chronic diseases in the world each year, the use of a good part of $41 billion in federal research funds administered by NIH, the use of more than a hundred billion private research fund in the U.S., the trillion of medical spending in the U.S., validity and accuracy of conclusions in a large number of published medical studies, and risk to civilization. The worst effect of those flaws is that it creates incurable notion to justify the failure of medicine. By trusting the flawed research model and treatments, medicine fails to study hundreds of well-documented cancer miracles and does not attempt to discover millions of undocumented miracles in cancer, heart diseases, and mental diseases. The ruined health wisdom among patients suffering "terminal" diseases is a strong aggravating factor that causes patient deaths because patients are misled by propagation that diseases are incurable. If one truly understands all flawed presumptions and all flaws in research and treatment models, one should see that diseases are curable among patients with the willpower to change. Unfortunately, the medical establishment has built highly sophisticated protective systems to discriminate against, preclude, and suppress any research findings that challenge the foundation of medicine.

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Author contribution

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Additional information

Due to the scope of the work, additional information will be provided in follow-up studies which will be posted in Preprint servers.

References

1. Cole T. Failures of Medicine. British Medical Journal. 1875; 6: 579-582.

2. Kresser C. Two Reasons Conventional Medicine Will Never Solve Chronic Disease. https://kresserinstitute.com/two-reasons-conventional-medicine-will-never-solve-chronic-disease/

3. Green AR, Carrillo JE, Betancourt JR. Why the disease-based model of medicine fails our patients. West J Med. 2002 Mar;176(2):141-3. PMID: 11897746; PMCID: PMC1071693.

Citation: Wu J, Zha P (2023) Flawed foundation is the root cause of failure of medicine and precludes cures for chronic diseases. Glob J Cancer Ther 9(1): 001-019. DOI: https://dx.doi.org/10.17352/2581-5407.000050

4. Advisory Board, Precision medicine fails for up to 93% of patients. Are its proponents selling 'false hope'? September 21, 2018, Accessed from https://www.advisory.com/daily-briefing/2018/09/21/precision-medicine

5. Wikipedia. List of incurable diseases. Accessed from https://en.wikipedia.org/wiki/List_of_incurable_diseases. Accessed on May 17, 2020.

6. Wu J, Zha P. Surgery, Chemotherapy and Radiotherapy May Promote Cancer Growth Speeds and Shorten Patient Lives. Glob J Cancer Ther.2022;8(1): 001-020. DOI: 10.17352/2581-5407.000043.

7. Tackling the burden of chronic diseases in the USA. Lancet. 2009;373(9659):185. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60048-9/fulltext

8. DeVol R. and Bedroussian A. An Unhealthy America: The Economic Burden of Chronic Disease. Milken Institute Report. 2007; 1-35.

9. Wu J, Zha P. Clinical trials cannot provide sufficient accuracy for studying weak factors necessary for curing chronic diseases. Glob J Cancer Ther.2022;8(1): 021-033. DOI: 10.17352/2581-5407.000044.

10. Krauss A. Why all randomised controlled trials produce biased results. Ann Med. 2018;50:312–322.

11. Bhatt A. Evolution of Clinical Research: A History Before and Beyon James Lind. Perspect Clin Res. 2010; 1(1): 6–10.

12. Helen Mary Walker. Studies in the history of statistical method. Arno Press. 1975.

13. Altman DG. Comparability of randomised groups. The Statistician. 1985;34:125-136.

14. Senn SJ. Covariate imbalance and random allocation in clinical trials. Stat Med. 1989;8:467–475.

15. Senn SJ. Testing for baseline balance in clinical trials. Stat Med. 1994;13:1715-1726.

16. Senn S. Controversies concerning randomization and additivity in clinical trials. Stat Med. 2004;23:3729-3753.

17. Senn SJ. Seven myths of randomisation in clinical trials. Stat Med. 2013;32:1439-1450.

18. Zhao W, Berger V. Imbalance control in clinical trial subject randomisation – from philosophy to strategy. J Clin Epidemiol. 2018;101:116–118.

