MMJ

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Michigan Medical Journal
is a journal produced annually by University of Michigan medical students. The aim of the Journal is to provide a forum for student achievements in medicine and literature. The objectives of the Journal are to provide an available medium for students to present their work, to develop writing and analytical skills, to promote awareness of student contributions to medicine and literature, to provide education in the field of medicine, and to develop valuable leadership and editorial skills.

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COVER ART:

Underwater photograph of juvenile Slender crabs (*Cancer gracilis)*, living within the Pelagia jellyfish. Photo by Joseph W. Dougherty.

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Letter from the Editor

As an eight-year-old child, I told my sisters that my dream was to cure cancer. While my oldest sister pretended to dissect broccoli heads in her quest to be a neurosurgeon (she is now a cardiologist) and my other sister cracked jokes about bowel movements (she is now on her path to becoming a gastroenterologist), I contemplated what my role would be in the future of cancer. I knew that a few of my great aunts had been stricken with breast cancer and that there were several other parts of the body that could be afflicted. It was much later that I had the opportunity to learn about cancer from both a scientific and humanistic perspective, during college and medical school, respectively.

As an undergraduate student, I decided to work in a cancer biology lab after reading a captivating *Newsweek* article about p53, a tumor suppressor gene that is mutated in several types of cancers. I was taken under the wing of a now tenured faculty member who took time at the start of his post-doc career to teach me how to grow cell lines in Petri dishes, how to stain them with immunofluorescence, how to talk to them, and how to nourish them even though they seemed to need no nourishment as they grew on top of and around one another without respect for boundaries. I distinctly remember peering under the microscope at HeLa cells, the immortalized cells of Henrietta Lacks, growing in odd-looking scary bunches. I thought to myself: I am looking at the killer, what thousands of people die from, the cells that grow out of control by dividing in the absence of brakes on their reproduction machinery.

In the first half of medical school, I learned about various cancers from an academic point of view, delving into the pathophysiology and treatment that is unique to various types of cancers. In the second half of medical school, I started to learn what it meant to people to have cancer, to their doctors, and to their families. Over the past year I have had the privilege of participating in the care of patients who were diagnosed with breast cancer, melanoma, squamous cell carcinoma of the skin, non-Hodgkin's lymphoma, multiple myeloma, colon cancer, prostate cancer, esophageal cancer, ovarian cancer, endometrial cancer, and pancreatic cancer. My experiences with them were invaluable, far more than any time spent with oncology textbooks.

This journal is meant to show that as medical students and students of other health professions, our experiences with cancer and the issues related to life-threatening disease are more than the immortalized stories of patients carved into our brains. It is meant to warm your heart, to make you cry, to provoke anger, and to offer hope. It is meant to show that sometimes surgery, radiation, chemotherapy, and the promise of vaccines and future technology cannot begin to put the salve on the deep and far-reaching wound that occurs when cancer strikes. It is meant to show you that while medical advances and doctors can be amazing and wonderful, the medical system is not perfect and that sometimes a patient will die alone, sometimes doctors aren't the way they "should" be.

As it is impossible to cover all aspects of cancer, or even several of the different types of cancers that exist, the pieces in this journal were chosen to reflect various aspects of cancer as it intersects with human life. These selections begin many discussions; we hope that they will stir you to think further about issues surrounding cancer and other serious life-altering conditions, such as people writing through their experiences and preserving a family record, the strength of patient networks that share information, how the patient can be the medical student's best teacher, how students teach each other, how quality of life is relative, and how mourning can bring life to death.

Chithra R. Perumalswami
Editor-in-Chief

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Flight

by Noelle Goodin

Heroes

At 9:00 a.m. on February 1st, 2003, the space shuttle Columbia exploded in the sky.

The nation and world paused in disbelief as the streak of bright flame cut the pristine blue morning. Memories of the Challenger flickered. Younger generations, raised alongside space flight, paused to reconsider the constants in their lives. A population jaded by the terrors of September 11 looked up — our mighty shuttle had fallen.

In a world enveloped in layers of social and political ambiguity, technology is our scaffold, our grip on all things other, untouchable, unknowable. With space, especially, we revel in the communion of science and magic — fiction turned fact, other made own. From our lowly and familiar world, the mysterious, brilliant stars beckon seductively, spinning their intricate circles above. We recognize and long for the romance of space; primal awe, handed down star-watcher to worshipper, fades slowly. Space travel becomes somewhat of an existential miracle, pulling us from our meager and chaotic lives into a brilliant, expansive, and universal Greatness. Astronauts become symbols of everyman's potential to touch majesty. They escape planet earth, turn around, and see the world spread out small beneath their feet.

They walk in air, fly without wings.

But on February 1st, they exploded in the sky.

And when our best attempts at connecting with the brilliance of space fail and when our heroes who touch the sky die, we can't help but realize our inescapable mortality and our overwhelming lack of control. The romance falters. Our understanding is unwound, our pretense stripped. We shudder.

