

# The Central Nervous System's Adaptive Changes Make Chronic Diseases Incurable

5 Jianqing Wu<sup>1</sup>, Ph.D., J.D. and Ping Zha<sup>2</sup>, M.D. (Chi. Med.)

Correspondence: [tempaddr2@atozpatent.com](mailto:tempaddr2@atozpatent.com)

1. End the Incurable Era (Independent researcher for cause), P.O. Box 689, Beltsville, MD 20704. [www.igoosa.com](http://www.igoosa.com).

10 2. Independent Researcher (Not affiliated with any entity), can be reached by using the above address.

**Keyword:** incurable disease, chronic disease, cancer theory, central nervous system, state memory, mutation, tissue ecosystem, emotion, stress, exercise, baseline biochemical and cellular processes.

## ABSTRACT

We examined special roles of the Central Nervous System (CNS) in an attempt to resolve the puzzle that chronic diseases cannot be cured by medicine. By exploring a skill-learning model, we found that the CNS is able to remember certain information reflecting biochemical and cellular (B&C) processes in the body. From the skill using ability, we found that the CNS is able to control basic B&C processes that drive and power the skill. From the ability to adjust forces and force direction of a physical act, we found that the CNS is able to adjust B&C processes that drive the physical act. From this adjustment capability, we further inferred that the CNS must also store information on the baseline B&C processes. As a whole, we found that the CNS can maintain information on baseline B&C processes, up-regulate or down-regulate the processes, and make comparisons in performing its regulatory functions. We found that chronic diseases are the results of deviated baseline B&C processes. Per the proved hypothesis, the CNS maintains deviated baseline B&C processes, and thus protects the body states of fully developed diseases. We then used the three CNS roles to explain that cancer progresses with increasing malignancy, cancer quickly returns after a surgery, cancer cells repopulate after chemotherapy and radiotherapy, cancer develops drug resistance inevitably, immune cells rebound after suppression, generally poor benefits of cancer drugs such as beta-blockers, etc. We further showed that long-term exercises generally push most, if not all, baseline B&C processes in diametrical opposing directions against the diseased B&C processes, implying that exercises play unique roles in reversing chronic diseases. Finally, we proposed several strategical approaches to resetting the CNS' state memory as the essential condition for curing chronic diseases.

## 15 INTRODUCTION

Chronic diseases cannot be cured by medicine, but we personally witnessed life miracles. Even based on isolated cases, we question the notion of incurable diseases. Neuroscience research has resulted in a body of evidence of the roles of the CNS on chronic diseases. To find root reasons for failure to find cures for incurable diseases, we examined the mind-and-body model which was once used in all medical systems in the world.

Fundamental hypothalamic systems control metabolism, circulation and the immune system [Buijs *et al*, 2006]. The functioning of these systems is strongly influenced by factors including sensory autonomic feedback and by circulating hormones. The central and peripheral nervous systems play important roles in controlling liver cytochrome P450 (CYP) [Wójcikowski *et al*, 2011]. The CNS is a mediating factor in the pathogenesis of diseases such as diabetes and hypertension. The hypothalamus at the intersection of the neuroendocrine and autonomic systems regulates glucose and blood pressure homeostasis [Han *et al*, 2016]. Acute and chronic psychological stress can increase the risk of heart attack by increasing circulating levels of platelet-leukocyte aggregates [Brydon *et al*, 2006]. Chronic stress is an emerging risk factor for heart diseases [Sundquist *et al*, 2005; Nemeroff *et al*, 1998]. Stress increases the pro-inflammatory response in caretakers of Alzheimer's patients [Kiecolt-Glaser *et al*, 2003].

A body of evidence has shown that the CNS regulates the immune system and inflammatory process [Wraith *et al*, 2012]. Stress made humans susceptible to infection and negatively affects wound healing by disrupting the production of proinflammatory cytokines [Kiecolt-Glaser *et al*, 1995]. Chronic stress plays a role in cancer proliferation and negatively affects immune system [Segerstrom *et al*, 2004]. Stress management can modify neuroendocrine dysregulation and immunologic functions and thus influence tumor development and progression [McDonald *et al*, 2005]. Stress-induced neuroendocrine activation induced a 30-fold increase in metastasis to distant tissues by  $\beta$ -adrenergic signaling, which increased the infiltration of M2 macrophages into the primary tumor [Sloan *et al*, 2010].

About hundred billion neurons in the brain are connected by the nerve system with fibers in the tissues in every part of the body. Partially based on the relationships between the CNS and diseases, we suspected that the brain regulates the health state of the body, remembers information about the tissues as special state memory, and uses the stored information in up-regulating or down-regulating B&C processes for the body. Those functions would serve as a protective mechanism for maintaining the body's stability but prevent chronic diseases from being reversed. If those CNS roles are confirmed, the failure to consider those roles would make all attempted

cures futile or unpredictable.

## METHODS

60

Subtle interactions between the CNS and the body cannot be studied in a dynamic condition. The state of medical art is limited to detecting neuronal signals at individual neurons such as genetically encoded voltage indicator (1997) and fluorescent labeled neurons (2012). We believe that it would take centuries before the meanings of neuronal signals can be interpreted, and it would take even a longer time before the subtle differences in neuronal signals and their firing and traveling patterns can be linked to chronic diseases.

65

The three CNS' roles we are now trying to prove in this article would directly affect medical landscape. If the CNS actively records disease information and then uses recorded information to maintain disease condition, a cure will not succeed unless effective measures are directed to the CNS. The three roles will affect medical research model, treatment model, personal health management, and achievement of longest personal lives, etc.

70

75

One of the authors started thinking potential CNS roles two decade ago. Despite rapid developments in neuron-science, no direct evidence is still unavailable. However, evidence discovered in the last two decades allows us to prove the three CNS roles indirectly. We will prove them by relying on common knowledge, personal experiences, and established knowledge.

80

Evidence that the CNS regulates B&C processes are systematically reviewed to understand how the CNS regulates basic metabolism, the immune system, hormonal functions, etc.

85

Primary evidence is extracted from a skill leaning model. Every person knows how to learn a skill such as performing a complex physical act such as a triple loop in ice staking. One advantage of this approach is that learning a skill is everyone's experience and thus every person can appreciate implied and derived facts. Such a model vividly reveals how the CNS and the body interact in every increment of time. We found that the skill learning model is the best model we can imagine. Human beings as well as some animals have three abilities: skill learning ability, skill refining ability, and skill reusing ability. From the three abilities, we establish a skill learning model, a skill refining model, and a skill reusing model. By analyzing detailed activities in the CNS and the body for the three models, we identify evidence for the three CNS roles.

90

95

We then apply the three CNS roles to solve several puzzles, conflicts and controversies in cancer research to test whether they reasonably reflect the workings in the human body. While our test is limited to cancer, the

findings can be used to resolve puzzles in other chronic diseases such as obesity, high blood pressure, heart diseases, metabolic syndrome, etc.

100

## RESULTS

### A. The CNS' Memory of B&C Processes

To show how the brain remembers information concerning B&C processes, we will consider how a person learns the skills of performing a physical act.

#### 1. Evidence of the CNS "Memory" of B&C Processes

The skills for performing physical acts can be remembered. After a person has learned swimming or riding a bicycle, such skills are "remembered" as explicit memory. The person can still swim or ride a bicycle many years after disuse of the skills. However, neither "skills" nor "acts" can be stored in the brain. What could be stored are information that would be used in generating neuronal signal firing patterns that control a series of physical acts for the skills.

When a person performs a physical act such as making a triple-loop in ice-skating, the act is driven by a series of neuronal signals which modulate B&C processes. Such a physical act was believed to be driven by motor functions involving both the primary motor cortex and secondary motor cortices.

Motor functions and sensory functions cannot take place without the support of underlying B&C processes. Those functions are driven and powered by relevant B&C processes. Every physical act can be traced to changes in B&C processes in different parts of the body. Each physical act is driven by CNS signals or environment stimuli (as in an involuntary case). In both situations, the CNS sends distinctive neuronal signals (for convenience, we use neuronal to mean neural as well) to relevant parts of the body. Such signals cause different muscles to contract and cause different body parts to collaborate in right forces, directions and timings. In addition, the CNS also regulates heart beat rate, nerve signaling activities, body temperature, organ operating capacities, etc. In performing the act, the CNS must also get from the body feedback neuronal signals to be used as the basis for adjustments. For a physical act, the brain generates a distinctive neuronal signal pattern -- different neuronal signal activities in different parts of brain in different time. Detailed real-time neuronal patterns cannot be acquired due to overwhelming complexity of the subject and limited technologies, but evidence of changed brain neuronal signal patterns can be acquired by using MNI technologies [Kleemeyer *et al*, 2017].

When a person performs a triple loop jump, the CNS sends neuronal signals to cause the legs to generate a large amount of force. When the body

140 is spinning in the air, the CNS's sends signals to different parts and receives feedback signals from different parts in attempt to maintain body balance, to cause the body to do necessary acts to facilitate body's rotation in the air. At of time of landing, the body prepares the feet for absorbing force. The jump involves the firing of neuronal signals which are expected to influence the following functions:

145 (1) Alter B&C processes for different parts of the body in a time-dependent course. For example, at the movement of jumping, a great force is generated in the leg muscles responsible for the jumping.

150 (2) Make different parts of the body to cooperate when the body is spinning in the air. The body maintains proper a shape and position in every time interval.

(3) Improve the body's ability to detect spacial position. The body must jump to a right height, and rotate in a suitable speed so that three loops will be finished at the moment that the body touches the ground.

155 (4) Force the body to make adaptive changes in the structures and functions of the body to support the skill. A long time training program will cause the body to develop strong bones, strong muscles, and strong joints. We infer that such neuronal signals of the CNS can cause the body to slowly alter body structures.

160 (5) A large number of other changes are made to support the skill. In each attempt, the CNS and the body must exchange neuronal and neural signals in round trips.

We show that each of the component act is backed up B&C processes as shown in the table below.

165 Table 1. Physical Activities and Neuronal Signals for Performing A Triple Loop.

Physical Act	Directly Involved B&C Processes	Controlling Signals	Baseline B&C Processes	Comments/References
Jump force.	Sliding filaments in the leg muscles.	Impulse frequency and number of motor units.	Controlled by neuronal signals (action potential and motor units).	Implied.
Body orientation.	Sliding filaments in different parts of muscles.	Same as above.	Same as above.	Common sense.

