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How cancer arises from chronic inflammation, based on complexity theory
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In 1991, President Richard Nixon announced the War on Cancer in the United States. Despite massive expenditures of time and money by our top talent, we have failed to win this war. Although the US cancer death rate has declined steadily, cancer still kills 600,000 Americans annually. It is the second leading cause of death, soon to become #1.

This failure is due to our reliance on reductionist thinking, which holds that the whole is equal to the sum of the parts, that curing cancer is analogous to replacing a bad part in a refrigerator. Instead, we propose that physicians and scientists embrace complexity theory, recognizing that the behavior of the whole is greater than the sum of the behavior of the parts, due to important interactions between the parts. The COVID19 pandemic provides a good analogy. Its resolution will not be due to fixing a bad part or finding a magic bullet, but to a host of changes affecting all aspects of the disease, including prevention, early detection and treatment.

We previously summarized the laws of complexity and self-organization as they relate to cancer and proposed that most adult cancer is due to nine chronic cellular stressors, one of which is chronic inflammation.

Chronic inflammation is associated with numerous cancers, summarized in our poster and paper. This includes chronic inflammation due to bacteria, such as *Helicobacter pylori* for stomach cancer and lymphoma and *Salmonella typhi* for gallbladder cancer. Chronic inflammation is associated with parasitic liver flukes causing cholangiocarcinoma and Schistomiasis causing bladder cancer. Viruses can have direct oncogenic effects, but also act by stimulating chronic inflammation, as with Hepatitis B and C. Other mechanisms through which chronic inflammation causes cancer include autoimmunity, as in Hashimoto thyroiditis causing thyroid lymphoma, trauma induced chronic inflammation, such as gastroesophageal reflux causing esophageal adenocarcinoma and immune system dysfunction. The most important may be excess weight, a major risk factor for adult solid cancer, mediated through subclinical chronic inflammation.

How does chronic inflammation trigger carcinogenesis, within a complexity theory perspective? Our biologic networks are delicately balanced at a critical state between stimulating and dampening forces, with built in control mechanisms to keep the organism on path. We suggest that chronic stressors, including chronic inflammation, disturb this balance and create network instability. Locally, these instabilities are amplified and may produce intermediate states that often are detectable histologically, such as dysplasia. We also speculate that they may produce intermediate states detectable only by molecular patterns in other cancers, such as glioblastoma or Hodgkin lymphoma. Ultimately, these network instabilities may propagate into neighboring cells and eventually into systemic network changes. Together, the network changes affecting the target cells, their microenvironment and the immune system produce what is called a cancer attractor state, which is difficult to reverse.

Curative treatment must target not just driver mutations, but numerous aspects of the systemic cellular networks which create and sustain the malignancy. We do need to kill or limit the primary tumor, but must use more diverse treatment combinations than for the curative childhood malignancies, which typically have no risk factors or associated chronic stressors. However, removal of the primary tumor may not cause reversion of altered networks throughout the body to normal. We must move these networks towards more stable attractors or less hazardous states; since they are relatively stable, we may need to first use agents that destabilize them to make them sensitive to treatment.

We need to promote maturation and differentiation pathways, and we suggest stimulating physiologic pathways which halt processes associated with malignancy, such as embryonic rapid cell division, physiologic chronic inflammation, wound healing and liver regeneration. We need to reduce or antagonize the nine chronic stressors and treat microenvironmental factors supporting the tumor. We need to identify and counter factors relating to immune system dysfunction and germ line variations supporting the tumor. Finally, better screening and optimization of rational medical care are important. We cannot create a world

without cancer, but by focusing on all factors supporting tumor growth, we can reduce the death and misery it causes.