At least I shuddered. My jaded view of the world and its unpredictability was overcome when I learned about the shuttle through my friend Cathy. Cathy lived in Texas where the shuttle's failure was tangible through the pieces that fell to earth. Only weeks before the explosion, Cathy's roommate, a 23-year-old only child, had lost her remaining parent. In a darkly cosmic twist of fate, Cathy's mother had died of breast cancer around the time of the 1986 Challenger explosion; Cathy was seven. Seventeen years later, with a suddenly very alone and needy roommate, a shuttle falling to pieces around her, and a child's memory of a mother's death, Cathy told me of the explosion. She said, "Every time I turn around someone next to me is crying, and someone else is dead. The year the Challenger crashed was the same year my mom died... I can remember feeling the exact way I feel now, just being a lot shorter."

Friends

I once had a friend tell me that when bad things happen, it's better to not think about them, to just move on and forget about whatever had happened. He then quoted a scientific study, which found that victims of sexual assault who never talked about their trauma were 'better adjusted' than those who were persuaded to discuss their abuse. This friend is considering becoming a psychiatrist.

Undeniably, there are times when emotional distance and mental security are necessary. There are times when over-replaying part of a life can be destructive. To simply ignore life because of its uncertainties and potential for trauma, however, to separate yourself from the joys and sorrows of the people and the world around you — could there be a *worse* way to live? A few years ago fate pulled me close to death, but for some reason let go. This experience will always be a part of me, but for that I am glad.

Photo by Joseph W. Doherty

It was dusk. I was driving with a friend across a smooth Arkansas interstate. Returning from Alaska and with only six hours of driving ahead, we both felt home and safe. At a turn in the road, however, one of the tires — checked only days before — exploded without warning. The vehicle couldn't be controlled, much less turned, and it veered over into the median where it began to flip. On first impact, the door and window slammed in around me, briefly knocking me unconscious. The vehicle continued to roll, tumbling across the median and into fast, oncoming rush-hour traffic, where it came to rest. An 18-wheeler semi-truck happened to be the closest oncoming vehicle.

Both my friend and I were wearing seatbelts or else we'd certainly have been dead already. But even wearing seatbelts wasn't enough — we were lucky.

Eighteen wheels left approximately 18 feet of skid marks, a truly precious stretch of black across the highway and not our parents' lives. Thank God the driver was paying attention and it wasn't a few hours later and darker. Thank God we didn't roll into any other vehicles — and we weren't crossing a bridge or alongside a cliff. Considering the circumstances, things ended up *very* well. My friend had significant knee damage but was discharged almost immediately. I spent only a few days in an intensive care unit with a mild concussion and amnesia, followed by a few months of physical rehabilitation. Not bad compared to instant death on the interstate. By far, the most challenging aspect of recovery was working through the mental and emotional impact of traveling briefly alongside that tangential fate.

A friend of mine was driving down the interstate with the love of his life when their vehicle rolled over. They were also on their way home after a roadtrip. They were both wearing seatbelts, as well, or else they wouldn't have lived through the accident. And in some ways they were really lucky — they rolled over into the grassy shoulder, away from traffic. My friend, riding passenger, was barely hurt; he spent a couple of nights in the hospital and was discharged. The girl, however, who had been knocked unconscious during the roll, didn't regain consciousness after the accident as I did. She presented with unexplainably low blood pressure and was taken into surgery to check for cardiac tamponade, deadly hemorrhage into the space surrounding her heart. During surgery, no bleeding was found, but she experienced fatal arrhythmia and died.

My friend remembers finding one of her boots yards away from where the car landed. On the other side of a hill. Still laced up. He wonders how it could have come off so easily and been thrown so far.

Distance

In 1988, I watched the space shuttle Discovery take off in Cape Canaveral, Florida. We came in throngs, haunted voyeurs of technology and magic. This was the first launch since the Challenger.

We gathered en masse around despondent metal bleachers positioned as though by accident, held in with salty weeds, sandy water, and empty horseshoe-crab husks. If you gazed out across the water, though — peered intently through the heat-hazed central Florida swamp — you would realize that a significantly large metal platform was present on the other side. Today, it held an enormous ship, caped in the blinding glare of reflected sun, nose aimed to sky. *Wow*. Surrounded on all sides by brown cattails and flat sandy marshes, the otherworldliness of the shuttle was striking. Even more striking was that when the smoke and fire first poured out of the rockets, blooming thickly, subserviently, around their brilliant metal creator — there was no sound.