Body parts collaboration.	Sliding filaments in collaborative parts.	Same as above.	Same as above.	Common sense.
Regulation of metabolism (ATP).	Increase energy production for the whole body by blood circulation system.	Alter the vascular system and involved muscles.	Raise energy production over baseline values in involved parts.	All metabolic processes involving glucose, protein, fats, etc.
Actions caused by ASN.	Make a fight-and-flight like adjustment for the body.	CNS signals, ASN actions, and hormonal actions.	Up- and down-regulation, depending on parts or organs.	A large number of different changes are well known.
Inhibit other CNS' activities.	The requirement of focus will lead to highly inhibited state.	Inhibit neuron activities that are not required for the triple loop.	Down-regulation or push below baseline values.	Common sense, personal experiences, and ancient teachings.
Waste removal.	The normal processes.			Implied.
Physical properties adjustments.	Temperature, pH, mechanical properties, etc.		Changes over baseline values.	Perceivable by anyone.
Adaptive changes in body structures.	Affect capillary density, bone strength, and nerve action efficiency, etc.		Changes over baseline body structures.	It works by long-terms effects.

This table is not intended to show all details. Involved B&C processes include metabolic processes for proteins, glucose, fats, etc. They could include carbohydrate metabolism (glycolysis, Krebs cycle, pentose phosphate pathway, etc.), cellular respiration, amino acid metabolism, nucleotide and protein metabolism, lipid metabolism, cell signaling, vitamin and cofactor metabolism, etc.

The skill-learning model implies that the CNS remembers certain information which is essential for performing a triple loop. The person is able to make incremental adjustments: when a prior act is poorly executed, he will

180 make compensatory measure to make successful landing. This implies that the CNS must get feedback in every incremental time and can change B&C processes in support of the skill. Since the person can reuse the skill, the CNS must be able to use stored information which can control B&C processes in support of the skill.

## **2. Evidence of the CNS' Comparative Mechanism For Controlling B&C Processes**

185 The skill-refining model implies that the CNS can cause the body to adjust the amount of force and force directions by changing B&C processes. In practicing a triple loop jump, the person can learn how to achieve a suitable jump height by keeping jumping while trying to control force amount and force direction. The exact mechanism for making adjustments is not necessary to make this factual finding. If a prior jump fails to reach a required  
190 height, the person can try another jump by using an increased amount of force. This implies that the CNS not only remembers the amount of force and force direction used in the prior jump, but also knows how to change them in a quantitative way. This ability is extraordinary: after a person is presented with three persons photos, the person can identify them. This ability implies  
195 that the CNS is able to make comparisons, which will be referred as the comparative mechanism. The CNS must use its own comparative mechanism in making a comparison.

200 The comparative mechanism is frequently used in every person in applying force. Adjusting force amount and force direction for performing a physical act can be realized only adjusting B&C processes against baseline values. Since each physical act is driven and powered by B&C processes, the CNS must "know" the baseline values of B&C processes. The baseline values may be the speeds of B&C processes, relative rate ratios of different B&C processes, and properties such temperature, pH, mechanical activities, etc.

205 If a person wants to apply about 1 lb more force in a certain direction, the CNS must have an ability to adjust muscle groups, motor unit pool and motor unit (the number of muscle fibers innervated by the neuron), impulse frequencies, etc in a reasonable accuracy so that about 1 lb more force will be generated. The feasibility of this adjustment depends on the CNS ability  
210 to recall muscle groups, motor pool, motor units, control impulse frequencies, etc. in prior jumps. This ability is like human ability to recall a brief visual impression of an object many days after seeing it. If the CNS could not recall any such prior information, the person may apply far too much force or too little force. Without this comparison mechanism, human acts would be  
215 erratic and unpredictable. All they can do is nothing but routine accidents.

Human ability to improve accuracy of physical acts is reflected in how a person can improve accuracy of throwing a dart on a target. The first a few throwing attempts by a newcomer may miss the target by large margins.

220 However, if the person keeps practicing it, he can improve throwing accuracy slowly and consistently. Such progressive improvements also imply that the CNS has a comparative mechanism to adjust force amount and force direction. We infer that improvements can be achieved ultimately by adjusting B&C processes against baseline B&C processes.

225 Quantitative adjustments of force and force direction can be explained by the sliding filament theory [Lumen]. The force generating unit of muscles comprises actin and myosin chains, which can slide past one another. Ignoring details, energy for the release and movement of the myosin head along the actin filament comes from ATP, which is produced in metabolic processes. The force generated is proportional to motor pool size, motor units, 230 frequencies of the impulse signals, etc. To increase force, the CNS may get more motor units, raise frequencies of the impulse signals, or do both. The relationship between the frequency of the impulse signals and the contributory force of a single motor unit must be predictable so that the CNS can adjust the amount of force. While the number of motor units and the frequencies of the impulse signals directly affect force, muscle contraction 235 force must be ultimately limited by energy availability.

Baseline B&C processes in the human body are like operational baselines in machines such as car idle engine speed, a scale's tare reading, spectroscopic baseline signals, etc. Similar things must exist in the human body 240 except that they are ultimately defined by baseline B&C processes. Their existence does not depend on the correctness of the sliding filament theory or other theories used to explain the force-controlling mechanism.

In performing a triple loop jump, actual B&C processes must be altered according to required force and energy. In preparing for the jump, the 245 body takes a lower position which can help generate more force. In making the jump, the body generates great force. In both the preparation moment and jumping moment, different muscles run B&C processes at suitable levels. The CNS signals can cause the body to make qualitative adjustments of states. In performing each of the incremental steps, the CNS selects different 250 muscle groups, uses different motor units, and apply different impulse frequencies to achieve right amount of forced in right force directions. In each case, the CNS must know and use the baseline B&C values.

Neuronal signals that drive a physical act, if viewed on a time course, may comprise component neuronal signals, transmitting from different parts 255 of the brain through different channels to nerve fibers or motor units in different parts of the body in different time increments. Muscle contraction is not the only activity for performing the act. The neuronal signals must include other components for up- and down-regulating various B&C processes in different parts or organs. In addition, the physical act may be accompanied 260 by corresponding changes which may be triggered, for example, by the autonomic nervous system.



A comparative mechanism is also implicated in perceiving sensory properties such as temperature, structures, smells, vibrations, textures, colors, etc. under various conditions. It is also used in perceiving complex things such as a room's comfortable levels, element patterns in an image, moving trajectories of multiple objects, light flash patterns (as in Christmas trees), etc. The information to be compared must involve the use of B&C processes.

### 3. Evidence of the CNS' Regulation of Body State

When the person reuses the skill of performing a triple loop, the person causes the CNS to replay the neuronal signal firing pattern for the skill. The neuronal signals cause the body to up- and down-regulate B&C processes for different parts of the body in a time-dependent manner. The neuronal signals reflect certain information that is once stored as state memory. This memory is similar to implicit memory in psychology, but our focus is not on information that is studied in psychology. What we are interested is the portion of information that is directly responsible for controlling B&C processes or organ functions, physical properties, body structures, etc. For this reason, we refer it as state memory despite its similarity to implicit memory. State memory is stored information, which, upon being called to run in the brain, can generate the same neuronal signals pattern that drives the B&C processes in support of the skill.

In using the skill, the up- and down-regulation of B&C processes cannot be realized without "using" correspondent baseline B&C values. For example, when the body is in a preparation stage, the legs bear little force; to make the body to jump to certain height in a right direction, the CNS signals must cause the body to increase force by a right amount and use different muscles. We infer that the CNS has a mechanism to determine how to change the B&C processes for each increment of time in performing the act. If we focus at the B&C processes, all the CNS does is to change relative speeds of various involved B&C processes in different times.

When a person performs different physical acts, the CNS sends different neuronal signal patterns. While swimming, riding a bicycle, performing a triple loop, and doing anything look different, they are driven by using the same B&C processes. The only differences are the relative speeds of different B&C processes in different parts of the body in different times.

Implied by the derived facts, what is actually remembered is information carried in the neuronal signal patterns, which, after traveling to multiple target tissues, are able to alter B&C processes that drive the physical acts. Stored information is retrieved from the brain to be used to regenerate the same neuronal signal patterns that drive the same acts. In order to conduct up- or down-regulation of the B&C processes, the CNS must use respective baseline B&C values in the relevant part of the body in every increment

of time.

305 At the level of muscle contraction, adjustments to force and contrac-  
 tion velocity are in part based on muscle tone. Muscle tone is the state that  
 muscles are in partial contraction, which is important for generating re-  
 flexes, maintaining posture and balance, and controlling other function of or-  
 310 gans such as the heart. Muscle tone is controlled by the sensory muscle spin-  
 dle, which measures muscle stretch. At this level, the CNS must be able to  
 track such tone as well as any incremental state of muscle contraction. Each  
 of incremental contraction is ultimately driven by relevant B&C processes.  
 What the CNS can alter are the speeds of relevant B&C processes in differ-  
 ent parts of muscles, tissues, and organs in different time increments. Com-  
 315 parisons are used in the learning processes and the refining processes.

The state memory is not limited to learning skills. It is also reflected in  
 forming habits, personalities, likeness, durable looks, etc. We will attribute  
 this kind of memory to chronic diseases state, tendency of disease relapse,  
 and increased cancer malignancy.

320 The CNS can cause body structures to make adaptive changes.  
 Marathon runners can develop strong legs; martial artists may develop  
 unique strong parts, depending on the arts they practice; bicycle riders de-  
 velop leg features suitable for doing large circular motions; and people who  
 carry loads regularly on shoulders can build stronger shoulders. Exercise  
 325 may increase muscle fiber number in each motor unit and help the body to  
 develop large motor pools. The CNS neuronal signals can influence body  
 structures by long-term effects.

Neuronal signals must be the kind that can influence B&C processes  
 that are fully supported in genes. Available B&C processes that the CNS can  
 330 regulate must exist or could exist in the body. However, neuronal signals  
 may directly or indirectly affect gene expression signatures which thus affect  
 the speeds of one or more B&C processes.

### **B. Chronic Diseases Are Caused by Deviated Baseline B&C Processes**

335 We now extend CNS state memory, CNS regulatory function with com-  
 parative mechanisms established on the skill model to chronic diseases.  
 While the skills of performing a physical act appears to be very different  
 from chronic diseases, they share common B&C processes. We will show  
 chronic diseases are results of deviated B&C processes.

340 Chronic diseases are developed by years to decades. One definition  
 best reflecting the development time is provided in Booth *et. al.* [2012]. The  
 long development time implies that the body slowly loses its functional ca-  
 pacity for maintaining life. Functional capacity ultimately comprises a large  
 number of B&C processes. What is much detrimental are lost imbalances.  
 Functional imbalances include biochemical process imbalance such as more  
 345 calories being stored than used; structural imbalance may be outgrow tis-

sues and bones in permitted spaces or lost tissues; material demand imbalance, for example, occurs when oxygen provided is insufficient for sustaining threshold metabolism; and physical property imbalances include deviated body temperature, deviated blood pH, and altered mechanical properties (e.g., increased blood viscosity). A long development time of chronic disease implies that observed structural changes are very small in given times.

