The use of antioxidants during chemotherapy has been a controversial topic, with questions raised about whether or not supplementary antioxidants may lead to benefit or harm. Keith I. Block, MD, medical director of the Block Center for Integrative Cancer Treatment; founder and editor-in-chief of the peer-reviewed medical journal Integrative Cancer Therapies; and director of integrative medical education at the University of Illinois, College of Medicine, is an internationally renowned and leading expert on this topic and spoke about his clinical experience, research and views. His conclusions are that the data suggest benefit from antioxidant use during chemotherapy and be cautious that treatment must be individualized.

Data Support Antioxidant Use During Chemotherapy

An Interview with Keith I. Block, MD

Jane Hart, MD

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Jane Hart: Why has the use of antioxidants during chemotherapy been a controversial topic?

Keith I. Block: When it comes to chemotherapy and antioxidants used concurrently, the questions are: “Do antioxidants increase or decrease the efficacy of anticancer agents? Do antioxidants protect normal tissue and reduce toxicity or do they actually protect cancer cells from the effect of chemotherapy? Or does none of this occur, and do antioxidants simply have no effect either way?”

It shouldn’t be surprising that this is a controversial topic. Misleading headlines and, unsubstantiated warnings detailing the dire consequences of any supplementation are often met with an equally forceful and enthusiastic endorsement of any and all supplementation. Where is the “middle ground” approach—the voice of reason?

For example, a recent headline regarding research conducted at Northwestern Memorial Hospital, in Chicago, Illinois, read: “Popular Herbal Supplements May Adversely Affect Chemotherapy Treatment.”1 The article stated that “there is growing evidence that these popular supplements may intensify or weaken the effect of chemotherapy drugs and in some cases, may cause a toxic, even lethal reaction.” The article went on to name a number of different compounds that may do this.

While reading this article, I could not help but wonder: “Where did this perspective come from?” So, I gathered some members of my research team here at the Block Center, and we reviewed any and all recent literature to determine if there were any meaningful scientific data supporting this contention that supplements weaken chemotherapy or may cause toxic or even lethal reactions. I asked the question because, over the past decade, we have performed extensive systematic research reviews (now published), analyzing these very questions, and had not seen any data supporting such a claim.

What my research team and I reported after this more-recent search was similar to what we have found in past searches. Of more than 2300 studies and nearly 5000 patients that we reviewed, not a single study we reviewed showed any clinical evidence of antioxidant use interfering with chemotherapy.

So, from my perspective, it is very important to understand why this controversy exists and why there has been a mainstream perspective that advises to not include antioxidants during chemotherapy. In fact, if the actual scientific data don’t show interference or harm, while also demonstrating a clinically valuable reduction in side-effects and often improved responses, one might ask why such a raging debate like this exists at all!

JH: What are some specific concerns that triggered fearful reactions regarding the use of antioxidants during chemotherapy?

KIB: There are several factors contributing to the confusion surrounding this topic, including the ways in which we tend to conduct research, specific study results, and the ways in which those results have been interpreted.

Let’s start with the issue of research methodology. For instance, researchers prefer study designs that have few or no confounding variables. This means designing a trial that limits additional factors that can exert an influence on the result and lead to a lack of clarity as to the true experimental effect. Because a major focus is on getting “clean” research, it is easier to study one intervention at a time. The idea of using several interventions at the same time—for example, a combined group
Several research studies have shown is that, when antioxidants are included in a person’s therapeutic regimen, toxicity is reduced and the degree of therapeutic results. What our two published systematic reviews have suggested is that, when antioxidants are included in a person’s therapeutic regimen, toxicity is reduced and the patient is more successful at adhering to a chemotherapy regimen.\(^2,3\) Several research studies have shown that maintaining an optimal dose and avoiding a delay in the treatment schedule, while completing a full course of chemotherapy, unquestionably leads to better outcomes.

A single-intervention approach, however, has been unchanged and has been rigidly upheld for most of the past 6 decades. Restricting treatment to only one or two pharmaceuticals limits the ability to hit multiple targets. With a negligible change in mortality among most cancers from the 1950s to date, there is a great need for a more comprehensive, multigeted strategy that addresses better the multiple defects that make up most malignant disease. It turns out there is great potential for natural compounds to address multiple targets, while reducing side-effects and improving treatment tolerance.