19. Althouse AD, Abebe KZ, Collins GS, Harrell Jr FE. Response to "Why all randomized controlled trials produce biased results". Annals of Medicine. 2018;50(7):545-548.

20. Widpedia, Reference ranges for blood tests. Accessed on August 20, 2020. https://en.wikipedia.org/wiki/Reference_ranges_for_blood_tests

21. Pennisi E. The human genome. Science. February 2001;291(5507): 1177–80.

22. Auton A, Brooks LD, Durbin RM. A global reference for human genetic variation. Nature. October 2015;526 (7571): 68-74.

23. Misteli T. Beyond the sequence: cellular organization of genome function. Cell. February 2007;128 (4): 787-800.

24. Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. Cell. 2007;128 (4): 669-81.

25. Ogino S, Fuchs CS, Giovannucci E. How many molecular subtypes? Implications of the unique tumor principle in personalized medicine. Expert Rev Mol Diagn. 2012;12(6): 621-8.

26. Ogino S, Lochhead P, Chan AT. Molecular pathological epidemiology of epigenetics: Emerging integrative science to analyze environment, host, and disease. Mod Pathol. 2013;26(4): 465-84.

27. Liu Y-Z, Wang YX, Jiang CL. Inflammation: The Common Pathway of Stress-Related Diseases Front. Hum. Neurosci. 2017;11:316.

28. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007;21(7):901-12.

29. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601–30.

30. McCann SM. NY Acad Sci. Neuroimmunomodulation: Molecular aspects, integrative systems, and clinical advances. 1997. https://doi.org/10.1111/j.1749-6632.1998.tb09542.x

31. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol Res. 2014; 58(2-3):193-210.

32. Webster Marketon JI, Glaser R. Stress hormones and immune function. Cell Immunol. 2008;252(1-2):16–26.

33. Pedersen AF, Zachariae R, Bovbjerg DH. Psychological stress and antibody response to influenza vaccination: a meta-analysis. Brain Behav Immun. 2009;23(4):427-33.

34. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection—a meta-analysis of prospective studies. Psychosom Med. 2010;72(8):823-32.

35. Walburn J, Vedhara K, Hankins M, Rixon L, Weinman J. Psychological stress and wound healing in humans: a systematic review and meta-analysis. J Psychosom Res. 2009;67(3):253-71.

36. Hawryluck L, Gold WL, Robinson S, Pogorski S. Galea S, Styra R. SARS Control and Psychological Effects of Quarantine, Toronto, Canada. Emerg Infect Disv. 2004;10 (7),1206-12.

37. Lutgendorf SK, Sood AK, Anderson B. Social support, psychological distress, and natural killer cell activity in ovarian cancer. Journal of Clinical Oncology. 2005;23(28):7105-7113.

38. Lutgendorf SK, DeGeest K, Dahmoush L. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain, Behavior, and Immunity. 2011;25(2):250-255.

39. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. Future Oncology. 2010;6(12):1863-1881.

40. Sloan EK, Priceman SJ, Cox BF. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Research. 2010;70(18):7042-7052.

41. Sundquist J, Li X, Johansson SE, Sundquist K. Depression as a predictor of hospitalization due to coronary heart disease. Am J Prev Med. 2005; 29: 428-433.

42. Brydon L, Magid K, Steptoe A. Platelets, coronary heart disease, and stress. Brain Behav Immun. 2006;20: 113-119.

43. Wójcikowski J, Daniel WA. The role of the nervous system in the regulation of liver cytochrome p450. Curr Drug Metab. 2011;12(2):124-38.

44. Chandra RK. Nutrition and The Immune System: An Introduction. American Journal of Clinical Nutrition. 1997;66: 460S-3S.

45. Keusch GT. The History of Nutrition: Malnutrition, Infection and Immunity. Journal of Nutrition. 2003;133:336S-40S.

46. Ritz BW, Gardner EM. Malnutrition and Energy Restriction Differentially Affect Viral Immunity. Journal of Nutrition. 2006;136:1141-4.