We will show exercises, chronic diseases, and cancer can constantly interact with each other through their shared baseline B&C processes. Diseases cannot create a new B&C process that does not exist in the genes of the mankind. “No cancer exhibits any trait which cannot be found in some normal tissue as the expression of normal genomic activity.” [Prehn 2014]. The most the CNS could do is to alter gene expression signatures which affect some aspects of relevant B&C processes. Most, if not all, chronic diseases are manifested as structural changes. Structural changes in body parts or organs can be caused only by altered, abnormal or imbalanced B&C processes. The long development time implies that small deviations in the B&C processes can cause chronic diseases by their long-term effects.

Chronic disease development, cancer development and long term exercises like performing a triple loop all influence shared baseline B&C processes. Their common effects are shown in below table.

Table 2. B&C Processes For a Triple loop-induced State, Chronic Diseases and Cancer.

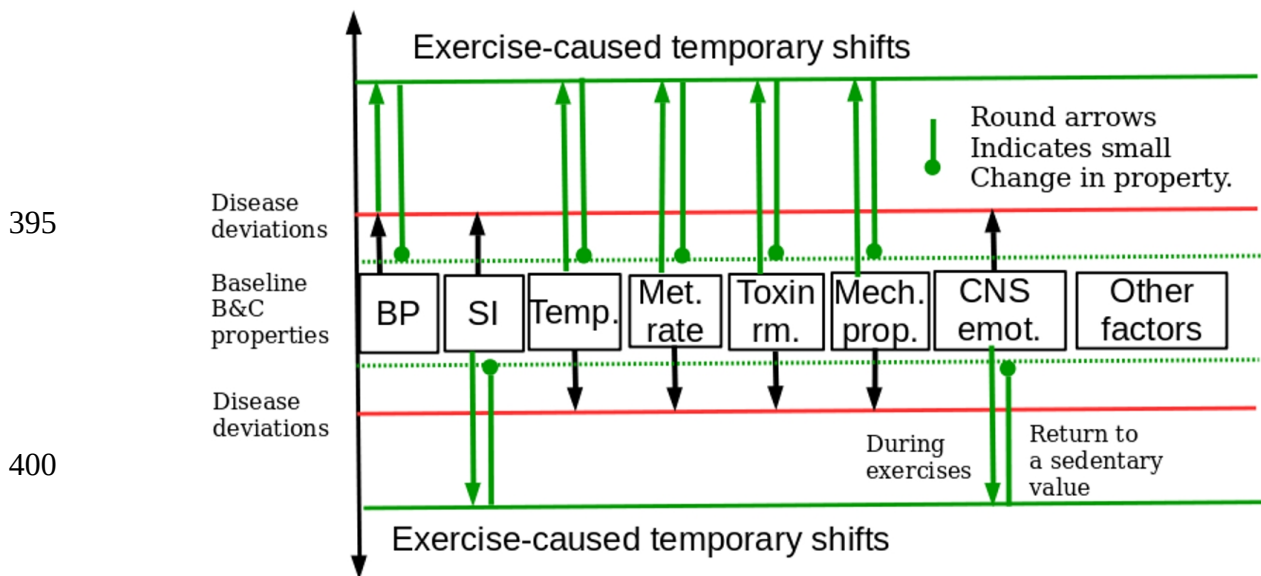
Events (Skill or Diseases)	Basic B&C processes	Changes in B&C Caused by Event	Most Important Changes Caused by Event	Duration of Changed B&C Processes
Triple Loop.	All known B&C processes.	Changes caused by event appear as deviations from baseline values.	Energy metabolism, nerve functions, and vascular system.	Temporary or as peaks, but subside slowly.
Chronic Disease.	All known B&C processes.	Changes are merged into the baseline values as new baselines.	All potential epigenetic changes, depending on diseases.	Permanent (as baseline B&C processes values).
Cancer.	All known B&C processes.	Changes are merged into the baseline as new baselines.	Gene expression signatures; angiogenesis; neurogenesis,	Permanent (as baseline B&C processes values).

			growth levels, apoptosis, etc.	
--	--	--	-----------------------------------	--

Since a chronic disease exists on a 24-hour basis, deviations of baseline B&C processes are merged into baseline values. If a person's blood vessels are plagued slowly, blood pressure at the rest condition will go up slowly but further higher blood pressure appears when the person does exercises. Similarly, if a person's liver, kidney, or lung function is diminished, the state would exist on a 24-hour basis.

Shown in Figure 1, changes in state caused by exercise, disease development, and cancer development are relative to similar baseline B&C processes. Since B&C processes cannot be characterized easily, we will use as measures health properties that directly reflect B&C processes. The properties shown in the figure include blood pressure, systemic inflammation, tissue temperature, absolute metabolic level, toxic removal rate, mechanical properties, CNS emotional responses, etc. Each of the health properties reflects relevant B&C processes. As indicated by the black arrows, a chronic disease alters baseline B&C processes slowly, causes some properties such as blood pressure, systemic inflammation level, CNS emotional responses to shift upwardly, but cause other properties such as tissue temperature, mechanical activity level etc. to shift downwardly. The red lines were where the affected B&C would be. Figure 1 shows only some health properties that are common in chronic diseases, but any of a large number of other health properties might be involved. Moreover, an identical health property may behavior differently, depending on tissues or organs.

390



395

400

405 **Figure 1 Changes in B&C processes caused by diseases, cancer and exercise are relative to shared baseline values.**

As shown in Figure 1, exercises have both instantaneous effects and long-term effects. Exercises raise blood pressure temporally, but removed fats allow blood pressure to go down slowly. Long term exercises slowly reduce systemic inflammation level. Exercises can raise body temperature slightly within the normal temperature ranges, increase the tissue's mechanical vibrations, and improve the body ability to remove toxins. Exercises temporarily inhibit emotional hormonal activities. Exercises are expected to cause the Autonomic Nervous System (ANS) to take a number of well known coherent actions. As shown by two dashed green lines in Figure 1, exercises can slowly correct deviations in baseline B&C processes by long-term effects.

We have shown that human beings must maintain the stability of baseline B&C processes. Changes caused physical acts and deviations caused by diseases cannot have any meaning if they are not referenced to respective baseline values. The execution of every physical act depends on the CNS ability to know baseline B&C processes. Similarly, influence triggered by emotional factor depends on the CNS ability to know baseline B&C processes. The ability to maintain baseline B&C processes is essential for maintaining the stability of personal looks, size, health condition, physical strength, personalities, etc.

Based on the above derived facts, we found that the CNS stores as a special state memory, information on deviated B&C processes, and the CNS attempts to maintain deviated B&C processes. We therefore inferred that the CNS is responsible for maintaining the disease state.

### **C. Additional Evidence of the CNS' Memory of Baseline B&C Processes**

State memory of the CNS is reflected in how the body keeps same looks, same habits, same homeostatic properties, same likeness in tastes and smells, same circadian cycles, same personalities, etc. None of those things can be directly stored in the brain as memory. What can be stored is information that can control B&C processes. Each of those properties are related to B&C processes: looks reflect facial structure which is a result of B&C processes; habits are physical acts that are driven by B&C processes controlled by CNS neuronal signals; likeness in tastes and smells are controlled by B&C processes in sensory functions; circadian cycles are controlled by B&C processes; and personality is a reflection of thinking processes that are driven by B&C processes.

State properties are maintained by using information that controls the characteristics of B&C processes. Such information, upon running, generate neuronal signals that control the relative speeds of B&C processes and inter-

actions of different B&C processes in different parts of the body in different times. If any B&C process that affects any healthy property is changed, related health property will change accordingly. The state memory of the CNS is an essential component for maintaining the stability of the body's structures and functions.

Another piece of evidence of state information is the fact that a person can still feel pain of a diseased limb even after the limb has been amputated. This fact demonstrates that the pain is a replay of stored state information reflecting the amputated limb but not just a result of a stimulation of diseased limb.

Figure 1 indicates that exercises can correct deviated B&C processes in a way no medicines can.

#### **D. The CNS' Conflicting Dual Roles In Cancer Progression**

Cancer becomes a puzzle for more than a century. Although cancer progression may occur through clonal evolution (Nowell, 1976), potentially the full malignant potential of a cancer is present at the time of cancer cell transformation [Bernards *et al*, 2002]. Cancer point-mutation rates are comparable to normal cells, progression from a large adenoma to cancer require about 17 years, and generally the same mutations are present in primary tumors and their metastases [Wang *et al*, 2002; Wood *et al*, 2007; Jones *et al*, 2008]. Increasing malignancy in cancers cannot be explained by clonal selection of mutations in most cases. Cancer can occur without mutations or mutations may be product of cancer. Revolving around this progression puzzle are a large number of phenomena such as cancer cell repopulation, increased cancer proliferation speeds, shorten time for cancer returning, and increased drug resistance, etc., all of which are responsible for cancer's hazard.

We will consider the CNS' state memory and regulatory roles in attempt to explain increasing malignancy. We show that the CNS is a dual-edged sword. It first does whatever it could to prevent or stop cancer proliferation, and, in a later phase, does whatever it could to promote cancer growth. Cancer develops from struggles to triumphs.

##### **1. Cancer's Early Struggles For Survival**

Assuming that a set of mutated cells  $C_1, C_2, \dots, C_j$  formed in a tissue or an organ in different times from age one to age 40 (See Figure 2), each of the mutated cells has a potential to become a cancer but none can gain momentum of proliferation. Some cancer cells become extinct; but others stay in dormancy for long times.