Next we have to look at and address research that has contributed considerably to the antioxidant–chemotherapy controversy. There were two large, randomized clinical trials: One was conducted looking at the effects of \(\beta\)-carotene and \(\alpha\)-tocopherol—The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [ATBC]\(^4\) and the Beta-Carotene and Retinol Efficacy Trial [CARET].\(^5\) respectively. What was of interest, was that neither of these studies had anything to do with chemotherapy. However, both of these studies demonstrated the labile nature of some antioxidants.

The CARET study evaluated \(\beta\)-carotene in a group of more than 29,000 Finnish men. The surprise was that men who took the supplement had a higher incidence of lung cancer than the group who did not take the supplement. The study, however, had many inherent and significant flaws. First, the researchers used synthetic \(\beta\)-carotene. Considerable research has shown synthetics to be a problem, compared to natural and whole plant–based supplements—in this case, from carotenoids. Second, the group had considerable exposures to tobacco and alcohol. Though frequently ignored, we know that an individual’s internal environment can influence the effect of a drug or supplement profoundly. This is particularly true with a labile, unstable compound such as \(\beta\)-carotene. It would be hard to dispute that these subjects had internal environments that were considerably burdened with oxidative stress. With a terrain of this nature, one could easily expect that \(\beta\)-carotene would easily convert from a protective antioxidant to a risky pro-oxidant. Thus, it was not at all surprising to me that the researchers found an increase in lung cancer among the synthetic \(\beta\)-carotene users. Because \(\alpha\)-tocopherol was also given as a single nutrient, and it has similar labile properties, it should be no surprise that, in a subject with considerable oxidative stress, this also showed an increase in risk.

I believe that, with a population of nonsmokers taking a more stable “mixed” and “natural” carotenoid–based supplement, we would see a very different—and, quite possibly, favorable—outcome. Full antioxidant protection is dependent on a “network effect” in which secondary antioxidant compounds provide an electron cushion to diminish, or even eliminate, risk of injury from a free radical with unpaired electrons. The fact is, soil affects a tree’s growth and health. In this same way, a patient’s internal milieu affects the way a supplement, particularly one such as \(\beta\)-carotene, affects a patient’s or study subject’s response.

Nonetheless, other than \(\beta\)-carotene and \(\alpha\)-tocopherol, as a rule, based on existing literature, nonsynthetic antioxidants show no such risk, particularly when they are taken in a form that is closer to the way they grow in nature.

As I already mentioned, what makes even less sense, in terms of the ongoing controversy, is that neither of these studies had anything to do with chemotherapy. In other words, what effect this would have on chemotherapy has been nothing more than speculation. The opinions suggesting not combining antioxidants with chemotherapy have been generalized from studies with flawed interpretations in which no chemotherapy was included. Meanwhile, for the most part, the actual trials that combine both chemotherapy and antioxidants together have shown either no adverse effect or a favorable one.
Then, in addition to the early studies that helped frame part of the mainstream position, in 2005 and 2006, Bariatti et al. made international headlines regarding their randomized study, which examined the use of antioxidants to prevent adverse effects related to radiation therapy, and the effects of antioxidants on mortality in patients with head and neck cancer. The results showed that patients receiving supplements had significantly fewer severe acute side-effects than patients not receiving supplements, but patients taking specifically α-tocopherol and β-carotene supplements also had increased recurrence rates of cancers and lower survival rates.

These results were heavily publicized, and the impact spread, leading to a dangerous and erroneous message: “All antioxidant use is harmful!”

But, the media never jumped on the later study that shattered the earlier results and echoed what was evident among most of the earlier antioxidant studies. In 2008, the researchers went back and reexamined their 2005 data, and acknowledged that they made some mistakes in their interpretations. When the scientists looked at the actual subjects, it turned out that the participants who had lower survival rates when they used antioxidants were the participants who were smokers. But, when the smokers were removed from the group, there was no problem with antioxidant use. So, the take-home message to patients should have been: “If you continue to smoke while receiving chemotherapy and radiation therapy, you can expect problems to arise, and supplements—specifically α-tocopherol and β-carotene—won't necessarily prevent problems, and may even have harmful consequences.”

