Dr. David Blask, MD, PhD. Courtesy of Tulane University

Chronobiology, Circadian Rhythm Disruption, and Melatonin Part 3

One of the most fascinating plenary sessions at the 2011 Society for Integrative Oncology conference was "Circadian Disruption and Cancer," shedding light on innovative research for promising new cancer therapies. Research from the past 30 years shows that both cancer cells and normal cells have their own circadian rhythms, and when chemotherapy and tumor resections are timed properly, there are less serious side effects, with greater efficacy and significantly longer survival rates.[1,2,3] This work has significant implications for the practice of oncology; while currently practiced by cutting-edge physicians and oncologists, it is still relatively unknown in mainstream oncology.

By **Claudette Baker,** Dipl OM (NCCAOM), LAc

Claudette Baker, Dipl OM (NCCAOM), LAc, president emeritus AAAOM (1996-8) and ILaaom (Illinois) (94-97 & 2002-5), has been practicing Oriental medicine with a focus on oncology since 1985. She is the founder/medical director of the Glenview Healing Arts Center. A pioneer and leader in the AOM profession nationally and locally, Ms. Baker has worked to incorporate Oriental medicine into the Illinois and U.S. health care delivery system, taught Chinese herbal medicine for oncology, is an SIO member, and is currently the chairperson of the State of Illinois Board of Acupuncture.
cb@claudettebaker.com www.claudettebaker.com

For the past three decades, medical oncologist William Hrushesky, MD has been a pioneer in the emerging field of chronotherapy (the study of the time structure of all living things). He holds several patents related to chronotherapy. Before his retirement, Dr. Hrushesky was research director at Dorn Veterans Affairs Medical Center and professor at the University of South Carolina school of Medicine and the Norma J. Arnold School of Public Health. His presentation, "In Cancer as All Else: Timing is Everything," discussed evidence about the intersection of time and biology and how this intersection affects the host-cancer balance. He illustrated this across multiple frequency ranges, i.e., the circadian frame of reference, the menstrual cycle, and seasonal host-cancer balance. His latest research indicates that sunspot cycles may have an effect on human physiology and the host/cancer balance.[4]

Dr. Hrushesky presented a first-of-its-kind chronotherapy study showing how human ovarian cancer proliferation, cytotoxic chemotherapy, toxicity, and efficacy as well as patient survival all depend on the specific time of day that two particular drugs are given to treat this disease. In this study inter-abdominal lavage fluid

was removed via catheter placement to identify the cells from 35 post-surgical patients with advanced ovarian cancer. It was found that each day both the normal mesothelial cells and the cancer cells proliferated in an organized manner in each individual and that there was both a personal rhythm and a prominent group rhythm to this process.

The group rhythm revealed that the DNA synthetic capacity of the ovarian cancer cells peaked in the morning hours and the mesothelial (benign) cell DNA synthesis peaked in the evening hours—essentially at opposite times of the day. Because human ovarian cancer cells proliferate most aggressively in the morning hours, this provides the opportunity for optimal timing of anti-proliferative chemotherapy administration. This includes all the agents that focus on any target of proliferation during the time when there is high tumor cell vulnerability and low normal tissue toxicity.[5]

excretion levels as well as those from 19 healthy young women volunteers were measured and compared.

The data showed that the patient's levels were much higher than the volunteers' levels. (People with metastatic cancer produce higher quantities of cortisol; however, the cortisol may be excreted at the appropriate time throughout the 24-hour cycle.) When her and the volunteers' levels were superimposed in a graph, the changes in cortisol excretion throughout the day for both the patient and the 19 women indicated that her body was keeping perfect circadian organization even with metastatic cancer.