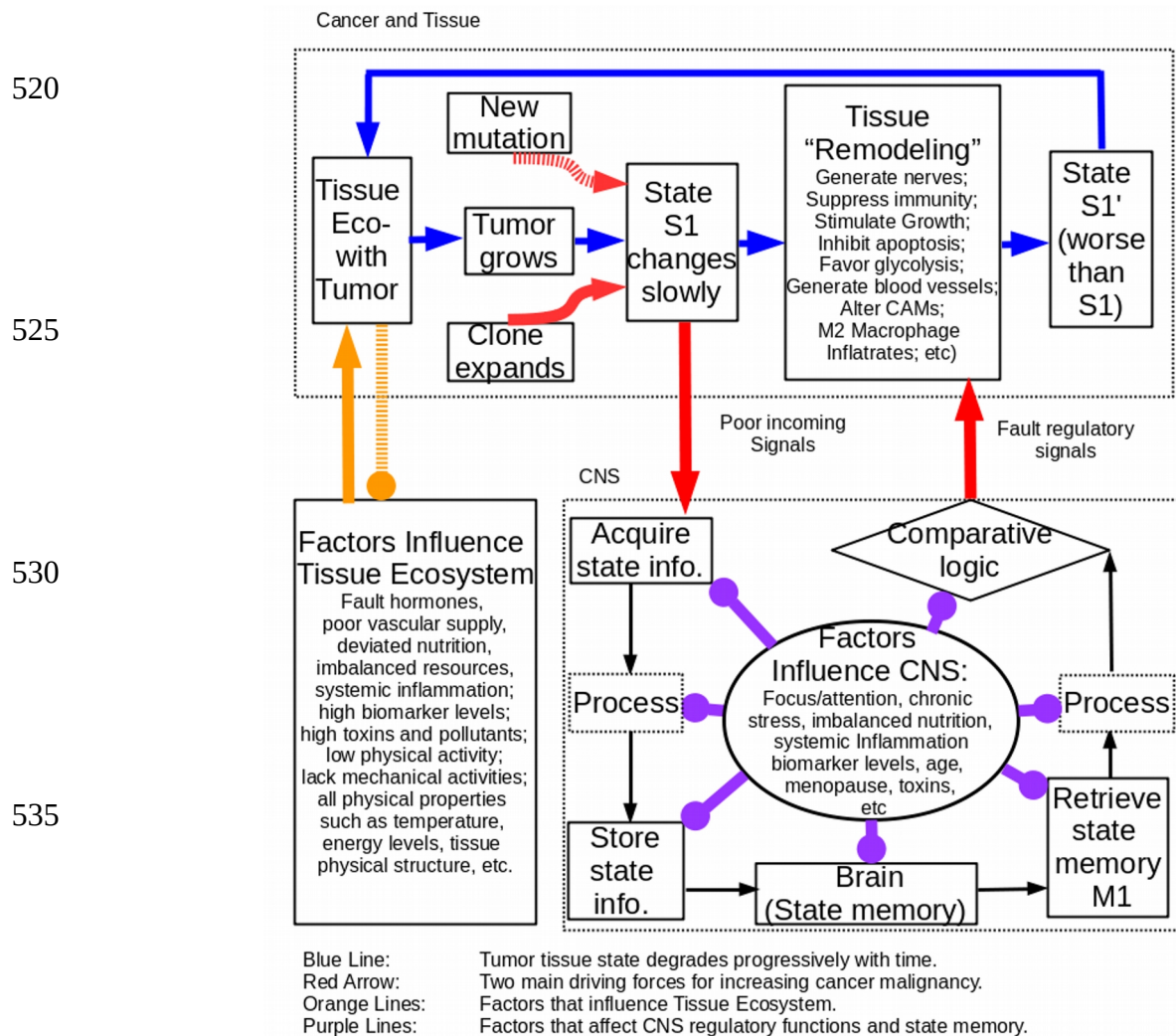
In the early stage, the cancer does not have dominant influences in the tissue, and the CNS regulates the tissue with an attempt to reject or inhibit clonal expansion. A cancer initiation factor is fault tissue ecosystem, which reflects a big mismatch between the living environment of human beings and

490 that human genes are adapted to [Hochberg & Noble, 2017]. As shown in  
Figure 2, the tissue ecosystem further degrades as a result of strikes of  
chronic stress, systemic inflammation, infection, trauma, foreign objects, etc.  
Existing mutations and degraded tissue ecosystem slowly favor cancer initia-  
tion and proliferation.

495 The state information is sent to the CNS'. The CNS state memory is  
stored on re-writable media like computer memory, stored information is  
slowly altered with increasing tumor size and degrading tissue ecosystem.  
The CNS becomes weaker and weaker with age advancing; emotional  
strikes, chronic stress, chronic inflammation, etc. slowly weaken the CNS's  
500 CNS control include hormonal disorders, menopause, aging, imbalanced nu-  
trition, changes of lifestyles, etc. Those factors help cancer cells to gain pro-  
gression momentum. A cancer cell with mutations accumulated at young  
ages may increase its growth speed at a late age.

505 After the cancer has reached a sufficiently large number of clones, de-  
stroying the tumor would be too dangerous for the host body. The CNS will  
change its role from rejecting and inhibiting cancer cells to accepting and  
protecting cancer cells. This is done by using the comparative mechanism  
shown inside the CNS block in Figure 2. Only the CNS has an inhere ability  
510 to make such a determination. By altering neuronal signals (e.g., the red ar-  
row), the CNS instructs the immune system to protect the tumor, and at-  
tempts to remodel the tumor tissue.

515



**Figure 2 Clonal expansion in a primary site, with help of the CNS, promotes cancer growth and increases cancer malignancy.**

## 545 2. The CNS Builds Nervous Networks for Controlling Cancer

550 Due to chaotic inner structures, or diminished CNS regulatory capacity, the cancer maintains diminished B&C processes. The inner tissue of the tumor lacks normal nerve networks [Willis *et al*, 1973]. It is predicted that what the CNS detects is an unhealed wound with growth deficiency. To fix the problem, the CNS must find a way to communicate with the tumor before it can instruct the tissue to remodel itself. The CNS' control of cancer depends on nerve fibers inside the tumor even when the cancer proliferates. Cancer and the nervous system can communicate [Khasraw *et al*, 2010;



555 Toothaker *et al*, 2009; Mravec *et al*, 2008]. When cancer spreads, immune functions, inflammation, organic micro-environments and bone marrow are involved [de Visser *et al*, 2006; DeNardo *et al*, 2008; Wu *et al*, 2009; Solinas *et al*, 2010; Nguyen *et al*, 2009; Sung *et al*, 2007; Calorini *et al*, 2010].

560 Due to chaotic structural organization inside the tumor, communication between the tumor and the CNS is expected to become worse and worse with the tumor growing. The CNS thus must attempt to regulate tumor inner tissue. One required condition is that the CNS needs nerve supports inside tumors. The connections between the CNS and cancer through synapse, non-synapse or humoral modulation make it possible to establish reciprocal interactions and communications between cancers and the CNS. Neuro-neoplastic synapses exist between nerve fibers and tumor cells [Palm *et al*, 2007, Zanker *et al*, 2007], and that neurogenesis, like angiogenesis, is also a trait of cancer cells [Albo *et al*, 2011; Palm *et al*, 2007; Varner *et al*, 2007; Ayala *et al*, 2008]. In primary and pre-metastatic sites, cancer cells can actively establish connections with nerve fibers and receive signals from the CNS. Even 570 bone marrow can be innervated by the nervous system, including the ANS and noradrenergic sympathetic nerve fibers [Miyani *et al*, 1998; Canaani *et al*, 2011; Benestad *et al*, 1998; Artico *et al*, 2002, Imai *et al*, 1997].

575 The CNS can communicate with the immune system by bidirectional neural-immune interactions. Their interactions mainly take place through the neuronal and immune signal molecules including hormones, neurotransmitters, neuropeptides, cytokines or their receptors, all of which have been demonstrated to contribute to the process of metastasis [Grivennikov *et al*, 2010; Lin *et al*, 2007; Karin *et al*, 2005].

### 3. The CNS Cripples Anti-Tumor Immunity

580 Cancers have aptly been described as “wounds that do not heal” to indicate the similarities of their microenvironments [Dvorak, 1986 and 2015]. Macrophages can exist in a spectrum of species from M1 type to M2 type [Xue *et al*, 2014]. They play different roles in wound healing. M2 macrophages, which are present later in the healing process, antagonize the 585 inflammatory response and allow initiation of healing. The M2-like macrophages produce anti-inflammatory cytokines, suppress anti-tumor immunity, and promote angiogenesis and matrix remodelling, which favors tumor progression and metastasis [Huang and Feng, 2013; Aras *et al*, 2017].

590 By relying on the shaky nerve network, the CNS regulates antitumor immunity by controlling Tumor Associated Macrophages (TAMs) (See “Tissue Remodeling” in Figure 2). Possible changes include those that are summarized in Noy and Pollard [2014], as follows:

595 (1) TAMs express effector molecules including cell surface receptors, cytokines, chemokines and enzymes and thus inhibit immune responses by interaction of TAMs receptors ligands with their counterpart death/inhibitory

receptors expressed by the target immune effector cells.

(2) TAMs also express the ligand receptors for PD-1 and CTLA-4 that upon activation suppress cytotoxic functions of T-cell, NKT cells and NK cells.

600 (3) TAMs also express the ligand for the death receptors FAS and TRAIL that triggers in target cells caspase dependent cell death (apoptosis).

(4) TAMs also express the non-classical HLA-G that inhibits T cell function through interaction with the co-stimulatory signal of T cells ILT2, and HLA-E that inhibit NK cells through CD94 (also known as NKG2).

605 (5) TAMs secrete the cytokines IL-10 and TGF $\beta$  that inhibit T cells effector functions and induce regulatory functions, and chemokines CCL5, CCL20, CCL22 that recruit nTreg cells.

(6) TAMs secrete Arginase I that inhibit TCR  $\zeta$  chain re-expression in activated T cells by the depletion of L-arginine.

#### 610 **4. The CNS Orchestrates Tissue Remodeling Activities**

To cure the “unhealed wound” as part of the tissue remodeling effort, the CNS takes concerted and coherent regulatory actions. The CNS cannot send neuronal signals both to protect the cancer cells on one hand, and destroy them on the other hand. The regulatory coherency of the CNS is a nature acquired in evolution. The CNS not just cripples the immune system, but also causes macrophages to switch from M1-like types to M2-like types, and uses them as arms to remodel tissues and resolve inflammation.

The inner region of the tumor is expected to have inferior nerve fiber networks than those in normal tissues. What the CNS detects is a tissue having diminished metabolic levels and diminished growth potential. To the CNS, cancer is an “unhealed wound.” Thus, what the CNS naturally does is to remodel the tissue: it causes the cancer-residing tissue to raise growth signals to encourage inner cells to grow, make cancer tissue insensitive to anti-growth signals, reduce cancer cell death speeds by disabling cell apoptosis, build more blood vessels to improve blood circulation, and lift cell replication number limit to allow more or unlimited cell divisions, etc. All of those actions will promote cancer growth. Those are well known B&C processes in cancer biology [Hanahan & Weinberg, 2000].

630 Other cellular processes regulated by the CNS range from general cell metabolism and to cell specific processes, such as differentiation, morphology, motility, secretion, neurotransmission, and gene transcription. As a part of remodeling effort, the CNS instructs the tissue to repress transcription of cell-to-cell adhesive molecules (CAMs), proteolyze the extracellular cadherin domain, switch expression of N-CAM from a highly adhesive isoform to poorly adhesive form, and changes expression of integrin subtypes.