But guess what? There was no such take-home message. The mainstream media did not pick up the revised story in the same way that the 2005 report made international news. There were no headlines about the reanalysis showing no harm from supplement use when the subjects were non-smokers, unlike the global headlines that followed the flawed first article. What is of interest is that, even when the subjects smoked before or after the radiation therapy, but not during the therapy, there was no adverse effect on survival. Of course, no-one should be encouraging smoking anyway. And it is clear that smoking is the culprit here, not the supplements. Also, to reemphasize my point, this study had nothing to do with chemotherapy. My main point is that, if we are going to be evidence-based today, we have to be specific and look at what the evidence is today. Though many of the studies we found in our reviews of the literature on randomized trials of antioxidants given with chemotherapy did not have the statistical power and precision that one would ideally want, the best data we found from these two exhaustive systematic reviews showed a consistent and favorable impact when it came to combining antioxidants with chemotherapy for patients with cancer.

**JH:** Help us put the results from the studies you just mentioned into proper perspective.

**KIB:** Sure. Let me explain some of what I have said differently while sharing some important background with you to understand these trials better.

Under specific conditions, we know that an antioxidant can turn into a pro-oxidant, and certain agents are more vulnerable to this than others. I frequently refer to these labile compounds as having a Jekyll/Hyde nature. For instance, a compound such as β-carotene—particularly if it is synthetic and not a mixture of carotenoids, given to an individual with a markedly high, oxidatively stressed environment—(such as what one would find among smokers) has the potential to convert to a pro-oxidant.

In addition, some of the assumptions and interpretations of these studies were simply wrong. It is not realistic to suggest that β-carotene or any micronutrient alone could possibly compensate for all the harmful consequences of long-term exposure to cigarette smoking. Of interest in the CAR-ET study, before the intervention, the individuals with the highest β-carotene levels actually had lower rates of cancer and heart disease. Irrespective of what transpired by the end of the study, these subjects retained the lowest risk of these problems.

The important point is that, clearly, there is something about the internal environment of a patient that influences what happens to the compound itself. If a person has been highly challenged with oxidative stress (such as from smoking) that patient is far more likely to have an adverse effect from supplementation. However, studies show that people with higher blood levels of β-carotene because of a healthier diet and lifestyle, do not end up with higher rates of lung cancer.

In the cancer setting, I would never recommend that a patient take a single ingredient agent of α-tocopherol or β-carotene. I might suggest a plant-based extract of carotenoids or of mixed tocopherols. I think it is potentially problematic to look at single nutrients, because they do not have the electron cushion I spoke of earlier. We can refer to this as having a “network” effect of antioxidants.
As mentioned above, network antioxidants refer to the coupling process through which the antioxidants can encounter powerful unpaired free radicals and neutralize them successfully by providing an additional electron to stabilize what would otherwise become a pro-oxidant. Thus, following the sharing of its paired electron, the network antioxidant now carries an unpaired electron and shifts to become a weak oxidant. A second antioxidant passes on an electron to the weak oxidant, now stabilizing it as well. It is this network effect that can diminish and quiet the adverse impact of pro-oxidants.

To provide an analogy, this is like a big “semi” truck that blows a tire on a major highway. Theoretically, if, before the truck triggers a multicar collision, another truck came alongside the semi and offered the use of a spare tire, the crash could be avoided. In the body, a network antioxidant can actually do this. It can share and pair up as an extra electron and prevent the unstable, unpaired electron from creating an “oxidative crash.”

Of course, this process expends protective antioxidants, thus requiring a fresh supply of antioxidants. If one has many different antioxidants available, they are able to provide spare electrons and protect each other from shifting to a more-worrisome pro-oxidative state. But if there is only one antioxidant around—as in the case of a single nutrient (which is, more often than not, a synthetic)—and it passes its electron off, now the patient’s body is stuck with a free radical that has a greater likelihood of causing damage.

The overall effect of eating a diet or taking whole-plant-based supplements, rich in antioxidants, is to prevent the generation of oxidants, while establishing a high degree of antioxidant power. Taking a combination of antioxidants, as opposed to a single nutrient, provides such a network effect. I recommend supplements to my patients that are whole-plant-based. These supplements are more stable and less likely to convert to pro-oxidants.