The crowd was hushed, nervous, and hopeful. Breathless. Across the river the shuttle expelled bright orange heat. Power. We expected thunder to accompany the visual excess, yet there was no synchronous blast. No roar. Nothing. The sound took a full six seconds longer to make its way through the heavy sky, across the river, and to our expectant ears miles away. It was in that soundless moment that I was most struck by what I was witnessing. Would I ever again so clearly see the significance of time, space, distance, and raw man-made power? Here, space and distance were so real that light and sound traveled through them as seemingly unrelated entities, this *in spite of* shared birthright — the unforgettable technological beast across the haze. These same divine entities, Space and Distance, were what would eventually be ignored, though — overcome in the flight of that bizarre and virile star-gazer. A flight that would carry it into an entirely different realm where there would be *no* sound! A realm which the Challenger never reached. A realm from which the Columbia never returned.

I couldn't help remembering this launch when I heard about Columbia's explosion. Do we truly understand space, time, and distance, or are we just pretending — creating meaningful stories, victories and geniuses, as

another way of escaping our lives grounded on the planet earth — as an easier way of touching the stars? Perhaps the Discovery had actually been lifted off the earth by our post-Challenger hopes, prayers, and humility. And maybe Columbia fell, pulled down by our forgetfulness and vanity.

I wondered if the first people to see the Columbia shuttle explode were struck by the silence. A silence which would have lasted even longer than the silence in the swamp. A soundless explosion in the sky, echoed only later by the terrifying roar hounding the failed shuttle its long distance back to earth.

Uncertainty

I permanently lost over 12 hours of memory from the concussion I sustained in my roll-over. I don't remember any of the accident, the ride in the ambulance, or my time in the emergency department. I awoke into the quiet, sterile dimness of a pre-dawn hospital room, surrounded by plastic lines, wires, and hoarsely beeping machines. Amnesic, drugged, and groggy, I struggled to re-determine who I was and how I was connected to the situation; I waded through layers of half-realizations and cycling emotions, repetition necessary for my still-reeling neurons to chisel down this new world. Each time I began to understand the significance of my surroundings, I felt an echo of that knowledge — from the last time I had begun to understand. Many of these realizations were stillborn, lacking the vitality necessary to stay above the surface of my mental storm. Again and again, I would become paralyzed with fear, worrying about the friend who had been traveling with me. And each time, I'd feel sharp but rootless echoes of that same terror, as though from a previous life or (worse) some prophetic vision. When someone assured me that my friend was fine — for the hundredth time perhaps — my worry would subside only partially, resounding fear continuing to war against the quieter reverberations of relief. I couldn't help but wonder which truths were more real.

I felt lost, vulnerable, and trapped. A plethora of tubes reached into me, tying me down with plastic and metal; my mind spun circles in the distance. Fortunately the assurances continued to build upon each other, and my understanding traced the right neural pathways, the right way, the right number of times — an ancient spell remembered. The echoes became loud enough to stick, but with an odd multiplicity of experience nonetheless; a shroud of uncertainty covered the undeniably real. Everything looked, felt, and sounded gray, washed out.

Yet I was covered in cuts that would ooze bright red blood or liquid-pearl pus if I shifted too much. My left arm and both legs were swollen to about twice their normal sizes; splatters of blood and disinfectant covered the arm and were dried into my scalp and hair; dark craters adorned my feet and ankles, engine oil stigmata chemically burned into my skin.

If I had been any less drugged or confused, I probably would have gone into shock from the frighteningly unreal state in which I awoke. As it was, I still occasionally locked up, fear and sympathetic drive taking over whenever the drugs and half-made memories faded. There was one thing that rescued me during the bewilderment, though. When I awoke into that pre-dawn, blood-encrusted fog, my dad was beside me holding my hand. I felt shattered, tossed, and adrift, but my daddy was with me so everything was going to be okay.

Even after my memories started to form, I couldn't remember many specifics about the hospital. I have almost no recollection of my many doctors: they were mostly men; they had white coats; one of them signed my discharge. More than that I cannot say. One nurse, however, was permanently etched into my heart. He had a slight build and brown hair, wore green scrubs and a halo. He was sent from heaven to wash my hair.

For over 48 hours, my waist-length hair had been tangled and matted in a half ripped-out bun. Where the door and window had scraped against my scalp, the hair was shorn down. These new spikes emerged raggedly through crusted blood, sweat, and sticky disinfectant, which dripped orange-red down my forehead contrasting with the dark dried blood. I looked a little rough. Godsent, my nurse took it upon himself to clean me up while I sat dazed, uncertain, and silent in my bed. It took over an hour, but the constant tangled pulling finally ended, the itchy, ripped skin quieted. Immediately, I began to feel more *right* — one step closer to who I used to be.

The six-hour ride home from the hospital was another unique experience: pounding head, crescendoing nausea, and syncopated bursts of pain pushed their way through underlying mental cloudiness. Our route allowed us to visit my grandfather, though, a blessed intermission. My grandfather came from generations of farmers, immigrants, and soldiers. When he was eighteen, he went to fight in the Second World War as expected. He was a ground soldier, as were many of his friends, and he watched countless people die — many of whom were his friends. And in this time of life and death, military-made cowards and heroes, the men who

impressed him the most were the doctors — those who were saving, not taking, lives. My grandfather was so affected that, when he returned to the states, he made good use of the GI Bill, becoming a doctor himself. He practiced medicine for over 50 years.