635 The remodeling effort will reach other parts of the body. The CNS may

recognize tissues by secreted chemicals and expressed proteases. The CNS may use cancer secreted chemicals including cancer biomarkers as identification of cancer cells. If such chemicals are found in a secondary tissue, the  
 640 CNS treats the cancer cells as remodeling subject. The CNS protects any tissue that is permeated by such biomarkers. The host person eventually loses immunity against the cancer, and the cancer can grow with little restrictions.

In the primary tumor, cancer cells crowd in a space with physical constraints with unfavorable nutritional competition. Thus, it is more favorable  
 645 to move cancer cells to new locations. The most widely observed changes are impaired cell-to-cell adhesive molecules and the docking of active proteases on the cell surface which can facilitate invasion by cancer cells into nearby tissues. The docking of active proteases on the cell surface can facilitate invasion by cancer cells into nearby stroma, across blood vessel walls,  
 650 and through normal epithelial cell layers.

The cancer changes its state from S1 to S1' in Figure 2. The cycle shown in blue arrows can keep going on daily basis. Progressive changes in the CNS's state information is written as the CNS state memory. The state memory changes from the type with an effect of rejecting cancer cells to that  
 655 with an effect of protecting cancer cells. What the CNS achieves is increasing cancer growth speed, helping cancer cells survive, and promoting cancer metastasis. The remodeling efforts result in maximum cancer malignancy.

## 5. CNS Roles Revealed in Gut-Brain Axis

One example of CNS roles is the gut brain axis. The gut is bidirectionally  
 660 connected with the nervous system through the so-called "gut-brain axis" (GBA), which includes the central nervous system (CNS), the autonomic nervous system (ANS), the enteric nervous system (ENS), the hypothalamic pituitary adrenal (HPA) axis and the entero-endocrine system (EES). Hormones and neuro-hormones secreted at each of these listed GBA  
 665 levels may modulate the gastro-intestinal digestive and metabolic activities, and vice-versa [Carabotti et al. 2015]. One can infer that neuronal signals can interfere with gastro-intestinal digestive and metabolic activities and thus affect the tissue ecosystem where the tumor may reside. (Many known mechanisms are known).

## 670 6. The CNS "Learns" Skills For Promoting Cancer Growth

The CNS regulatory capabilities were acquired in evolution, and thus are built in human genes. The CNS starts using regulatory capabilities since the birth. The CNS learns regulatory capabilities whenever there is a first  
 675 need. For an adult person, most of regulatory capacities might have been used. After the CNS uses an acquired or modified regulatory capability for any tissue, the CNS masters it and can use it in other tissues. Changes caused by CNS regulatory actions are up- and down-shifts in regulated B&C processes. The CNS may alter B&C processes by influencing gene expres-

sion signatures.

680 The diversity of regulatory capacities determines how cancer can differ  
and change, how different cancers behave in the body, and how cancers  
evade drug actions, how cancer cells repopulate after they are removed, etc.  
The cancer's apparent intelligence in response to treatments actually re-  
685 flects the intelligence of the human brain. That is why cancer is hard to de-  
feat.

We believe that the CNS's adaptive changes play even a bigger role  
than clonal selection and tissue ecosystem alternations. We could view each  
cancer as a masterpiece of the CNS. It is the best way to explain the  
Bernards' cancer progression puzzle. Any attempt to fix one of a large num-  
690 ber of immune system properties or one single health property will invite  
counteracting responsive actions of the CNS. That is why single or a few  
drugs cannot cure cancer, and nor chronic diseases.

### **E. The CNS Promotes Future Cancer By Using Acquired Skills**

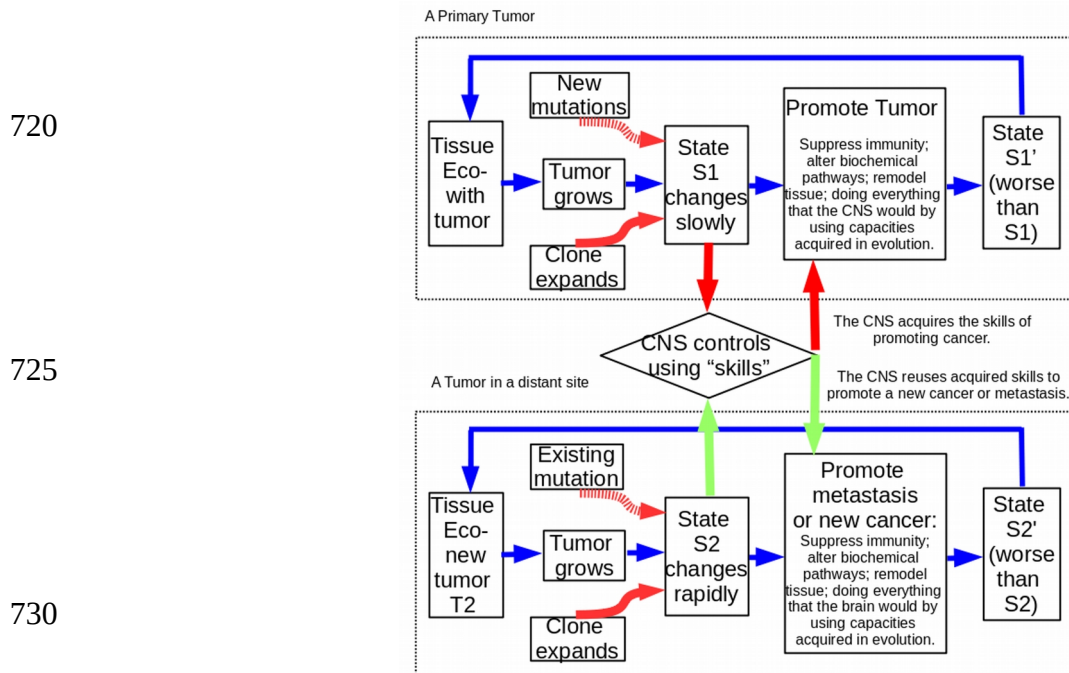
695 We will show how the primary tumor influences cancer metastasis  
through acquired "skills." As shown in Figure 3, the CNS can use its ac-  
quired skills to make another masterpiece cancer at a new site or distant tis-  
sues.

#### **1. The CNS Uses Acquired "Skills" to Promote Future Cancer**

700 As long as the CNS has learned to protect and promote the primary  
cancer, it can teach the body to promote a new cancer's growth at faster  
speeds. This is like reusing a skill that a person previously acquired. Com-  
pared with normal neuronal signals, cancer-promoting neuronal signal pat-  
terns reflect a large number of alterations which have an effect to up- and  
down-regulate B&C processes in different parts of the body. In addition, the  
705 CNS may alter gene expression signatures for oncogenes and tumor-sup-  
pressing genes, and expressions of genes affecting neurogenesis, angiogene-  
sis, cancer cell growth, etc. Even after the primary tumor has been removed,  
the cancer-promoting neuronal signals remain in the state memory.

710

715



**Figure 3 The CNS promotes metastasis and future cancer by sharing acquired “skills”.**

735 The CNS uses the acquired “skills” to promote cancer growth. For example, raised inflammation levels for the body will cause the CNS to attenuate immune response including switching macrophages from M1-like to M2-like types. Figure 3 shows that the CNS can use the same skills from the primary tumor to a metastasis site. The CNS would orchestrate bone marrows to produce more monocytes for generating M2-like macrophages in an attempt to repair the tumor tissue in the distant site T2. The large number of M2-like macrophages will protect cancer cells at the distant tissue T2. The M2-macrophages will cripple immune responses against the metastasis cancer. The CNS will do everything to promote the metastasis as it did to promote the primary tumor.

740 Like learning any skills, the CNS memory and skills will improve with time because its state memory can be reinforced and the reuse of the CNS skill also improves the CNS’s ability to promote the deviated B&C processes in support of malignancy. By using acquired skills, the CNS causes the body to conduct all remodeling activities to create another masterpiece cancer at much shorter time. The CNS adaptive changes are responsible for increasing malignancy. Time windows for the first, the second, the third and the fourth cancer may look like 10 to 50 years, 3 years, 1 year, and 6 months. Cancer may erupt in a single place in the first time, two or more places in the second time, and multiple places in the third time.

## F. Evidence Supporting the CNS' Roles

We will apply the CNS roles to interpret conflicting or controversial phenomena such as repopulation of cancer after cancer treatments, increasing cancer malignancy, aging-related cancer occurrence pattern, adverse impacts of chronic stress, and adverse impacts of systemic inflammation on cancer outcomes, etc.

### (1) New Evidence on Exercise's Benefits

We showed that exercise and cancer share same B&C processes. Exercise can influence CNS signal exchange efficiency which play a crucial role in controlling cancer growth.

Engaging in exercise following the diagnosis of cancer has a great protective effect against cancer-specific mortality, cancer recurrence, and all-cause mortality, based on the 11 meta-analyses [Cormie *et al*, 2017]. Specifically, superior levels of exercise following a cancer diagnosis were associated with a 28%–44% reduced risk of cancer-specific mortality, a 21%–35% lower risk of cancer recurrence, and a 25%–48% decreased risk of all-cause mortality. Such great benefits can be explained by exercise's roles of influencing B&C processes through the CNS as shown in Figure 1. Exercises can slowly reduce the deviated B&C processes to ones that do not support cancer proliferation.

### (2) Systemic Inflammation

It is well known that systemic inflammation promotes cancer growth (Krall *et al*, 2018) by a tumor-extrinsic mechanism. In surgical wounded mice, inflammatory monocytes, the precursors of TAMs, are mobilized systemically in response to surgical wounding, increase their availability for recruitment into tumors. The authors suggested that TAMs may promote tumor outgrowth by countering T cell-mediated growth restriction. They found that PD-L1 expressed by the large number of TAMs deactivated cytotoxic T cells and thus promoted tumor growth.

The destiny of the inflammatory monocytes can be explained in light of Figure 3. Before surgical wound was inflicted, the CNS of the mouse acquired state information on its systemic inflammation. The severe systemic inflammation caused by the surgical wound caused a big difference between current inflammatory state and the non-inflammation state reflected in the CNS memory. Therefore, the CNS attempts to reduce inflammatory level by altering macrophages species or deactivating M1-like species. So, immune suppression is an expected action of the CNS in response to the wound.

### (3) Cancer Develops Resistance to Cancer Drugs

Cancer drug resistance is influenced by drug inactivation, drug target alteration, drug efflux, DNA damage repair, cell death inhibition, EMT, inherent cell heterogeneity, epigenetic effects, or any combination of these mech-

anisms [Housman *et al*, 2014].