The biochemical environment or terrain that cells reside in significantly makes an impact on cellular health. If the cell environment is disrupted—whether through oxidative stress, hyperglycemia, or a pro-inflammatory state—then a person could not only be at greater risk for initiating and developing disease but would also be at increased risk for promoting an existing disease. A microenvironment in disarray is a setup for a poorer response to conventional treatment.

**JH: Based on current research and your ongoing review of the literature, what does the literature actually say about the use of antioxidants during chemotherapy?**

**KIB:** In the first of our two systematic reviews, we looked at the question: “Do antioxidants interfere with the efficacy of chemotherapy or not?” In other words, do antioxidants impair the therapeutic benefits of chemotherapy treatment or not? A year later, we performed another systematic review, and, in that study we asked: “Do antioxidants reduce the toxicity from chemotherapy, given that we know from considerable research that reducing side-effects prevents dose reductions or treatment-schedule delays, thus, leading to improved outcomes?” In both articles, we searched the literature systematically for randomized controlled trials in which antioxidants were given to patients with cancer at the same time that they received cancer chemotherapy drugs that act through free-radical mechanisms.

The summary of these two articles is that the existing research to date shows that antioxidants improve treatment outcomes, increase survival times, increase tumor response, or all of the above. While some studies did not show an effect (probably because dosing was too low), we found that the vast majority of studies showed that antioxidant supplementation during chemotherapy significantly reduced toxicity. The third thing we found was that no trial reported a significant decrease in treatment efficacy, which suggests that there is no evidence of antioxidants interfering with chemotherapy.

In summary, no clinical trial evidence to date suggests negative effects of antioxidants on chemotherapeutic efficacy. Thus, even though more research would always be of value, it is hard to understand why the dire warnings against the use of antioxidants with chemotherapy persist, when the available data clearly show a consistently favorable effect.

As I mentioned above, some of the research studies we analyzed demonstrated that patients who take antioxidants are able to maintain the recommended dosing and schedule better for their chemotherapy. This is clinically relevant because, if we can keep patients from having to reduce dosing or delay treatment, then patients will respond to treatment far better. Knowing this, it would then make sense to assume there would be greater interest among the members of the research community to study the clinical use of antioxidants and natural products.

**JH: Please talk about some specific studies that show benefits of antioxidant use?**

**KIB:** Absolutely. Let’s look at a small sampling with some specific findings from the studies we reviewed showing the benefits of antioxidant use together with chemotherapy.

Of the studies we reviewed looking at the use of glutathione with chemotherapy, six of the seven published randomized trials combined glutathione with platinum-based drugs to treat a variety of cancer types. Toxicities from platinum-based chemotherapy are common and include neuropathy, ototoxicity, and myelosuppression, among others. This is particularly relevant because such toxicities can limit dosing, delay scheduling of the next cycle of chemotherapy, and interrupt and prevent the completion of treatment. The primary objective of these studies was to evaluate the neuroprotective effects of glutathione. Smyth et al. showed that 58% of patients taking glutathione were able to receive a full cycle of chemotherapy, compared with 39% of patients in a placebo group (P = 0.04).

Six studies on neurotoxicity reported similar or greater reductions in neurotoxicity in glutathione groups, compared with control groups.

In two studies by Cascinu et al., significant reductions in toxicity were seen in glutathione groups compared with control groups. In both articles, we searched the
difference in occurrence of neurotoxicity was seen between patients on glutathione (17%) and the control group (89%) ($P = 0.0001$). In the other study, with 52 patients who had advanced colorectal cancer, 26% of the control group experienced grade three or four neurotoxicity, while none of the patients in the glutathione group experienced grade three or four neurotoxicity ($P = 0.01$).

The patients in all of these studies received from 1500 up to 3000 mg/m² of glutathione daily. The bottom line is that, by limiting chemotherapy-related toxicities, we give patients a better quality of life [QoL], help them complete their chemotherapy regimens, and improve their responses to treatment and the resulting outcome.

Melatonin is another controversial topic, because, until recently, most of the research came from one group, so people may dismiss the findings. Nonetheless, the data are impressive. Lissoni et al. reported statistically significant increases in survival rates for study participants with advanced non–small cell lung cancer who were taking melatonin supplements. Response rates, meaning the percentage of patients who had clinically relevant tumor shrinkage, were significantly higher in patients taking melatonin in two of the three Lissoni et al. studies. The response results were 35% versus 18% ($P < 0.05$) and 34% versus 15% ($P < 0.001$). In one of the studies, the number of patients with progressive disease was significantly lower in a melatonin group, compared with a control group, 12% versus 39% ($P < 0.01$). In that same study, neurotoxicity was 18% in the group, that took melatonin versus 41% in the control group. Thrombocytopenia was 14% in the melatonin group versus 20% in the control group.