47. Levander OA. Nutrition and Newly Emerging Viral Diseases: An Overview. Journal of Nutrition. 1997;127: 948S-50S.

Citation: Wu J, Zha P (2023) Flawed foundation is the root cause of failure of medicine and precludes cures for chronic diseases. Glob J Cancer Ther 9(1): 001-019. DOI: https://dx.doi.org/10.17352/2581-5407.000050

48. Schaible UE, Kaufmann SH. Malnutrition and Infection: Complex Mechanisms and Global Impacts. PLoS Medicine. 2007;4: e115.

49. Alice M, Tang ES, Semba RD. Nutrition and Infection, in Kenrad E., Nelson C.M.W., editors. (eds.) Infectious Disease Epidemiology: Theory and Practice, 3rd edn. Burlington, MA: Jones & Bartlett Learning. 2013.

50. Beck MA. Selenium and Vitamin E Status: Impact on Viral Pathogenicity. Journal of Nutrition. 2007;137: 1338-40.

51. Beck MA, Handy J, Levander OA. Host Nutritional Status: The Neglected Virulence Factor. Trends in Microbiology. 2004;12:417-23.

52. Nelson HK, Shi Q, Van Dael P. Host Nutritional Selenium Status as a Driving Force for Influenza Virus Mutations. The FASEB Journal. 2001; 15: 1846-8.

53. Beck MA, Williams-Toone D, Levander OA. Coxsackievirus B3-Resistant Mice Become Susceptible in Se/Vitamin E Deficiency. Free Radical Biology and Medicine. 2003;34:1263-70.

54. Barnett JB, Hamer DH, Meydani SN. Zinc: a new risk factor for pneumonia in the elderly. Nutr Rev. 2010; 68(1): 30-37.

55. Kanneganti TD, Dixit VD. Immunological Complications of Obesity. Nature Immunology. 2012;13: 707-12.

56. Karlsson EA, Beck MA. Diet-Induced Obesity Impairs The T Cell Memory Response to Influenza Virus Infection. The FASEB Journal. 2009;23: 110-3.

57. Karlsson EA, Sheridan PA, Beck MA. Diet-Induced Obesity Impairs the T Cell Memory Response to Influenza Virus Infection. The Journal of Immunology. 2010;184:3127-33.

58. Monteiro R, Azevedo I. Chronic Inflammation in Obesity and the Metabolic Syndrome. Mediators of Inflammation. 2010. pii:289645.

59. Nieman DC, Henson DA, Nehlsen-Cannarella SL. Influence of Obesity on Immune Function. Journal of the American Dietetic Association. 1999; 99: 294-9.

60. Kanneganti TD, Dixit VD. Immunological Complications of Obesity. Nat Immunol. 2012;13:707-12.

61. Smith AG, Sheridan PA, Harp JB. Diet-Induced Obese Mice have Increased Mortality and Altered Immune Responses when Infected with Influenza Virus. Journal of Nutrition. 2007;37:1236-43.

62. Aroor AR, DeMarco VG. Oxidative stress and obesity: the chicken or the egg? Diabetes. 2014 Jul;63(7):2216-8. doi: 10.2337/db14-0424. PMID: 24962921.

63. Hardell L, Carlberg M, Söderqvist F, Mild KH. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. International Journal of Oncology. Published online September 24, 2013.

64. Frei P, Poulsen AH, Johansen C. Use of mobile phones and risk of brain tumours: update of Danish cohort study. BMJ. 2011; 343: d6387.

65. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Opinion on Potential health effects of exposure to electromagnetic fields (EMF). 2015.

66. Singh R, Gautam N, Mishra A, and Gupta R. Heavy metals and living systems: An overview. Indian J Pharmacol. 2011 May-Jun; 43(3): 246-253.

67. Carver A. and Gallicchio VS. Heavy Metals and Cancer, IntechOpen, 2018. http://dx.doi.org/10.5772/intechopen.70348

68. Yuan W, Yang N, and Li X. Advances in Understanding How Heavy Metal Pollution Triggers Gastric Cancer, Hindawi Publishing Corporation. BioMed Research International. 2016. http://dx.doi.org/10.1155/2016/7825432

69. Romaniuk A, Lyndin M, Sikora V. Heavy metals effect on breast cancer progression. Journal of Occupational Medicine and Toxicology. 2017; 12:32.