800 After a drug is used for some time, cancer cells population will decline as a result of drug action. Mitigating or eliminating drug effects is an inherent ability of living organisms to defeat poison and such ability was developed in evolution. The CNS must do everything it can to resist changes in state. If the body is unable to reach a pivotal point of both reducing cancer cells and resetting the CNS state memory, the CNS will do as much as it could to help cancer cells to survive by promoting drug-resisting mechanisms. Since some cancer cells have been killed, the CNS attempts to restore lost cancer cells and thus encourages cancer repopulate. Compared with cell mutant selection, the CNS may play a much bigger role in the development of drug resistance.

#### (4) The Role of Chronic Stress In Promoting Cancer

810 Sloan *et al* [2010] used a mouse model to study stress effects and found that chronic stress increased a metastasis of primary breast tumor cells to distant tissues by 38-fold versus controls as indicated by luciferase signal. Stress increased metastasis in clinically relevant tissues, with a 37-fold increase in the lung and a 67% increase in the lymph nodes. It was further found that stress-induced recruitment of immune cells was specific to macrophages. These effects were mediated by  $\beta$ -adrenergic signaling, which increased the infiltration of CD11b + F4/80 + macrophages into the primary tumor and thereby induced a prometastatic gene expression signature accompanied by indications of M2 macrophage differentiation.

820 Chronic stress triggers changes in brain structure, including differences in the volume of gray matter versus white matter, as well as the size and connectivity of the amygdala. Such changes may impair CNS capacity for storing state memory. When the CNS is overloaded by activities caused by chronic stress, the CNS' function of regulating the body's state is interfered. In addition,  $\beta$ -adrenergic pathway on stromal cells is used in promoting cancer survival, growth and metastasis.

830 The CNS roles explain how chronic stress affects cancer outcomes. Chronic stress interferes with the CNS roles by overloading signal transmission along hypothalamus and emotion-sensitive regions and thus interfere with the comparison mechanism. In an attempt to repair the "unhealed wound," the CNS suppresses the immune system, up-regulate  $\beta$ -adrenergic signaling path, orchestrates bone marrows to generate more monocytes to be recruited into the primary site and other distant sites, causes macrophages to switch from M1-like types to M2-like types in both the primary and metastatic sites, and differentiate the monocytes into M2-like macrophages. The system-wise changes thus result in immunosuppression and promote cancer proliferation.

#### (5) Tumor Cell Repopulation After Radiotherapy

840 Tumor cells repopulation plays a major role in the response of tumors to radiotherapy or chemotherapy. Although overall tumor response rates associated with paclitaxel and platinum range from 70% to 80%, 50%–75% of individuals relapse within 18 months after completing a first-line therapy [Salani *et al*, 2011].

845 The mechanism of tumor cell repopulation was unknown, and repopulation cannot be simply caused by the greater availability of oxygen and nutrients resulting from the reduction in tumor mass. After a large number of cancer cells have been destroyed, the CNS attempts to restore the existing state by sending the same regulatory signals to the tissue where the cancer once situates. The CNS will promote the B&C processes in favor of restoring the prior cancer-promoting state. It will try to restore old metabolic pathways, old structural features, old signals-exchanging patterns, and old immune responsive levels. A sharp rise of cancer cells is natural and proper response of the CNS, which is driven by state memory.

### **(6) Cancer Cell Repopulation After Induction Chemotherapy**

855 For patients with stage III non-small cell lung cancer treated with induction chemotherapy, delayed initiation of subsequent radiotherapy (RT) may allow for repopulation in the interval between the induction chemotherapy and the subsequent radiotherapy [Chen *et al*, 2011].

860 This is the most typical cancer cell repopulation caused by the CNS. In this case, an induction chemotherapy is relatively short, and thus the CNS has strong tendency to use its regulatory action to restore the prior cancerous state as long as the body has required biological resources. It is natural that a delay will result in rapid rise of cancer cell population.

### **(7) Cancer Returns after Surgery**

865 Although some cancers recur many years after tumor resection, a substantial fraction of patients develop overt metastases relatively soon after resection of their primary tumors [Colleoni *et al*, 2016; Cheng *et al*, 2012; Hüsemann *et al*, 2008]. These patients are represented in a sharp rise in the risk of distant recurrence that begins 6 months after surgery and peaks 6 to 870 12 months later.

Slow cancer returns may be caused by altered lifestyles, diets and mental management that can alter tissue ecosystem by restricting required resources for cancer growth. The cancer return peak of 6 to 12 months seems to be largely controlled by the CNS's regulatory actions and the minimum time for creating enough cancer cells.

### **(8) B Cells Suppression Caused by Chemotherapy**

Many studies have reported effects of chemotherapy on lymphocytes in breast cancer patients during the therapy itself or up to 3 months after the last chemotherapy cycle, with a consensus that chemotherapy reduces circu-



880 lating lymphocyte levels.

A study [Verma *et al*, 2016] tried to understand the longer term's impact of chemotherapy, and found that patients receiving epirubicin and cyclophosphamide [EC] or 5-fluorouracil, epirubicin and cyclophosphamide [FEC] showed significantly greater B cell depletion compared to the EC+TAX (e.g., 2 EC cycles followed by further cycles of the taxane, docetaxel) group at 2 weeks after treatment (depleted to 3% vs 8% respectively). The EC/FEC group, who suffered the greatest depletion, recovered B cells significantly more quickly than the EC+TAX group, with the difference between the groups reversed and significant at both 6 months and 9 months.

890 The recovery of the immune system is a manifestation of the roles of the CNS. The recovery pattern would depend on the CNS state memory, original immune cells mixture, effects and duration of chemotherapy, and biological resources in support of the recovery. The general trend should be that the types of immune cells with greatest depletions will recover more. 895 Certain changes caused by chemotherapy may prevent the state going back to what the CNS attempts to restore. Thus, the final state is a perturbed immune system which is as close as what the CNS tries to restore.

### **(9) Cellular Memory (The Body's Memory)**

Cui *et al* [2017] found that the recurrence of ovarian cancer may be 900 linked to cytotoxic chemotherapy drugs that induce PGE 2 production, despite the chemotherapy is used to kill tumor cells. They found that cleaved caspase 3 can results in the release of arachidonic acid (AA) from membrane phospholipids, which ultimately triggers production of the growth signal prostaglandin E2 (PGE 2). Both AA and PGE 2 can stimulate cell 905 proliferation and tumor growth. Therefore, they suggested that caspase 3 activation ultimately lead to cancer recrudescence through the AA metabolic pathway.

The experiment was done with a Transwell system for co-cultures of SKOV3 cancer cells, and thus the CNS does not control the tissue. Instead, 910 the cellular behaviors are controlled by genetic and epigenetic changes that can persist in cells in a culture. The finding cannot be applied to real humans where the CNS controls cancer growth.

In vitro, due to lack of CNS regulations over the tissue ecosystem, other pathways or biochemical steps required for cell apoptosis may be 915 impaired so that caspase 3 release appears to be an apparent step for promoting cancer recrudescence. Caspase 3 concentration may be elevated due to impaired or blocked downstream apoptosis steps. In real humans, ovarian cancer cell repopulation is most probably induced by the CNS's regulatory signals. If the chemotherapy had been used for a sufficiently long 920 time, the CNS might have attempted to protect the state.

The patients in the Cui *et al* study received two to four short-course

regimens of chemotherapy (2–4 months) and it was unlikely that the state memory could be reset in such a short time. It is expected that, upon ending chemotherapy, the CNS attempts to restore the prior-treatment state which is characterized with a low activity of apoptosis. Thus, we believed that Caspase 3 release cannot be true cause for cancer cell repopulation in humans. Instead, cancer repopulation is a typical rebound driven by the CNS memory.

### **(10) Other Chronic Diseases**

The CNS roles satisfactorily explain that chronic diseases, even after cured, have strong tendency to return. The body favors regaining lost weight after losing weight; high blood pressures are difficult to manage, and metabolic syndrome are hard to fix all due to the CNS's effort to restore the prior states.

### **(11) Mysteries of Ancient Healing Exercises**

We could not produce suitable evidence from ancient medical systems. Before modern medicine arrived, every medical system in the world used the holistic model which includes mind as part of cure. In China, use of exercises to train mind can be found in every aspect of culture, including novels, stories, common sayings, language, biographies, movies stories, etc. While current medical model ignores such evidence, their probative value is not any less. Support for the CNS roles can be “experienced” by certain people who are able to pay subtle attention to inner health condition.

## **DISCUSSION**

### **A. New Strategies For Fighting Cancer**

A best strategy implied from the CNS roles is preventing cancer before the cancer has become the subject of CNS protection. When a cancer has fully grown, the cancer has caused the CNS to flip its decision from destroying the tumor to protecting/remolding the tumor, a cure must be a comprehensive program with multiple components. Since acquired mutations cannot be undone now, viable intervening points are the tissue ecosystem and the CNS.

(1) On strategy is retraining the CNS and strengthening the signal exchanging efficiency so that the CNS will not keep getting false “insufficient growth” signals. If the CNS can acquire sufficiently strong growth signals from the cancer-residing tissue, it will attenuate, down scale, or even stop its remodeling activities and change neuronal signals for controlling TAMs. Restoring the immune system and changing CNS signals should be the primary goal. Doing extensive well designed mind-targeted exercises should be considered as a primary component of cure because it is the only measure

that can retrain the CNS functions.

965 (2) The second strategy is controlling diet, nutrition and life-style factors to alter tissue ecosystem properties so that they are close to ones found in evolution. Such properties are changed to be unfavorable to cancer growth. Cancer growth may be slowed, stopped or even reversed only by restricting necessary nutrition/resources, changing multiple health properties simultaneously, creating cancer-hostile tissue ecosystem, etc. An effective  
970 treatment program must be maintained in a sufficiently long time to have the CNS memory reset.

975 (3) Since the CNS is an active promoter of cancer proliferation and metastasis, management of emotion, fears and chronic stress is a central task for fighting cancer. Those factors can affect the CNS through hypothalamus and amygdala. Since hypothalamus plays a central role in integrating the endocrine and nervous systems, chronic stress can adversely affect neuroendocrine and compromise the CNS normal functions. Since amygdala is the vulnerable region for shocks and fears [Phelps and LeDoux, 2005], management of emotion should be viewed as an indispensable measure for fighting  
980 cancer.

## **B. Implications For Future Medical Research**

In the entire medical history, the CNS's memory and its regulatory roles were never considered. Neglecting CNS regulatory role prevents chronic diseases from being reversed. This is a problem that must be addressed in future medical research.  
985

### **1. The CNS' Roles Should Be Considered in Cancer Research**

Our findings reveal a fundamental problem in the cancer treatment paradigm. In early times, chemotherapy, radiotherapy and surgeries were used without understanding cancer biology, and the CNS's roles. The current  
990 standard of care was developed by comparing treatment methods with presumed best treatments. Later studies were conducted by comparing new drugs or new methods with approved drugs or accepted methods. Thus, new treatments developed by conducting circular comparisons with old methods are questionable.