Living In the Stars

No matter how much in charge of our destinies we think we are, no matter how much we long to turn around and see the world spread out for us, it is not to be. This realization, tangible to me when I rub my hand across my scars or feel my shoulder jut up where it's not supposed to, changed me and continues to change me years later. Sometimes I am resentful of how my experience aged me; I regret the innocence that I lost to it. Usually, though, humbled and grateful, I appreciate the tumbling — for allowing me to better understand life and what it means to me, for restoring in me a childlike appreciation for the world, and for granting me better understanding for others experiencing loss, pain, or fear.

Again and again, we tell ourselves stories and create answers in hopes of gaining a sense of control over the world, but the unexpected can still happen and frequently does. We can live as healthily as possible and follow all safety rules but still get cancer or die strapped into our cars. We can follow in the wake of probabilities, best guesses, and standardized treatment guidelines but still lose patients too young, too faultless, and too utterly irreplaceable, needed, and loved to lose. NASA engineers can base decisions on expected outcomes and safety guidelines, but shuttles can still explode. We are on this world and of this world — it isn't small or spread out beneath our feet.

So sometimes we shudder, spinning tightly with the earth around us. But perhaps this is not such a bad thing. Maybe it's even a wonderful thing. Life can be breathtakingly beautiful in a myriad of unexpected ways, and even the terrifying times can teach us and bring us closer together. As for me, I will move on but I won't forget. And I'll strive to carry the romance without the pretense.

I will be a doctor, not a soldier. I will wash the blood off of someone who can't. I will hold someone's hand.

I will believe in technology, but I will put my trust in magic.

Sometimes I will fly among the stars. Sometimes I will fall. Sometimes I will hold my breath and wait in silence.

Chernobyl: A Legacy of Disaster

by Gregory Gurda

Photo by Joseph W. Doherty

The day's forecast called for mild, sunny weather, followed by drenching rain. Overhead, gray sparrows chirped with excitement, gentle wind flirted with sparsely growing trees and cattle grazed leisurely on the fresh green grass — a picture perfect spring morning. Nearby, a gasping concrete colossus produced a continuous stream of clouds, remnants of the water used to cool its scorching core. Within the structure, operators were running a routine, though still experimental, safety protocol. A few human errors and mechanical failures, however, led to quickly rising temperature and pressure in the core reactor, reaching a point where little could be done to avert a catastrophe. Explosions pierced the quiet setting, as fire, smoke and flashing lights bred fear and chaos.

This somewhat embellished scenario describes the initial events of the most serious nuclear accident in history — the April 26th, 1986 meltdown at the Chernobyl power plant in Ukraine. A steam explosion and the fire in the graphite core of the reactor led to a release of over 10^{19} becquerels (Bqs) of radioisotopes, including ^{131}I, ^{90}St, ^{134}Cs and ^{137}Cs.[4] Concentrated radiation spread over large areas of Ukraine, Belarus and Russia. Lower levels seeped into Eastern and Northern Europe, and increased levels of radionuclides were detected throughout the northern hemisphere.[6] Between 10 and 20 million people received significant exposure, with contaminated soil and ground water covering an unexpectedly large area of 150,000 km^2 (59,700 mi^2), due to fallout exacerbated by heavy rainfall.[7] Given the sheer scope of the disaster, it is not surprising that it had serious health and psychosocial repercussions for all of those involved.

The health risks implicated with exposure to radiation can be divided into short and long-term effects. On account of extremely high doses required to produce acute radiation poisoning, the threat of acute onset mortality and morbidity due to the Chernobyl disaster was limited to employees in the plant at the time of the accident and the cleanup workers. Among the workers in the plant and the 300,000 to 600,000 people involved in mitigation activities, several hundred were exposed to whole-body radiation and 134 developed acute radiation sickness, including 28 who died within four months.[4] Long term effects, on the other hand, were somewhat harder to ascertain, and affected all those who received significant exposure due to the fallout. Thus far, the only substantiated long-term consequence of the Chernobyl disaster has been an increase in juvenile papillary carcinoma of the thyroid, especially in Ukraine, Belarus and western Russia. In the decade following the accident, the number of cases of juvenile thyroid cancer in those three countries totaled approximately 1,800, whereas in Belarus alone the incidence of the disease rose from 6 to 583 cases per decade (including an over 32-fold increase in the most contaminated Gomel region).[4] In addition, several studies point to an appreciable increase in childhood leukemia,[6] and there is at least anecdotal evidence of a connection to adult GI tract cancers, neuroblastoma and other forms of thyroid cancer.[5,6] Verifying the association between radiation exposure and the aforementioned diseases, however, has been challenging and there is no international consensus to date. The difficulties in finding the necessary evidence lie in the weak epidemiological infrastructures of the most affected countries, poor record keeping, and coincident economic and social changes.[4] Indeed, since cancer takes years to develop and depends on many contributory factors, the increases in the rates of incidence of some of the rare cancers mentioned above may not be large enough to be noticeable.