70. Chowdhury R, Ramond A, O'Keeffe LM. Environmental toxic metal contaminants and risk of cardiovascular outcomes: systematic review and meta-analysis. BMJ. 2018;362:k3310.

71. Lamas GA, Navas-Acien A, Mark DB, and Lee KL. Heavy Metals, Cardiovascular Disease, and the Unexpected Benefits of Edetate Disodium Chelation Therapy. Am Coll Cardiol. 2016; 67(20): 2411-2418.

72. Sharma B, Singh S, and Siddiqi NJ. Biomedical Implications of Heavy Metals Induced Imbalances in Redox Systems. Hindawi Publishing Corporation. BioMed Research International. 2014. http://dx.doi.org/10.1155/2014/640754

73. Marth E, Jelovcan S, Kleinhappl B. The effect of heavy metals on the immune system at low concentrations. Int J Occup Med Environ Health. 2001;14(4):375-86.

74. Anyanwu BO, Ezejiofor AN, Igweze ZN and Orisakwe OE. Heavy Metal Mixture Exposure and Effects in Developing Nations: An Update. Toxics. 2018; 6 (65):1-32.

75. Caffo M, Caruso G, La Fata G. Heavy Metals and Epigenetic Alterations in Brain Tumors. Current Genomics. 2014;15:000-000.

76. Gorini F, Muratori F & Morales MA. The Role of Heavy Metal Pollution in Neurobehavioral Disorders: A Focus on Autism. Rev J Autism Dev Disord. 2014; 1:354-372.

77. American Heart Association. Get the Scoop on Sodium and Salt. Last Reviewed: Apr 16, 2018. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/sodium-and-salt

78. Ge S, Feng X, Shen L. Association between Habitual Dietary Salt Intake and Risk of Gastric Cancer: A Systematic Review of Observational Studies. Hindawi Publishing Corporation. Gastroenterology Research and Practice. 2012. doi:10.1155/2012/808120

79. Strnad M. Salt and cancer. Acta Med Croatica. 2010;64(2):159-61.

80. Lee S-K and Kim MK. Relationship of sodium intake with obesity among Korean children and adolescents: Korea National Health and Nutrition Examination Survey. British Journal of Nutrition. 2016; 115: 834-841.

81. Teucher B, Dainty JR, Spinks CA. Sodium and Bone Health: Impact of Moderately High and Low Salt Intakes on Calcium Metabolism in Postmenopausal Women. Journal Of Bone And Mineral Research. 2008. doi: 10.1359/JBMR.080408

82. He FJ and Li J. Effect of longer-term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325 doi: 10.1136/bmj.f1325

83. Melin VE, Potineni H, Hunt P. Exposure to common quaternary ammonium disinfectants decreases fertility in mice. Reprod Toxicol. 2014 Dec; 50: 163-170.

84. Hrubec TC, Melin VE, Shea CS. Ambient and Dosed Exposure to Quaternary Ammonium Disinfectants Causes Neural Tube Defects in Rodents. Birth Defects. Res. 2017;109(14):1166-1178.

85. Mahmood A, Eqan M, Pervez S. COVID-19 and frequent use of hand sanitizers; human health and environmental hazards by exposure pathways. Sci Total Environ. 2020. 27;742:140561.

86. Watt BE, Proudfoot AT, Vale JA. Hydrogen peroxide poisoning. Toxicol Rev. 2004;23(1):51-7.

87. Tipton CM. The history of "Exercise Is Medicine" in ancient civilizations. Adv Physiol Educ. 2014;38(2):109-117.

88. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2:1143-1211.

89. Cormie P, Zopf EM, Zhang X, Schmitz KH. The Impact of Exercise on Cancer

Citation: Wu J, Zha P (2023) Flawed foundation is the root cause of failure of medicine and precludes cures for chronic diseases. Glob J Cancer Ther 9(1): 001-019. DOI: https://dx.doi.org/10.17352/2581-5407.000050

Mortality, Recurrence, and Treatment-Related Adverse Effects. Epidemiologic Reviews. 2017;39(1):71-92.