Dr. Hrushesky then questioned whether her cancer was keeping a circadian rhythm and decided to keep track of her symptoms. She had very few symptoms upon waking in the morning, but by noon the lesions began itching, and by early evening, the itching was severe and painful. The same pattern occurred each day. Every

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In a subsequent study conducted by Dr. Hrusheky et al. at the University of Minnesota General Clinic Research Center's Metabolic Unit, patients were randomly selected for either Group A (adriamycin at 6 AM and cisplatin at 6 PM) or Group B (cisplatin at 6 AM, adriamycin at 6 PM). The drugs, doses, order of the drugs, and the interval between the doses were the same in both groups, varying only in the time of day that the drugs were administered.

Toxicity, dosage modifications, serious complications (transfusions, infections, bleeding) and ultimately patient survival were examined. It was found that the patients in Group A who received the anti-proliferative agent in the morning hours, when the cancer cells were most vulnerable, had far fewer modifications of doses and dose reductions. Even though **Group A had much higher doses because** they had fewer modifications, **they had less than half** the serious complications as did Group B. In addition, Group A's treatment timing resulted in a **fourfold higher 5 year survival rate than patients in Group B** who received the drugs at the opposite time of day when the normal cells were more vulnerable to the anti-proliferative agent. This data shows highly significant differences.[6]

Dr. Hrushesky also presented the case of a female dairy farmer who came to the research center presenting with metastatic epidermoid carcinoma originating from the auricle of her ear. She had 250-300 metastases but was feeling fairly well. Biopsies of her normal skin and the tumors were taken to determine if there was a circadian organization to the actual mitotic index cellular proliferation of her cancer and of her normal skin. Her urinary cortisol

three to four hours the patient's healthy skin and two of the tumor nodules were biopsied. Results indicated that proliferation in the normal skin had a normal circadian rhythm and that normal DNA synthesis was turned off during the night just before awakening.

This exact process also happened in the cancer cells, indicating that not only does the body remain coordinated, but the cancer remains coordinated as well. Because radiation therapy is important in treating squamous (epedermoid) cell cancers, if this woman had been treated with radiation in the late afternoon, there would most likely be a tremendous therapeutic advantage since many more cancer cells would be undergoing mitosis at that time, and therefore more vulnerable to the radiation.[7]

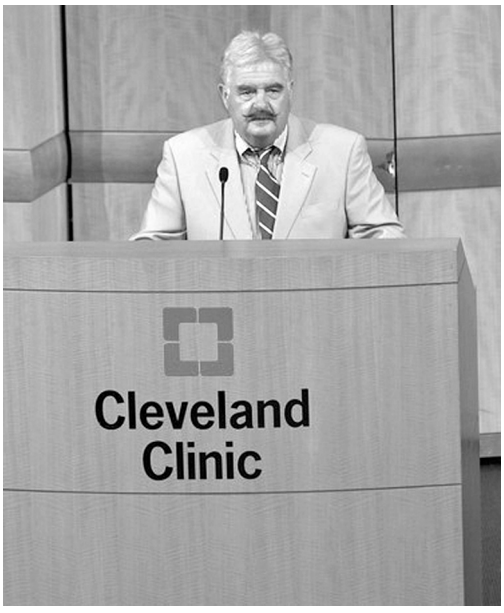
One of the most important points Dr. Hrushesky emphasized was that "all symptoms, including pain, have a circadian rhythm, and if one simply takes a careful temporal history of the patients symptoms, it will become clear when to apply temporal pharmacology. You do not want to 'snow' someone in the first 6 hours of the patient's day when they are feeling best and are able to eat and move about most effectively without pain. Pharmaceuticals should be given when they are most needed, and that can be determined by taking a careful temporal history."