Cerea et al. also tested melatonin. In this study, disease stabilization rates (partial response plus stable disease) were significantly higher in patients taking melatonin, compared with a control group, 86% versus 44% ($P < 0.05$). In studies by Argyriou et al. and by Pace et al., patients who received vitamin E had a significantly decreased incidence of neurotoxicity, compared with control groups. The results were: 31% versus 86% in the Pace study ($P < 0.01$). In a study by Wadleigh et al., patients who received vitamin E had significantly decreased oral mucositis, compared with a control group.

Falsaperla et al. studied ellagic acid. Their study showed that patients with prostate cancer who were taking supplement as they were receiving chemotherapy had significantly decreased neutropenia, compared with a placebo group, 33% versus 75% ($P < 0.05$).

A small randomized controlled trial looked at the cardioprotective effects of CoQ10 in patients taking anthracyclines. One of the dose-limiting effects of doxorubicin (a classic breast-cancer drug that is used to treat a number of different cancers) is cardiomyopathy. In this CoQ10 study, the decline in left-ventricular function—reflecting injury to the heart muscle—was a third less in a CoQ10 group, compared with a control group. Specifically, some of the signs of the injury, such as septal-wall thickening, in the CoQ10 group were zero, while they were evident in 19% of the patients in the control group. The same thing occurred with septal-wall motion abnormalities—0% injury in the CoQ10 group and 20% injury in the control group. This was a small trial, but, nonetheless, the results are compelling.

**JH:** Share with us why these findings showing benefit from antioxidant use during chemotherapy make sense to you.

**KIB:** We know that free radicals actually drive cancer, and we also know that some—but not all—cancer chemotherapies work through a free-radical mechanism. Even with the chemotherapy drugs that do work through free radicals, using antioxidant supplements is a bit like putting Saran Wrap in front of a lightning bolt. The idea that antioxidants are enough to actually stop the effectiveness of the drugs for attacking cancers is not consistent with any existing scientific literature. I am sure it is possible to make an antioxidant that is so powerful that it could potentially interfere with the drugs’ action on cancer, but with the antioxidants presently in use—and particularly, those that are food-based or are concentrates—there is not much to suggest it is possible to interfere in this way. However, when it comes to side-effects, as we see from the studies above, there is a demonstrable protective effect on normal cells and tissues as well as a clinically relevant reduction in side-effects.

We also know that a tremendous amount of the toxicity that occurs with chemotherapy is the result of oxidative stress, and if we reduce this oxidative stress, patients will not only tolerate treatments better, but the logic and the data show that patients do respond better to these treatments. I do not believe that antioxidants have much of a chance of interfering, a position supported by the literature.

**JH:** Is there any one recent study that stands out in your mind that you are particularly excited about and that supports your view?

**KIB:** There was a prospective cohort study by Nechuta et al., with a title: "Vitamin Supplement Used During Breast Cancer Treatment and Survival." In this study, researchers determined which patients in their study group used or did not use supplemental antioxidants in the first 6 months after breast-cancer diagnosis and during cancer treatment. The outcomes evaluated were total mortality and recurrence. There were nearly 5000 women, between ages 20 and 75, from Shanghai, China, who had invasive breast cancer and researchers studied these women between March 2002 and April 2006. Vitamin use shortly after breast-cancer diagnosis, including during chemotherapy, was associated with a rather dramatic reduction in mortality and recurrence risk. The researchers commented: “Our results do not support the current recommendation that breast cancer patients should avoid supplements.”

It is important to note that there is one item that the researchers included about this issue with respect to radiotherapy: While the reduced mortality was found when the women used chemotherapy with antioxidants, antioxidants had no
It is important to note there is no research to date suggesting that antioxidants cause by antioxidants. Still, even in a case such as this, it is important to not simply give advice but to actually provide or refer patients to hands-on training. We must be willing to teach and equip our patients to follow the recommendations that we encourage. Because of the complexities of a cancer diagnosis, I believe every patient deserves a comprehensive individualized integrative program [see About the Block Center for Integrative Cancer Treatment].