90. Holmes MD, Chen WY, Feskanich D. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;293(20):2479-2486.

91. Meyerhardt JA, Heseltine D, Niedzwiecki D. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol. 2006;24(22):3535-3541.

92. Des Guetz G, Uzzan B, Bouillet T. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. Gastroenterol Res Pract. 2013;2013:340851.

93. Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. Med Oncol. 2011;28(3):753-765.

94. Lahart IM, Metsios GS, Nevill AM. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. Acta Oncol. 2015;54(5):635-654.

95. Friedenreich CM, Neilson HK, Farris MS. Physical activity and cancer outcomes: a precision medicine approach. Clin Cancer Res. 2016;22(19):4766-4775.

96. Li T, Wei S, Shi Y. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports Med. 2016;50(6):339-345.

97. Otto SJ, Korfage IJ, Polinder S. Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. Support Care Cancer. 2015;23(5):1237-1250.

98. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol. 2014;25(7):1293-1311.

99. Wu W, Guo F, Ye J. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. Oncotarget. 2016;7(32):52095-52103.

100. Zhong S, Jiang T, Ma T. Association between physical activity and mortality in breast cancer: a meta-analysis of cohort studies. Eur J Epidemiol. 2014;29(6):391-404.

101. Bortz WMT, Bortz WM 2nd. How fast do we age? Exercise performance over time as a biomarker. J Gerontol A Biol Sci Med Sci. 1996; 51:M223-5.

102. Goldspink DF. Ageing and activity: Their effects on the functional reserve capacities of the heart and vascular smooth and skeletal muscles. Ergonomics. 2005;48:1334-51.

103. Sehl ME, Yates FE. Kinetics of human aging: I. Rates of senescence between ages 30 and 70 years in healthy people. J Gerontol A Biol Sci Med Sci. 2001; 56:B198-208.

104. Wu J, Zha P. Lung Damage Mechanisms For COVID-19 and Other Lung Infections, and Driving Force and Selectivity in Leukecyte Recruitment and Migration. Journal of Respiratory Diseases. 2022;1(2):16-27. DOI: 10.14302/issn.2642-9241.jrd-22-4132.

105. Christopher MP, Simon AJ, Jie Yang. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. https://doi.org/10.1101/2020.04.08.20057794

106. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203-209. PMID: 25830558; PMCID: PMC4367209.

107. Wu J, Zha P. Public Health Intervention Framework for Reviving Economy amid the COVID-Pandemic (2): Use of Personalized Mitigation Measures Beyond the Epidemiological Model Limits. Journal of Marketing Management and Consumer Behavior. 2022;4(2):33-51.

108. Michiels, C. Physiological and Pathological Responses to Hypoxia. The American Journal of Pathology. 2004; 164 (6): 1875-82.

109. Lowen AC, Steel J. Roles of humidity and temperature in shaping influenza seasonality. J Virol. 2014 Jul;88(14):7692-5. doi: 10.1128/JVI.03544-13. Epub 2014 Apr 30. PMID: 24789791; PMCID: PMC4097773.

110. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. Nat Rev Immunol. 2015 Jun;15(6):335-49. doi: 10.1038/nri3843. Epub 2015 May 15. PMID: 25976513; PMCID: PMC4786079.

111. Lawrence HA. Perspectives on Complementary/Alternative & Integrative Medicine (taught by Dr. Sonya Pritzker). Accessed from http://cewm.med.ucla.edu/education/anthro157.html.

112. Canaani J, Kollet O, Lapidot T. Neural regulation of bone, marrow, and the microenvironment. Front Biosci (Schol Ed). 2011 Jun 1;3(3):1021-31. doi: 10.2741/206. PMID: 21622251.

113. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Cuomo-Dannenburg G, Thompson H, Walker PGT, Fu H, Dighe A, Griffin JT, Baguelin M, Bhatia S, Boonyasiri A, Cori A, Cucunubá Z, FitzJohn R, Gaythorpe K, Green W, Hamlet A, Hinsley W, Laydon D, Nedjati-Gilani G, Riley S, van Elsland S, Volz E, Wang H, Wang Y, Xi X, Donnelly CA, Ghani AC, Ferguson NM. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Jun;20(6):669-677. doi: 10.1016/S1473-3099(20)30243-7. Epub 2020 Mar 30. Erratum in: Lancet Infect Dis. 2020 Apr 15;: Erratum in: Lancet Infect Dis. 2020 May 4;: PMID: 32240634; PMCID: PMC7158570.

114. EMBO. Mind-body research moves towards the mainstream. Mounting evidence for the role of the mind in disease and healing is leading to a greater acceptance of mind-body medicine. EMBO reports 2006;7 (4): 358-361.

115. Massey J. Mind-Body Medicine Its History & Evolution. June 1, 2015 In Mind/Body. Naturophathic Doctor News and Review. Accessed from https://ndnr.com/mindbody/mind-body-medicine-its-history-evolution/

116. Biological pathway. Wikipedia. Accessed from https://en.wikipedia. org/wiki/Biological_pathway

117. Metabolic pathway. Wikipedia. Accessed from https://en.wikipedia.org/wiki/Metabolic_pathway

118. Hanahan & Weinberg. The Hallmarks of Cancer. Cell. 2000;100: 57-70.

119. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. Engl J Med. 2018; 379:111-121.

120. Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. Drug Test Anal. 2011;;3(6):337-44.

121. Wikipedia, List of drugs by year of discovery. https://en.wikipedia.org/wiki/List_of_drugs_by_year_of_discovery.

122. Fardet A. and Rock E. Toward a New Philosophy of Preventive Nutrition: From a Reductionist to a Holistic Paradigm to Improve Nutritional Recommendations. Adv Nutr. 2014 Jul; 5(4): 430-446.

123. Fardet A. and Rock E. Perspective: Reductionist Nutrition Research Has Meaning Only within the Framework of Holistic and Ethical Thinking. Adv Nutr. 2018;9:655-670.

124. Cholewicki J, Pathak PK, Reeves NP, Popovich JM Jr. Model Simulations Challenge Reductionist Research Approaches to Studying Chronic Low Back Pain. J Orthop Sports Phys Ther. 2019;49(6):477-481.

125. Krakauer JW, Ghazanfar AA, Gomez-Marin A. Neuroscience Needs Behavior: Correcting a Reductionist Bias. Neuron. 2017;93: 480-490.

126. Hyland ME. Functional disorders can also be explained through a non-reductionist application of network theory. Behav Brain Sci. 2019;42:e12.

Citation: Wu J, Zha P (2023) Flawed foundation is the root cause of failure of medicine and precludes cures for chronic diseases. Glob J Cancer Ther 9(1): 001-019. DOI: https://dx.doi.org/10.17352/2581-5407.000050

127. Maguire G. Using a systems-based approach to overcome reductionist strategies in the development of diagnostics. Expert Rev Mol Diagn. 2013;13(8):895-905.

128. Bouchard C. Adaptation to Acute and Regular Exercise: From Reductionist Approaches to Integrative Biology. Prog Mol Biol Transl Sci. 2015;135:1-15.

129. Gutierrez CE, Kehoe K. Integrative cardiac care at Queen's Medical Center. Beginnings. 2009;29(4):8-9.

130. Fortney L, Rakel D, Rindfleisch JA, Mallory J. Introduction to integrative primary care: the health-oriented clinic. Prim Care. 2010;37(1):1-12.

131. Hansen KA, McKernan LC, Carter SD. A Replicable and Sustainable Whole Person Care Model for Chronic Pain. 2019 Mar;25(S1):S86-S94.

132. Dooris M, Farrier A, Froggett L. Wellbeing: the challenge of 'operationalising' a holistic concept within a reductionist public health programme. Perspect Public Health. 2018;138(2):93-99.

133. Hayward E. Life and Time Swimming Upstream: practising whole-person medicine in a reductionist medical culture. Br J Gen Practv. 2019; 69(682).