From the beginning, the Chernobyl disaster was shrouded in secrecy. The policy of deception and misinformation about the nature and scope of the accident created fertile grounds for fears and rumors. Some of the most persistent ones include gross exaggerations concerning the number of people who died and became disabled, as well as unsubstantiated claims about the increased incidence of skin cancer and birth defects.[7, 11] The perceived importance of the accident as a health

risk, the ambiguity of the information provided to the victims, and the general mistrust of the government led many to either paralyzing fear or complete denial.[7] A study of Estonian Chernobyl cleanup workers, for instance, found a substantial increase in suicide rates during the first 6.5 years following the accident, as well as fear and social withdrawal caused by uncertainty about the dose of radiation received and its effects.[10] Other studies have found higher rates of socially pathological behavior, such as drug and alcohol abuse, among those who were forcefully relocated on account of the disaster.[7] Thus, as aptly summarized by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), although reports of health effects caused by radiation have been greatly exaggerated, there is clear evidence of non-radiation related psychological disorders due to fear of radiation, rumors of detrimental health effects, stress of relocation, politicized handling of the accident and many other factors.

What lessons can be drawn from the Chernobyl disaster? Despite poor handling of the accident by the authorities of the former Soviet Union, the relocation and cleanup efforts have had some success, whereas ongoing media campaigns continue to increase awareness of the facts among those affected. The increase in childhood thyroid cancer helped to reveal the scope of iodine deficiency in the region and led to legislature mandating universal salt iodization in Russia.[1] Moreover, other epidemiological studies proved that several simple dietary measures, such as avoiding animal and plant foods exposed to significant levels of fallout or products that contain increased concentration of radionuclides such as milk, can significantly reduce health risks following a nuclear disaster.[4,6] In the United States, especially in the wake of the September 11, 2001 terrorist attacks, the threat of major radiation exposure gained increased immediacy. Dispersal of radioactive substances with or without the use of explosives, attacks on nuclear reactors or nuclear waste storage facilities and finally detonation of nuclear weapons are only a few of the possible scenarios of terrorist threats involving public exposure to radioactivity.[9] Despite the fact that there are plans to manage such events and well-developed infrastructure to handle emergencies, current reports agree that most metropolitan hospitals are still not adequately prepared.[10] In my opinion, the most important but underestimated aspect of any contingency plan should revolve around addressing the psychosocial issues that inevitably arise with a release of radioactive materials. As underlined by the ongoing events surrounding Chernobyl, the exposure to radiation can cause psychological distress in a group much larger than those exposed to clinically significant levels of radiation as well as produce symptoms as bad or worse than the physiological effects of radiation. In dealing with this issue, the goal ought to be prevention, specifically, "to maintain or restore trust, through openness, communication and decision-making that is both rational and participatory." [9]

In conclusion, the nuclear disaster in Chernobyl has raised important issues in a plethora of fields, including health care, demographics, politics, electrical energy production and international policy, among others, and it continues to teach us many unexpected lessons. The accident was unique in its scope, both as far as the sheer volume of radioactivity released into the atmosphere and the number of people affected. It revealed the unknown hazards of fallout radiation, the most important among them being increased rates of childhood thyroid cancer, and led to the discovery of new methods of prevention. It also underlined the importance of proper information management and the role of government and media, given the psychologically charged nature of radioactive pollution. Despite all that we have learned, our understanding of Chernobyl remains an evolving process and many factors, such as the continued psychosocial impact of radiation exposure, remains to be fully explored. The famous British author George Bernard Shaw once stated 'if history repeats itself and the unexpected always happens, how incapable must humans be of learning from experience.' Let us hope that he underestimated human resiliency and that the legacy of Chernobyl will not be forgotten.

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A Nudge to the Above

Photo by Joseph W. Dougherty

Like a mother bird nudging its
children out of the nest

the Ocean, that body of water
out of which we originally
arose

encourages us to reach toward
the heavens with every wave
as it provided us with life

it provides us with all we need
for this new life

oxygen, hydrogen, silicon for
microchips and reentry tiles

just as we were never meant to
swim

we were never meant to walk

- Adam Possner

Surviving Cancer: A Medical Student's Perspective

by Seth Blumberg

... Ten years ago, I never dreamed that I'd be so thankful that I can run a mile without collapsing, drink a glass of water without throwing up or pull my hair without it coming out. I live in the present and value my relationship with family and friends more than I ever did before. I have more respect and tolerance for feelings and beliefs that differ from my own. I have a more realistic perspective of problems facing society and I am also more eager to be involved in community service activities. In short I feel that my cancer experience has instilled a sense of "patient passion" in me. I view life as the exciting adventure it is, but have more patience to deal with obstacles and setbacks. My wish is that others could gain the insights of a cancer survivor without having to endure the negative consequences of prognosis and treatment ...