995 The cancer progressive puzzle is well known but has not been solved. A rapid regrowth of cutaneous or pulmonary metastases has been observed [Tubiana, 1988 and 1989]. This change is characterized by the ratio of the doubling time before treatment to that during the repopulation phase. In 31 human metastases in which it was measured, the value of this ratio ranged  
1000 from 2.5 to 5. This is roughly equivalent to 2.5 to 5 times increase in cancer growth rate constant. The large increase in progression speed is attributed to the CNS's regulatory function in a context when radiotherapy and chemotherapy impair the immune system and raise systemic inflammation. The surgical impacts demonstrated by Krall *et al*, 2018 can be further explained by

1005 the CNS roles. A high inflammation level caused by surgical wound would  
force the CNS to make great effort to remodel the tissue.

Including the roles of the CNS in some past studies could lead to different conclusions. Without considering the CNS roles, one could anticipate that blocking adrenergic receptors may prevent cancer from further progressing. However, blocking  $\beta$ -adrenergic signaling path will not stop the CNS from attempting to find alternative ways to raise cancer cell growth speeds. We suspect that the CNS uses its own comparative mechanism to decide when the CNS inhibits cancer or protect cancer cells. The switching point must be decided by the CNS because the CNS is only organ that is capable of making such decisions. A large number of factors including systemic inflammation, cancer type and tumor size, CNS communication efficiency, immune cells mixtures, tissue ecosystem, etc. should be presumed to influence the switching point. We further hypothesize that it must vary, depending on personal conditions.

1020 While a drug treatment like beta blocker may cause the cancer to use  
more time to find alternative paths, the treatment inevitably affects normal  
biological functions including blood glucose and uptake by skeletal muscle.  
Half or more of people who start taking a beta blocker stop within a year  
[Harvard Letter, 2008]. The latest meta study involving 319,006 patients  
1025 shows beta blockers have dubious benefits [Na *et al*, 2018]. Another meta  
study similarly found dubious benefits as judged by disease free survival and  
overall survival in an epidemiological or perioperative setting [Yap *et al.*,  
2018].

Notwithstanding isolated claims of benefits, use of chemotherapy in  
1030 treating cancer is proved to be unsuccessful. A systematic review concluded  
that the complete response rate of chemotherapy for most types of cancer is  
locked at about 7.4% [Ashdown *et al*, 2015]. A systematic evaluation of cancer  
drug approved by the European Medicines Agency from 2009 to 2013  
shows that most cancer drugs entered the market without evidence of bene-  
1035 fits on survival or quality of life [Davis *et al*, 2017]. Based on 13 studies,  
complete responses for thyroid cancer treatment are about 2.5% to 3.4% [Al-  
bero *et al*, 2016]. The true benefits of 'targeted' therapies are extending re-  
mission of cancer for a few months [Maeda and Khatami, 2018]. We believe  
that even the marginal benefits (without balanced by drugs' side effects) are  
1040 most probably due to patients' changed lifestyles that could not be con-  
trolled in population trails.

We believe that the path for conquering cancer is very long. What can-  
cer patients want are predictable cures and fair assurance that can alleviate  
fears and emotional pains. Medical researchers must seek new strategies  
1045 that are not confined by the conventional thinking and current research par-  
adigm. The three CNS roles imply that cancer generally cannot be cured by  
using one or few drugs alone. Those latest meta reviews have proved the

failure of drugs.

1050 Different roles of different macrophage species imply the importance  
of using a holistic approach. We believe that whether macrophages are prop-  
erly activated or differentiated with right types and proper ratios depend on  
subtle balances among a large number of factors. If the CNS' decides to ac-  
cept and promote cancer, the CNS will take coherent and concerted actions  
1055 in favor of cancer cell survival. Given the complexity of this dynamic system,  
future research should try to identify dominant state properties that can be  
correlated to cancer outcomes.

## 2. Improvements in Medical Research Methods

1060 Medical research methodology should be reconsidered in the following  
aspects. First, a state disease may be caused by only a small deviation from  
a disease-free state. A state, which is defined by a large number of B&C  
pathways, cannot be meaningfully evaluated by cherry-picking a few state  
properties. Second, given obvious differences in state properties between in-  
dividual persons, treatments cannot be based on measured individual state  
1065 state properties, but must be based on overall state condition. Third, accurate  
state properties cannot be based on population trials because great differ-  
ences in state properties among different patients are expected. Forth, in de-  
signing studies for understanding effects of diets, lifestyles, and mind regula-  
tion, one should consider how they interact with the CNS. Finally, animal  
models should be evaluated carefully because animals do not have the CNS  
1070 comparable to human's.

## 3. Roles of Emotion and Exercises in Fighting Cancer

1075 Chronic stress and fears can adversely affect cancer outcome [Sloan *et al*, 2010; Moreno-Smith *et al*, 2010; Lutgendorf, 2005 and 2011]. The three  
CNS's roles imply that both emotional management and exercise are very  
important in fighting cancer.

1080 Excessive neuronal signals caused by constant worries, emotional  
shocks, fears, etc. interfere with the CNS' regulatory functions. The medical  
community should develop a treatment paradigm that is able to adequately  
address patients' chronic stress and emotional pains. If the CNS regulatory  
function is erratic, the integrity of tissue cells cannot be maintained.

1085 We have shown that exercises can directly modulate baseline B&C pro-  
cesses against the driving forces of chronic diseases, as shown in Figure 1.  
Long-term exercises have great benefits in fighting cancer [Cormie *et al*,  
2017]. Exercises were long regarded as medicine in Indus Civilization, Yel-  
low River Civilization, Greece and its City-States, and Roman Empire [Tip-  
ton, 2014]. Moreover, exercises can improve the CNS' basic functions. Exer-  
cises in conjunction with emotional management may help the CNS regain a  
complete control over the cancer-residing tissue. Such measures may cause  
the CNS to stop its remodeling effort and restore its anti-tumor immunity

1090 signals.

## CONCLUSION

1095 Based on facts extracted from the skill-learning model in conjunction of established knowledge, we have shown that the CNS can store state information on basic B&C processes, use the stored information in regulating the body, and regulate the body by using a comparative mechanism. By using the three roles, the CNS maintains health state for a healthy person and the disease state for a disease. The mind-body interlock plays a crucial role in main-  
1100 taining structural and functional stability of the person. While the CNS memory is essential in maintaining health stability, it is the main obstacle to curing state diseases. No chronic diseases can be cured unless the state information in the CNS memory is changed or reset.

1105 The CNS plays a crucial role in cancer initiation, progression and metastasis. The CNS is like a double-edged sword. It first attempts to prevent, inhibit, or slow down cancer progression by sending neuronal signals to tissues. However, after the tumor size reaches a sufficient size, the dominance of cancer cells forces the CNS to change its roles. The CNS changes its roles from inhibiting and killing cancer cells to protecting cancer  
1110 cells by using “tissue remodeling” activities, which include immobilizing all of its massive regulatory capacities acquired in evolution. Cancer cannot be cured without altering the CNS regulatory features driven by CNS state memory. To restore the CNS state memory, measures must be taken to alter CNS memory directly, restrict biological resources for cancer growth on a  
1115 long-term basis, and make disturbances to a plurality of state properties of the cancer tissue.

The finding of the three CNS roles do not depend on any hypothesis, they are true even if our explanations are inaccurate and even if every theory we rely on is inaccurate. The three findings expose the root cause of the  
1120 failure to find cures for chronic diseases and cancer, and shed some light on the special roles of exercises as cures for chronic diseases. The CNS’s state memory and its regulatory roles will require re-interpretations of data in past medical studies involving chronic diseases. Moreover, the failure of finding cures for chronic diseases can be attributed to neglecting the crucial  
1125 roles of the CNS. A critical component of cures for chronic diseases is breaking up the mind-and-body interlock. Exercises are the most useful methods. Most mysteries of healing exercises can be explained by the three CNS roles.

1130

## REFERENCES

- Albero A, Lopéz JE, Torres A, de la Cruz L, Martín T. Effectiveness of chemotherapy in advanced differentiated thyroid cancer: a systematic review. *Endocr Relat Cancer*. 2016 Feb;23(2):R71-84.
- 1135 Albo D, Akay CL, Marshall CL, Wilks JA, Verstovsek G, Liu H, Agarwal N, Berger DH, Ayala GE. Neurogenesis in colorectal cancer is a marker of aggressive tumor behavior and poor outcomes. *Cancer*. 2011;117:4834-4845.
- 1140 Aras S and Zaidi MR, TAMEless traitors: macrophages in cancer progression and metastasis. *British Journal of Cancer*. (2017) 117, 1583-1591.
- Artico M, Bosco S, Cavallotti C, Agostinelli E, Giuliani-Piccari G, Sciorio S, Cocco L, Vitale M. Noradrenergic and cholinergic innervation of the bone marrow. *Int J Mol Med*. 2002;10:77-80.
- 1145 Ashdown ML, Robinson AP, Yatomi-Clarke SL, Ashdown ML, Allison A, Abbott D, Markovic SN, and Coventry BJ, Chemotherapy for Late-Stage Cancer Patients: Meta-Analysis of Complete Response Rates, Version 1. *F1000Res*. 2015; 4:232.
- 1150 Ayala GE, Dai H, Powell M, Li R, Ding Y, Wheeler TM, Shine D, Kadmon D, Thompson T, Miles BJ, Ittmann MM, Rowley D. Cancer-related axonogenesis and neurogenesis in prostate cancer. *Clin Cancer Res*. 2008;14:7593-7603.
- Benestad HB, Strom-Gundersen I, Iversen PO, Haug E, Nja A. No neuronal regulation of murine bone marrow function. *Blood*. 1998;91:1280-1287.
- 1155 Bernards R, Weinberg RA (2002) A progression puzzle. *Nature* 418:823.
- Brydon L, Magid K, Steptoe A. Platelets, coronary heart disease, and stress. *Brain Behav Immun* (2006) 20: 113-119.
- 1160 Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143-1211.
- Buijs RM, Scheer FA, Kreier F, Yi C, Bos N, Goncharuk VD, Kalsbeek A. Organization of circadian functions: interaction with the body. *Prog Brain Res*. 2006;153:341-60.
- 1165 Calorini L, Bianchini F. Environmental control of invasiveness and metastatic dissemination of tumor cells: the role of tumor cell-host cell interactions. *Cell Commun Signal*. 2010;8:24.
- Canaani J, Kollet O, Lapidot T. Neural regulation of bone, marrow, and the microenvironment. *Front Biosci*. 2011;3:1021-1031.
- 1170 Carabotti, M.; Scirocco, A.; Maselli, M.A.; Severi, C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous sys-

tems. *Ann. Gastroenterol.* 2015, 28, 203–209.