134. Manahan B. The whole systems medicine of tomorrow: a half-century perspective. Explore (NY). 2011;7(4):212-4.

135. Miles A. On the interface between science, medicine, faith, and values in the individualization of clinical practice: a review and analysis of 'Medicine of the Person' Cox, J, Campbell, AV. & Fulford, KWM, eds (2007). J Eval Clin Pract. 2009;15(6):1000-24.

136. Wikipedia, Reference ranges for blood tests. Accessed on August 20, 2020. https://en.wikipedia.org/wiki/Reference_ranges_for_blood_tests

137. Drugwatch, FDA Recalls. Accessed at https://www.drugwatch.com/fda/recalls/. Accessed on May 20, 2020.

138. Wikipedia. List of withdrawn drugs. https://en.wikipedia.org/wiki/List_of_withdrawn_drugs. Accessed on May 10, 2020.

139 ProCon.org. FDA-Approved Prescription Drugs Later Pulled from the Market. Last updated 1/30/2014. Https://prescriptiondrugs.procon.org/fda-approved-prescription-drugs-later-pulled-from-the-market/. 2020.

140. Pearce A, Haas M, Viney R. Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. PLoS ONE 2017;12(10):e0184360. https://doi.org/10.1371/journal.pone.0184360

141. Yoo J-K, Kim TS, Hufford MM, Braciale TJ. Viral infection of the lung: Host response and sequelae. J Allergy Clin Immunol. 2013; 132(6):1-28.

142. Shi Y, Wang Y, Shao C. COVID-19 infection: the perspectives on immune responses. Cell Death & Differentiation. 2020;27:1451-1454.

143. Handfield C, Kwock J, MacLeod AS. Innate Antiviral Immunity in the Skin. Trends Immunol. 2018 April; 39(4): 328-340.

144. Tay MZ, Poh CM, Rénia L. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology. 2020; 20:363-374.

145. Nutt, SL, Hodgkin, PD, Tarlinton, DM, Corcoran, LM. The generation of antibody-secreting plasma cells. Nature Reviews Immunology. 2015;15 (3): 160-71.

146. Tseng, CT, Perrone, LA, Zhu, H. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. J. Immunol. 2005;174:7977-7985.

147. Guerra FM, Bolotin S, Lim G. The basic reproduction number (R0) of measles: a systematic review. Lancet Infect Dis. 2017;17:e420-8.

148. Ridenhour B, Kowalik JM, Shay DK. Unraveling R0: Considerations for public health applications. Am J Public Health. 2014;104: e32-41.

149. Heesterbeek JAP. A brief history of R0 and a recipe for its calculation. Acta Biotheor. 2002;50:189-204.

150. Li J, Blakeley D, Smith RJ. The failure of R0. Comput Math Methods Med. 2011;2011:527610.

151. Cupit-Link MC, Kirkland JL, Ness KK. Biology of premature ageing in survivors of cancer. ESMO Open. 2017. http://dx.doi.org/10.1136/esmoopen-2017-000250

152. López-Otín C, Blasco MA, Partridge L. The hallmarks of aging. Cell. 2013;153:1194-217.

153. Golder S, Loke Y, and McIntosh HM. Room for improvement? A survey of the methods used in systematic reviews of adverse effects. BMC Medical Research Methodology. 2006; 6:3.

154. Cornelius VR, Perrio MJ, Shakir SA, Smith LA. Systematic reviews of adverse effects of drug interventions: a survey of their conduct and reporting quality. Pharmacoepidemiol Drug Saf. 2009;18(12):1223-31.

155. Willebrand R, Hamad I, Van Zeebroeck L, Kiss M, Bruderek K, Geuzens A, Swinnen D, Côrte-Real BF, Markó L, Lebegge E, Laoui D, Kemna J, Kammertoens T, Brandau S, Van Ginderachter JA, Kleinewietfeld M. High Salt Inhibits Tumor Growth by Enhancing Anti-tumor Immunity. Front Immunol. 2019;10:1141. doi: 10.3389/fimmu.2019.01141. PMID: 31214164; PMCID: PMC6557976.

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