Having cancer is an intense, scary experience, but a lot can be learned from it. My journey from cancer diagnosis to cancer survivorship has been full of surprises, inspirations and frustrations. Halfway through my journey to become a physician, I often find myself reflecting on these experiences and thinking about how they will affect my future career.

The first indication that I was sick occurred during my sophomore year at college when I found myself becoming 'tired of life.' I slept more, ate less, spent less time with friends and my motivation significantly decreased. As a naïve nineteen year old, I simply figured I was getting older and my metabolism was slowing down. I developed back pain after helping paint a deck, but I simply figured I had just pulled a muscle or pinched a nerve. By the end of the summer I was always taking naps in the afternoon. When I dropped a $400 thermometer and electrocuted myself by forgetting to unplug a piece of equipment before working on it, I knew that I was being dangerously careless, but I felt that my apathy was typical of a burnt-out college student. Life at home wasn't much better. My mother was constantly on my case for being 'slow,' but I took little notice of her because I thought she was just reacting to my parents' recent separation. Later in the summer I went on a trip to Peru with my dad. When I returned, I suffered from more back pain, nausea and lethargy. My mother insisted that I would have to see a doctor and I eventually gave in. One thing led to another and the internist asked me to miss the start of school so that I could visit Dr. K. I thought this was ridiculous — in my mind this had to be something minor. I think I would've just canceled the appointment and gone to school on time if my sister hadn't happened to be in a car accident that weekend. Luckily she was fine. I later learned, however, that minutes before her accident my mother had told her that she thought I had cancer.

Dr. K. listened patiently as I told him I thought I had a cold. While I was drinking my lunch (a liter of CAT scan prep) my dad suggested to me that my condition might be more serious than I believed it to be — he thought I had appendicitis. That afternoon I was diagnosed with cancer. My first thought was, "Oh my god. I'm going to die. How long will it take?" Dr. K, however, was quick to focus on the positive. He said that there were many treatment options and that there was no reason to believe that I wouldn't lead a normal life. I was shocked, but also filled with a genuine sense of relief. There was a reason why my life was miserable and there was hope that it would get better again! In the coming weeks, these feelings really helped me accept treatment as a positive intervention. Meanwhile my parents were in complete dismay — I think that in some ways it was harder for them than it was for me. The toughest part of my diagnosis was revealing the outcome to my sister. Trying to remain positive, I told her that even though I had cancer, I would be okay because successful treatments were available. She nodded and I was relieved because I felt she had taken the news well. Soon, however, I heard loud shrieks from the driveway. It was the worst feeling imaginable. I felt responsible for hurting her, and I felt powerless to do anything about it.

One of the first things my oncologist talked to me about was the possibility of infertility. He suggested I bank some sperm. The humbling nature of the exercise forced me to acknowledge the consequences of treatment. It was scary to try to comprehend the significance of it all. I had never really thought about parenthood or even marriage for that matter. Did I even want kids? I cried for the first time since my diagnosis.

The first week consisted of a lot of diagnostic tests. It took a couple of days to verify that I had stage IIIB Hodgkin's. Throughout the diagnostic procedures, I was appreciative of Dr. K's efforts to keep me up-to-date and for remaining as positive as possible. "You have Hodgkin's Disease, which is good because I was concerned you had non-Hodgkin's which would have been worse ... You are stage IIIB, which is good because you could easily have been stage IV." I had tumors in my pelvis, abdomen and neck. The largest were 7 cm in diameter and I think my spleen was three times its normal size. In addition, I had elevated calcium levels, elevated uric acid and anemia (hemoglobin of 10), all of which was a little unusual for this type of cancer and therefore I was sent to Stanford for a second opinion. I was thankful that although Dr. K. had no intention of abandoning me, he was humble enough to suggest that a large medical center might offer something he could not.

I went to Stanford with my parents and my sister. The hospital was huge, crowded and intimidating. The visit clarified just how sick I was. Dr. R. recommended that I participate in his clinical trial. This trial was designed to minimize long-term side effects by utilizing a broad spectrum of chemotherapy drugs and radiation. In the short run it would be tougher than the standard treatment, but I had age on my side. Dr. R assured me that the cure rate was at least as good as standard treatment. I enrolled in the trial. When I signed the informed consent form, I was quite aware that I was putting my life in the hands of virtual strangers.