1175 Chen CP, Weinberg VK, Jahan TM, Jablons DM, and Yom SS. Implications of Delayed Initiation of Radiotherapy Accelerated Repopulation after Induction Chemotherapy for Stage III Non-small Cell Lung Cancer. *Journal of Thoracic Oncology* Volume 6, Number 11, November 2011.

Cheng L, Swartz MD, Zhao H, Kapadia AS, Lai D, Rowan PJ, Buchholz TA, Giordano SH. Hazard of recurrence among women after primary breast cancer treatment—A 10-year follow-up using data from SEER-medicare. *Cancer Epidemiol. Biomarkers Prev.* 21, 800–809 (2012).

1180 Colleoni M, Sun Z, Price KN, Karlsson, Forbes JF, Thürlimann B, Gianni L, Castiglione M, Gelber RD, Coates AS, Goldhirsch A. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: Results from the international breast cancer study group trials I to V. *J. Clin. Oncol.* 34, 927–935 (2016).

1185 Cormie P, Zopf EM, Zhang X, Schmitz KH. The Impact of Exercise on Cancer Mortality, Recurrence, and Treatment-Related Adverse Effects. *Epidemiologic Reviews*, Volume 39, Issue 1, January 2017, Pages 71–92, <https://doi.org/10.1093/epirev/mxx007>

1190 Cui L, Zhao Y, Pan Y, Zheng, Shao D, Jia Y, He K, Li K, and Chen L. Chemotherapy induces ovarian cancer cell repopulation through the caspase 3-mediated arachidonic acid metabolic pathway. *Onco Targets Ther.* 2017; 10: 5817–5826.

1195 Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A, Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13, *BMJ* 2017;359:j4530.

de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer.* 2006;6:24–37.

1200 DeNardo DG, Johansson M, Coussens LM. Immune cells as mediators of solid tumor metastasis. *Cancer Metastasis Rev.* 2008;27:11–18.

Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 1986; 315:1650–9.

Dvorak HF. Tumors: wounds that do not heal-redux. *Cancer immunology research* 2015; 3:1–11.

1205 Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell.* 2010;140:883–899.

Han C, Rice MW, and Cai D. Neuroinflammatory and autonomic mechanisms in diabetes and hypertension. *Am J Physiol Endocrinol Metab.* 2016 Jul 1; 311(1): E32–E41.

1210 Hanahan & Weinberg. The Hallmarks of Cancer. *Cell*, Vol. 100, 57–70,



January 7, 2000.

A second look at beta blockers and blood pressure. A beta blocker alone isn't usually the best choice for simple, uncomplicated high blood pressure. *Harv Heart Lett.* 2008 Jun;18(10):4-5.

1215 Hochberg, ME & Noble RJ. A framework for how environment contributes to cancer risk. *Ecology Letters* (2017) 20, 117-134.

Housman G., Byler S., Heerboth S.h, Lapinska K, Longacre M., Snyder N. and Sarkar S., Drug Resistance in Cancer: An Overview. *Cancers* 2014, 6, 1769-1792.

1220 Huang YC, Feng ZP. The good and bad of microglia/macrophages: new hope in stroke therapeutics. *Acta Pharmacol Sin* 2013;34(1): 6-7.

Hüsemann Y, Geigl JB, Schubert F, Musiani P, Meyer M, Burghart E, Forni G, EilsR, Fehm T, Riethmüller G, Klein CA. Systemic spread is an early step in breast cancer. *Cancer Cell* 2008;13,58-68.

1225 Imai S, Tokunaga Y, Maeda T, Kikkawa M, Hukuda S. Calcitonin gene-related peptide, substance P, and tyrosine hydroxylase-immunoreactive innervation of rat bone marrows: an immunohistochemical and ultrastructural investigation on possible efferent and afferent mechanisms. *J Orthop Res.* 1997;15:133-140.

1230 Jones S, et al. Comparative lesion sequencing provides insights into tumor evolution. *Proc Natl Acad Sci USA* 2008;105:4283- 4288.

Karin M, Greten FR. NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol.* 2005;5:749-759.

1235 Khasraw M, Posner JB. Neurological complications of systemic cancer. *Lancet Neurol.* 2010;9:1214-1227.

Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R (1995) Slowing of wound healing by psychological stress. *Lancet* 346: 1194-1196.

1240 Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci USA* 2003;100: 9090-9095.

1245 Kleemeyer MM, Polk TA, Schaefer S, Bodammer NC, Brechtel L, and Lindenberger U. Exercise-Induced Fitness Changes Correlate with Changes in Neural Specificity in Older Adults. *Front Hum Neurosci.* 2017; 11: 123. Published online 2017 Mar 16. doi: 10.3389/fnhum.2017.00123.

Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest.* 2007;117:1175-1183.

1250 Lumen, Boundless Anatomy and Physiology, Control of Muscle Tension, Force of Muscle Contraction. <https://courses.lumenlearning.com/boundless->

[ap/chapter/control-of-muscle-tension/](#). Last Accessed July 16, 2019.

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

1255 Lutgendorf SK, DeGeest K, Dahmouh L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain, Behavior, and Immunity* 2011;25(2):250-255.

1260 Maeda H and Khatami M. Analyses of repeated failures in cancer therapy for solid tumors: poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs, *Clin Transl Med*. 2018; 7: 11.

McDonald PG, Antoni MH, Lutgendorf SK, et al. A biobehavioral perspective of tumor biology. *Discovery Medicine* 2005;5(30):520-526.

Miyan JA, Broome CS, Whetton AD. Neural regulation of bone marrow. *Blood*. 1998;92:2971-2973.

1265 Mravec B, Gidron Y, Hulin I. Neurobiology of cancer: Interactions between nervous, endocrine and immune systems as a base for monitoring and modulating the tumorigenesis by the brain. *Semin Cancer Biol*. 2008;18:150-163.

1270 Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. *Future Oncology* 2010;6(12):1863-1881.

Na Z, Qiao X, Hao X, Fan L, Xiao Y, Shao Y, et. al. The effects of beta-blocker use on cancer prognosis: a meta-analysis based on 319,006 patients. *OncoTargets and Therapy* 2018;11 4913-4944

1275 Nemeroff CB, Musselman DL, Evans DL Depression and cardiac disease. *Depress Anxiety* (1998) 8 (Suppl 1): 71-79

Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer*. 2009;9:274-284.

Nowell, P. C. (1976). "The clonal evolution of tumor cell populations". *Science*. 194 (4260): 23-28. doi:10.1126/science.959840. PMID 959840.

1280 Noy R and Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity*. 2014 July 17; 41(1): 49-61.

Palm D, Entschladen F. Neoneurogenesis and the neuroneoplastic synapse. *Prog Exp Tumor Res*. 2007;39:91-98.

1285 Phelps EA, LeDoux JE. Contributions of the Amygdala to Emotion Processing: From Animal Models to Human Behavior. *Neuron*, Vol. 48, 175-187, October 20, 2005.

Prehn RT. Cancers beget mutations versus mutations beget cancers. *Cancer Res*. 1994;54:5296-5300.

Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and di-

- 1290 agnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol.* 2011;204(6):466-478.
- Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychological Bulletin* 2004;130(4):601-630.
- 1295 Sloan EK, Priceman SJ, Cox BF, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Research* 2010;70(18):7042-7052.
- Sundquist J, Li X, Johansson SE, Sundquist K. Depression as a predictor of hospitalization due to coronary heart disease. *Am J Prev Med* 1300 (2005); 29: 428-433.
- Solinas G, Marchesi F, Garlanda C, Mantovani A, Allavena P. Inflammation-mediated promotion of invasion and metastasis. *Cancer Metastasis Rev.* 2010;29:243-248.
- 1305 Sung SY, Hsieh CL, Wu D, Chung LW, Johnstone PA. Tumor microenvironment promotes cancer progression, metastasis, and therapeutic resistance. *Curr Probl Cancer.* 2007;31:36-100.
- Tipton CM. The history of "Exercise Is Medicine" in ancient civilizations. *Adv Physiol Educ.* 2014;38(2):109-117.
- 1310 Toothaker TB, Rubin M. Paraneoplastic neurological syndromes: a review. *Neurologist.* 2009;15:21-33.
- Tubiana M. Repopulation in human tumors. A biological background for fractionation in radiotherapy. *Acta Oncol* 1988; 27: 83-8.
- Tubiana M. Tumor Cell Proliferation Kinetics and Tumor Growth Rate, 1315 *Acta Oncologica*, 1989;28:1, 113-121, DOI: 10.3109/02841868909111193
- Varner JA. Stem cells and neurogenesis in tumors. *Prog Exp Tumor Res.* 2007;39:122-129.
- Verma R, Foster RE, Horgan K, Mounsey K, Nixon H, Natuley S, Hughes TA, Clive RD. Carter. Lymphocyte depletion and repopulation after 1320 chemotherapy for primary breast cancer. *Breast Cancer Research* (2016) 18:10.
- Wang TL, Rago C, Silliman N, Ptak J, Markowitz S, Willson JK, et al. Prevalence of somatic alterations in the colorectal cancer cell genome. *Proc Natl Acad Sci USA.* (2002) 99:3076-80. 10.1073/pnas.261714699
- 1325 Willis RA. *The Spread of Tumors in the Human Body.* 3rd edition. Butterworths; London: 1973.
- Wójcikowski J, Daniel WA. The role of the nervous system in the regulation of liver cytochrome p450. *Curr Drug Metab.* 2011 Feb;12(2):124-38.

1330 Wood LD, et al. The genomic landscapes of human breast and colorectal cancers. *Science*. 2007;318:1108 -1113.

Wraith DC, Nicholson LB. The adaptive immune system in diseases of the central nervous system. *J Clin Invest*. 2012;122(4):1172-1179.

Wu Y, Zhou BP. Inflammation: a driving force speeds cancer metastasis. *Cell Cycle*. 2009;8:3267-3273.

1335 Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H, Nino-Castro AMallmann MR, Labzin L, Theis H, Kraut M, Beyer M, Latz E, Freeman TC, Ulas T, Schultze JL Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity*. 2014; 40(2):274-288.

1340 Yap A, Lopez-Olivo MA, Dubowitz J, Pratt G, Hiller J, Gottumukkala V, Sloan E, Riedel B, Schier R. *Br J Anaesth*. 2018 Jul; 121(1):45-57. Epub 2018 May 3.

Zanker KS: The neuro-neoplastic synapse: does it exist? *Prog Exp Tu-mor Res* 39: 154-161, 2007.

1345