As Dr. Hrushesky and his colleagues proceeded to study kidney cancer and breast cancer, in addition to colorectal cancer with metastatic disease to the liver, they found the same basic principals to be true about each of these diseases.[8,9,10] Both normal human tissue and human cancers keep circadian time, and tumor prognostic indicator values vary predictably with the time of day of their

sampling. Anti-cancer therapeutic targets are reproducibly and coordinately expressed within human cancers (in living human beings) at specific times of day. Optimal circadian timing of cell proliferation-targeted cancer therapies have improved cancer patient outcomes, and clock genes, since they effectively gate cancer proliferation, represent novel therapeutic targets.[11,12]

Dr. Hrushesky remarked, "The current practice of medical and gynecologic oncology disregards the timing of cytotoxic drug administration for ovarian cancer. This study shows that circadian timing of cytotoxic chemotherapy significantly affects the degree of damage to normal tissues, i.e., bone marrow, gut lining, platelet counts, and all of the serious complications of chemotherapy. It also affects normal tissue tolerance, as well as the anti-cancer activity, and subsequent survival of advanced ovarian cancer patients so that four fold or more survived if they received the drugs at the right time of day when they were least damaging to the patient and most effective."

Having spent decades studying how menstrual cycle hormones affect breast cancer in both rats and humans, Dr. Hrushesky et al. found that node positive breast cancer patients resected during the early luteal phase of the cycle a**re CURED by that resection 25% more frequently than if the resection is done at the follicular phase.**[13] This finding has been confirmed in more than a dozen retrospective studies and one prospective study. Based on this work, post-resection breast cancer metastatic spread depends upon what point in the fertility cycle the cancer is resected. Prognostic molecular markers predictive of breast cancer outcome and therapeutic response (ER/PR/Her2/MI/VEGF/bFGF) change meaningfully and predictably during each fertility cycle. Dr. Hrushesky and his colleagues believe that these time structures in host/cancer balance can be used to improve breast cancer outcomes by optimally timing preventive, diagnostic, and therapeutic strategies within the menstrual cycle. Understanding the mechanisms of these time structures will permit the development of peri-surgical neoadjuvant therapies to prevent post-resection breast cancer spread.[14,15]



Dr William Hrushesky, MD. Photo courtesy of the Helen Moss Foundation.

"Looking at the data from their numerous mouse breast cancer studies he and his colleagues found that the cancer growth rates were five to six fold during two annual peaks (January and September)."

Dr. Hrusheky reported his great surprise at the aggressive attacks and fury directed at him after he published his first studies suggesting that women should be resected at a specific time in their menstrual cycle. However, many such studies have been repeated over the years and support his findings. He said, "there is a two to threefold greater difference in young women with positive nodes regarding whether or not they receive adjuvant chemotherapy. EVERY woman in the U.S. with positive nodes receives adjuvant chemotherapy, and NO woman in the United States is resected at the appropriate time in her cycle unless it is *purely by accident.*"

He also found that tumors have seasonality, with two peak seasons for cancer. Looking at the data from their numerous mouse breast cancer studies he and his colleagues found that the cancer growth rates were five to six fold during two annual peaks (January and September). When resections were done, they saw that the curability was modulated substantially by seasonality—these findings occurred regardless whether it was a small, early, or late stage tumor. These are huge differences of great statistical significance. [16]

Along with human breast cancer incidence, other diseases also have two peaks each year (spring and fall); however, when examined in depth, conflicting evidence of seasonality was found. Candidate mechanisms for the seasonality of cancer include: seasonal sun exposure (vitamin D), seasonal night length (melatonin), seasonal dietary patterns, and seasonal activity differences. Based on this data, Dr. Hrushesky encouraged one of his top graduate students to perform a seasonal analysis by looking at the incidence of breast cancer diagnosis data worldwide. Data was collected across 2 to 53 years from 67 cancer registries in 64 geographic locations worldwide, representing 2.9 million women with breast cancer.[17]

The data confirmed that the incidence of breast cancer is greater away from the equator because seasonality is modulated by daylight, i.e., "white nights" when the sun shines almost continually during the summer months in the far northern and southern hemispheres. The amplitude of the annual rhythm has an exponential relationship; virtually all breast cancers occur during the spring and the fall near the Arctic Circle, while the seasonality is minimal away from the Arctic Circle, with incidence increasing up to fourfold in populations located away from the Equator.[18]