Meanwhile the back pain and nausea I had were getting worse and I constantly felt like I wasn't getting enough oxygen. I could only drive in a car if the windows were open and I felt nauseous when I was in a crowded room. I had trouble eating simple foods like a smoothie, and the only real relief I got was from a hot pad that I would put under my back at our hotel. It became tougher to tolerate the diagnostic tests, particularly the scans which required me to remain stationary for extended periods of time. My social worker also encouraged me to prepare a living will. Initially I wanted nothing to do with this and was somewhat upset by the discussion. I didn't want to plan for my demise, but in retrospect I appreciate that the issue came up.

When I returned from Stanford, I was admitted to the hospital because my kidneys were beginning to fail. I was given my first pain killer, a morphine derivative called Percocet®. It was the most amazing drug I have ever had! For the first time in months I felt pain-free and it was only then that I realized how much pain I had been in. Eating became a real problem. I could not eat more than a few bites without throwing up. At one point my physicians thought I might need surgery for an obstructive bowel disease, but luckily I avoided this. I remember Dr. K's early morning visits. He would just come into the room and plop himself down on a chair, just as if we were watching TV together. His relaxed attitude made me feel comfortable. Nevertheless, Dr. K. was concerned about the progression of my disease and a decision was made to start chemotherapy as soon as possible.

I stayed in the hospital for three nights. I had a lot of time to think about my illness and its effect on my psyche. I felt weak and I could tell that without treatment, my disease would kill me. This acknowledgment made it very easy to accept treatment. My initial concerns about the harsh effects of treatment seemed inconsequential. I was ready to take on any chemotherapy protocol on the planet. Furthermore, I found myself having to contemplate my own mortality. I became surprisingly comfortable with the concept of death. I learned to think of death as a very natural process and the ultimate resolution of pain and suffering. I was in no rush to die, however, and I did everything I could to maintain control — I made a point to visit the hospital patio, I insisted on carrying my bags when I was flown back to Stanford, and I even got a two-hour 'leave' so that I could check my e-mail! In retrospect, I was focused so much on trying to regain control of the present, I think I failed to appreciate how scared my parents were. My desire for control often made it harder on them.

I was too drugged up and exhausted to be scared of the chemotherapy — I just didn't know what to expect. I had heard a lot about how sick it would make me feel and I figured the infusion procedure must be really complicated with lots of tubes and bubbling fluid (clearly I had been watching too much TV). I was surprised to see how simple and quick it was. While I was getting my treatment, my social worker took care of my mother. This was definitely one of the best things anyone did during my entire treatment. It was an extraordinarily difficult time for her and given my state of mind, it was best that I didn't see how upset she was.

In the first week of chemo I lost 5 pounds (I weighed 147 pounds, 40 pounds less than my current weight). My oncologists were delighted because they said the 5 pounds came from my tumor! Once the tumor shrank, I was able to eat and drink without difficulty. In fact, I ate like a horse. Interestingly, when the tumors shrank, my pain actually got worse at times. It changed from

being a constant, dull pain to a sharper, fluctuating pain. My docs said that it was due to my organs shifting back into their normal place, so the pain was a good sign.

Dealing with the side effects of treatment was also a challenge. Besides boosting my appetite, some of the steroids I took played games with my mind. Sometimes, I would wake up in the middle of the night and feel totally wired. Like many patients undergoing chemotherapy, I also lost my hair. This didn't hurt, but it did cause some awkward reactions from strangers. I also became weak and anemic. In one instance I couldn't control the weight of a car door when I opened it and it scratched a nice, new car parked in the adjacent spot. The owner was pretty angry, though his attitude changed when my sister explained I had cancer. Despite the fact that this was only one of the many weird things that would happen, I remained upbeat. It helped that my family and the local community were very supportive.

I think I slept through most of chemotherapy, but when I was awake I slowly became aware that I was becoming very selfish. I had decided that I couldn't let anything stand in the way of my being as relaxed and as stress-free as possible. I was more abrupt with some people than I normally would be. I thought I would be able to keep up with some schoolwork, but I found it difficult to maintain concentration and motivation. I made a point to stay as active as possible. At the beginning of treatment I struggled to walk a few blocks, but by the end of chemotherapy I could handle a few miles. In fact I was feeling so healthy that I was quite surprised when my dad discovered that the cure rate for my stage was nowhere near 100%.

On December 28 I received my last chemo treatment. This was followed by a bunch of diagnostic tests that showed no evidence of cancer! I was not done yet, however, because I was told that I still needed nine weeks of radiation. I was in remission and felt so much better than I felt before chemotherapy, it took several discussions before my physicians convinced me that radiation was warranted. I was particularly disappointed that I would have to stay at Stanford for the duration of my treatment. The radiation sessions themselves were quick but humbling. I could not get used to the concept that my 'cure' required me to lie still in the middle of a lead-walled room that was filled with mutagenic beams.