**JH: What advice do you offer to oncologists and primary-care physicians who are struggling with these issues?**

**KIB:** One has to review the literature, and, when possible, look at meta-analyses and systematic reviews. Physicians, in particular, should be better than the lay public at recommending antioxidant use.

**JH: What do you recommend to patients who have cancer regarding antioxidant use?**

**KIB:** In my opinion, along with advising a network approach to whole plant–based antioxidants, it is very important that patients build on a solid foundation—one that includes a healthy lifestyle and a nutritionally sound, phytochemically rich diet that includes whole foods, whole cereal grains, legumes, soy, a wide selection of fruits and vegetables—preferably organic—possibly the addition of coldwater fish, and mostly plant-based proteins.

We need a comprehensive understanding of what is going on with patients who have cancer, which along with conventional workups and routine evaluations, will ideally include molecular, biochemical, nutritional and lifestyle profiles. This allows our medical team to individualize treatment to each patient’s unique needs. Clinicians need to ask patients about their physical fitness, sleep patterns, stressors, and dietary habits. Then, it is important to not simply give advice but to actually provide or refer patients to hands-on training. We must be willing to teach and equip our patients to follow the recommendations that we encourage. Because of the complexities of a cancer diagnosis, I believe every patient deserves a comprehensive individualized integrative program [see About the Block Center for Integrative Cancer Treatment].

**JH: What advise do you offer to oncologists and primary-care physicians who are struggling with these issues?**

**KIB:** One has to review the literature, and, when possible, look at meta-analyses and systematic reviews. Physicians, in particular, should be better than the lay public at avoiding the trappings of headlines. While voices against the use of antioxidants and natural compounds with conventional therapies get louder, one has to realize that these voices are not necessarily being driven by science, or at least not by good science. Of course, this is true for both sides of the supplement debate. I appreciate physicians who are trying to start from the perspective of “do no harm.” Many physicians will say: “Well, I do not want to do that (use antioxidants with chemotherapy patients) because it is really not proven yet.” But, if one is going to discuss “doing no harm,” then one must also recognize that patients are receiving conventional therapies that can have very serious and sometimes long-term side effects that can significantly make an impact on QoL.

So, as one evaluates natural products or any integrative treatment strategy appropriately, one needs to be sensitive to the risk–benefit ratio.

Now, let me throw in one caveat: This is all very applicable for patients with advanced disease. However, in the few cancers—very few, unfortunately—for which chemotherapy treatments have been markedly successful (such as Hodgkin’s disease), one could make a fair argument that a more-conservative approach that doesn’t include an aggressive antioxidant regimen might be appropriate. This approach would be taken in order to avoid even the remote possibility of interference caused by antioxidants. Still, even in a case such as this, it is important to note there is no research to date suggesting that such interference would exist or that an antioxidant regimen would be problematic. Similar conservative thinking could be applied reasonably to curable early stage disease as well. But, we must keep in mind that this is not true for the vast majority of patients who have cancer—they, unfortunately, are facing more-advanced disease where assistance with antioxidants to improve treatment tolerance also provides the potential for better outcomes.

**JH: Do you have any final comments?**

**KIB:** In summary, antioxidants are not “magic bullets.” They are necessary in terms of laying a solid health foundation to prevent and combat illness. As I have said in the past, a supplement program should be an enhancer to a healthy diet—not a substitute for a healthy diet. It is also important to remember that an unhealthy diet can sabotage even the best supplement program. When used with knowledge and caution as part of a full integrative treatment program for patients battling cancer or hoping to prevent a recurrence, I do believe selective supplement regimens, tailored to each patient’s clinical, biochemical and molecular needs, can be of considerable value. In addition, it is important to be sure to review supplements for adverse interactions with the medications one may be prescribing.

In my experience—and what I believe the scientific literature says today—it is unwise to utilize aggressive conventional treatments without, at the same time, providing personalized programs based on objective assessments that protect patients from the potential injury that conventional drugs and treatment can cause. In time we will learn more, and while I have my hypothesis of where we will be a decade from now, one can only utilize the best understanding of our research and science as it stands today.


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