According to Dr. Keith Block, chair of the 2011 SIO Conference and medical director of a center that delivers chronomodulated chemotherapy, "To put Dr. Hrushesky's work in perspective, a literature review will demonstrate that from the 1990s to the present, the best expected improvements in median survivals for new drugs is at or less than 4.5 months. The scientific data surrounding chronomudulation ranges from a 20% to a 400% improvement in median survivals. This suggests that the timing of chemotherapy

Dr. Keith Block, chair of the 2011 SIO Conference

infusions may be as or more important than the drug selection, making this one of the most significant breakthroughs in medical oncology in the past forty years. Yet the attention, interest, and support to pursue this important breakthrough in both the research and clinical settings is nearly nonexistent." [An article discussing the current practice of circadian therapy by Dr. Block is "Making Circadian Cancer Therapy Practical," Block K et al., *Integrative Cancer Therapies*, 2009, 8(4)371-386)].

Dr. David Blask, MD, PhD, professor at Tulane University School of Medicine and head of the Laboratory for Neuroendocrine Oncology in the Department of Structural and Cellular Biology, presented a fascinating and provocative paper, "Circadian Disruption of the Nocturnal Melatonin Signal, Its Impact on Human Breast Cancer Growth and Metabolism: Implications for Treatment and Prevention in Integrative Oncology." A world-renowned expert who has published over 300 journal articles, reviews, chapters, and abstracts on the negative health implications and increased cancer risk associated with melatonin suppression due to exposure to light at night (LAN), Dr. Blask's research has focused on the circadian control and therapeutics of cancer by melatonin. It has also focused on the consequences of the circadian disruption of melatonin production by LAN and cancer risk.

In addition to his interest in the circadian system—particularly its relationship to melatonin, breast cancer, and prostate cancer growth and metabolism—he is studying the relationship of melatonin as a "representative" of the environmental light/dark cycle at the biochemical level, where the circadian system regulates the timing of cancer metabolism and proliferation. He has also studied several environmental factors: how light at night disrupts the circadian rhythm, how the implications of this timing are cued by melatonin, and how it may impact the timing of chemotherapy.

Dr. Blask, having served as a member of a working group for the International Agency for Cancer Research of the World Health Organization, reported that "the risk of developing breast cancer is up to five times higher in industrialized nations than in underdeveloped countries,[19,20] and the WHO has *determined that night shift work is a probable carcinogen.*"[21] Light at night causes melatonin to be suppressed. The brighter the light, (especially blue/white) the greater the suppression that results in tumor growth rates increasing dramatically—three to four times greater—than when melatonin is present.

One leading hypothesis that may explain this is the ability of LAN to disrupt melatonin rhythm in nightshift workers, resulting in "broken timing." Breast cancers are very sensitive to melatonin; these tumors show rhythms of proliferation and metabolism that are cued by the melatonin signal, providing melatonin is there.[22,23] In epidemiological studies it has been reported that both female and male night shift workers are at a significantly increased risk of developing various malignancies including breast,[24, 25, 26, 27] colon,[28] prostate,[29] and endometrial cancer.[30]

A short description of this science: The suprachiasmatic nucleus (SCN) is the central biological clock that drives the timing of melatonin production during the night. It is active during the day and inactive during the night. Light through the retina, especially blue light during the day, is necessary for setting the rhythms of the SCN (circadian rhythm). The pineal gland produces melatonin, and the light-dark cycle synchronizes that timing through the eyes. All humans produce melatonin in a cyclic peaking manner, coincident with sleep, which is not required for melatonin production. Darkness, however, is an absolute requirement; melatonin is a "hormone of darkness."[31]

Humans have evolved to require total darkness at night, which allows melatonin production; however, if light at night is introduced (even with closed eyes), melatonin's peak production is suppressed within seconds and stays suppressed as long as there is light. Melatonin production peaks at 2-3 AM, when cortisol and the basal body temperature are at their lowest. Blue light at night, transcontinental jet travel, and space flight are detrimental to the circadian rhythm and to the production of melatonin, which is secreted into all body fluids, especially the cerebral spinal fluid. Humans should thus not be exposed to computer screens, cell phones, and florescent lights at night; however, melatonin is minimally sensitive to yellow-amber and not at all reactive to red light.[32]

Melatonin has a variety of mechanisms for inhibiting cancer growth. Blask and his research team have focused on the direct anti-proliferative effects of melatonin, stating that there are a number of peripheral oscillators called "clock" and "clock-related genes" which exist in both normal and cancer cells that may be coordinated through central mechanisms conveyed through the SCN via melatonin, core body temperature rhythms, possibly cortisol, and other as yet unknown processes.[33,34,35]

Melatonin also has an important interaction with another environmental factor called linoleic acid (LA). As the most prevalent essential polyunsaturated fatty acid in the Western diet, LA is a potent promoter of human tumorigenesis. According to Dr. Blask, Americans ingest too much LA. Cancer cells thrive in the presence of LA, not only as an energy source but also as a signaling molecule for cancer growth.[36] Linoleic acid is a potent promoter of human tumorigenesis because it is taken up by cancer cells and converted to the molecule 13-HODE (13-hydroxyoctadecadienoic acid) which ramps up the cancer activity and feeds back on the epidermal growth factor pathway as well as the insulin-like growth factor-1 (IGF1) pathway through MAPK and PI3K/AKT. Both pathways are of great interest for developing new targeted-therapies. Ultimately 13-HODE will increase the proliferative response.

Recent unpublished evidence from Dr. Blask's lab suggests that LA also stimulates glucose metabolism, specifically the Warburg effect (also known as aerobic glycolosis)[37,38,39] which is a very hot topic in cancer metabolism today.[40] Melatonin appears to down-regulate the bioenergetics of cancer growth by ramping down the Warburg effect and the resulting cascade towards tumor proliferation.

One of the primary ways melatonin inhibits tumor growth at certain stages in the circadian cycle is by suppressing the activity of epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK). This effect occurs via the melatonin-receptor-mediated blockade of tumor LA uptake and its conversion to 13-HODE, which normally activates EGFR/MAPK mitogenic signaling. This is a potentially unifying model for melatonin's chronobiological inhibitory regulation of cancer growth in maintaining the host-cancer balance. It is also the first biological explanation of how melatonin enhances the efficacy and reduces the toxicity of chemotherapy and radiotherapy in cancer patients.[41]

There are a number of pathways that melatonin affects; the list grows as the research accumulates. The proposed mechanisms of melatonin's oncostatic effects are: direct anti-proliferative and/or pro-apoptotic effects, indirect effects via neuroendocrine suppression of reproductive hormone production, antioxidant/free radical scavenging effects, and enhancement of immune activity.[42,43]

To demonstrate how the presence or absence of melatonin may affect human breast cancer, Dr. Blask's group used a specialized system called a "tissue isolated tumor model" where human breast cancers are grown in rats. The cancer is estrogen and progesterone receptor negative as well as HER2 NEU negative. This is known as "triple negative" cancer, which is a grade 3, poorly-differentiated infiltrating ductal carcinoma. They cannulate a single vessel that supplies the tumor in the rat and a single vein that drains the tumor, preventing human blood from circulating through the rat. In effect, this creates an isolated tumor-support system.

Blood samples are then drawn from healthy, pre-menopausal female medical student volunteers during the day when their melatonin levels are low, during the night when their melatonin levels are high, and then after exposure to light at night. The researchers perfused, or supplied, the tumors with one of the three types of human blood samples via the cannula directly to the human tumor. They found that when the tumors were perfused with either the daytime blood or the night time blood that was exposed to light for 90 minutes, melatonin production was suppressed and LA uptake was very high, allowing the tumors to proliferate. However, when they perfused, those same tumors with the melatonin-rich blood that was collected during the dark night, a very dramatic decrease in the uptake of LA occurred.[44]

Tumor metabolism and proliferation have thus shown to be impacted by at least three of the following known mechanisms, and each is affected by the presence or absence of melatonin: 1) Linoleic acid uptake by tumors and its conversion to 13-HODE (which causes the stimulatory effect),[45] 2) The Warburg effect, where there is an increase of glucose uptake and lactic acid production by the tumors,[46] and 3) Cell division in the tumors indicated by the incorporation of tritiated thymidine (deoxyribosylthymine) into DNA, which is an index of how rapidly the cells in the tumors are dividing. In response to these metabolic signals, the cancer cells have a very dramatic rhythm of DNA replication during the day, which is suppressed in the presence of melatonin during the night.[47]

When there is an intact light/dark cycle with an intact melatonin signal, all of these activities rise during the daytime, peak before the lights go off, and then drop dramatically during the night when melatonin is high. In the absence of melatonin due to light at night, the melatonin rhythm is lost, and these tumors metabolize and proliferate at a very high rate 24 hours a day, showing that melatonin is driving this rhythm.[48] [Dr. Blask has published an in-depth report with references on this topic.[49]]

Dr. Blask's team theorized that melatonin supplementation might be effective in controlling tumor activity. Using the same rat tumor model, they took blood from healthy volunteers during the day when melatonin was low and infused the tumors. Tumor activity, as expected, was high. Commercially available melatonin was given to the human subjects during the day; blood was collected an hour later and perfused into the tumors. The activity of the tumors was dramatically reduced with the melatonin-supplemented blood.[50]

In his closing remarks, Dr. Blask said that he and his colleagues "believe that melatonin is the first soluble, nocturnal, circadian, anti-cancer agent to be demonstrated in humans that regulates the timing of the circadian rhythms of both the metabolism and proliferation in human breast cancer and other cancers as well. Individuals who are circadian disrupted, i.e., cancer patients and anyone routinely subjected to light at night, may be losing the advantage of this naturally-produced melatonin signal that seems to give us some modicum of protection against the growth progression of cancer. Melatonin supplementation might be of some consideration for therapy and prevention of breast cancer."

Based on both Dr. Hrushesky and Dr. Blask's research and results, it is hoped that chronotherapy will become one of the standards of care for oncology in the near future. Despite the quality and breadth of the research being done in these areas, it must be noted that the type of resistance that providers of integrative oncology are facing from their own mainstream colleagues is akin to the strong resistance that acupuncture and Oriental medicine (AOM) has faced in the United States. The barriers to acupuncture are finally being removed at an increasingly rapid pace, thanks to the "gold standard" quality research that has been conducted over the past 10 years. This being said, the resistance to herbal medicine and nutraceuticals is still fairly strong.

These SIO reports are an attempt to prompt thoughtful discussions about the ways in which AOM and integrative oncology practitioners can work in a fully integrated way. The goal is to have AOM practitioners provide care on the same team with our Western counterparts and participate in patient treatment strategies in every cancer center in this country to provide complementary, holistic, non-toxic and individualized treatments for patients suffering with cancer.

The author thanks Dr. Block for bringing some of the most talented doctors and researchers from around the world to share their knowledge and to advance the field of Integrative Oncology. They have created less toxic, more effective, and promising therapies for cancer treatment. Thanks also to Dr. Stan Gerson, MD for encouraging all SIO conference attendees to "get the word out" about integrative oncology, Helen Moss for her role in bringing so many communities together as well as her Foundation's financial support, and to all the brilliant, talented, and deeply dedicated

researchers and medical providers who are building and practicing the field of integrative oncology. Their ground-breaking work is truly making a difference in many lives.

Helen Moss and Stan Gerson, MD.
Photo courtesy of the Helen Moss Foundation.

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