It was tough to live by myself at Stanford. I lived in this apartment complex called the H.O.M.E. (Housing of Medical Emergencies). I spent many lonely hours in a lazy-boy chair reading a novel or watching TV. At night I would wait for the phone to ring. I didn't care who called. I just wanted to speak to someone. At the same time, I felt full of energy and I wanted to go out and do things, but I didn't know how to get my life started again. Sometimes I would try to do something, but would not be able to follow through. Once, I got a free pass to the Stanford gym, but when I went inside and saw all the activity I was too scared. I didn't want to struggle with light weights or have a dizzy spell surrounded by all these strangers. I left, but I felt bad about it later. There were many days when I felt unhappy and frustrated with myself.

When I was at Stanford, I met and heard from a lot of patients. Unfortunately, not all of these interactions were positive. A patient with leukemia called my mother to tell her what a terrible parent she was to allow me to be radiated. Didn't she know how toxic radiation was? Why wasn't I receiving intravenous vitamin C instead? My mom didn't tell me about the call right away, but it certainly didn't help her spirits. In another instance, I received some books from someone who was in 'current remission after a tough battle with cancer.' I later learned that he had faked his illness. Needless to say, this interaction was upsetting — I was already self-conscious about all the 'sympathy' attention I had received.

Thankfully, other patients more than made up for the occasional problematic encounter. For instance, I will never forget the time Paige and her mother came to visit me at the H.O.M.E. I had never met them before, but Paige was eager to find out how I was coping. Paige was awaiting a heart-lung transplant to compensate for her congenital heart defects. I don't remember exactly what we talked about, but we spent a lot of time laughing and made a deep connection. Paige's ability to view her condition in a positive way was truly inspirational. I often thought about her and her family when I was feeling down. There was also a five-year old with a brain tumor who was receiving radiation at the same time as I did. When he brought me a popsicle one day, I knew that we too had a bond. The seventy-year-olds I talked with were also supportive, but would be angry that I had to deal with cancer at such a young age.

On March 20, I received my last treatment. I'll never forget the day. It was great! REALLY GREAT! When the H.O.M.E. caretakers gave me their heartfelt departure wishes, I kept screaming, "I'm outta here. I'm outta here." In retrospect, it was probably disrespectful, but on that day I couldn't have felt better!

The first few weeks after treatment were the most amazing weeks of my life. It felt as though I was born again. I gained such joy from the simplest activities — waking up after a good night's sleep, being hungry, running, eating, and so on. I have more physical scars from those first few weeks than any other time in my life and it was a little traumatizing for those around me. Everything seemed like such an adventure. I had been sick for so long that I had forgotten what it was like to be healthy. A week after I finished treatment I thought I was 100% recovered and then the following week I felt even better.

I was so excited to return to school! While all my classmates were complaining about the homework assignments, the size of their dorm room and the cafeteria food, I couldn't control my enthusiasm. When I was receiving treatment one of my biggest motivating thoughts was that I would be able to go back to college and show my friends how unimportant some of their concerns were. When I was back in school and heard people complain I would say something like, "I used to think ____ was a problem, but last year I had cancer and now I realize it's unimportant." Unfortunately, my speeches seemed to have little effect. It seemed like people just chose to complain to someone else instead. That was really frustrating to watch and my enthusiasm diminished over time. Equally frustrating was when I would talk to people about cancer, often someone would make comparisons to their life that I felt were really inappropriate. As a result, I found myself becoming self-conscious about having had cancer and decided to stop talking about it. Eventually I learned to become comfortable with the concept that different people are going to have different concerns and you can't change that easily, but this took a while to accept.

An inspiring event occurred late in my junior year that renewed my respect for my friends. My classmate, Tom, asked me if I would participate in the annual KELROF race (a 24-hour, 10-person team relay race where everyone takes turns running a mile). I initially tried to avoid participating in it, but in the end we turned the event into a fund-raiser for the American Cancer Society. It was very exciting to know that I was now in a position to help future patients. I shocked myself by running 27 miles and attending a wedding a few hours after the race ended. I couldn't believe that my body held up so well and I finally felt like I had made a full recovery. More importantly, KELROF made me feel good about my friends from college. When I saw the energy they put into this event, I realized my feeling of isolation was just a perception attributable to the uniqueness of my experience.

For the first couple years after treatment, I had follow-up appointments every 2-3 months. These were nerve-wracking. About a week before my appointment I would notice myself doing things to 'prove' that I was cancer-free. I would eat a lot, and I would go to the gym and lift as much as I could. Sometimes I would even do stupid things like running across a busy street or vaulting over a fence that I normally would have considered too high. During my visits, I found myself watching my doctors' every move, especially their eyes. I wanted to know what they were thinking and the longer things took, the more scared I got. When I received a clean bill of health, however, I was always elated. Each time I felt like I had just been granted a few more months of freedom.

In November of my senior year, I had a recurrence scare. Some of my lymph nodes had enlarged and my doctors ordered a surgical biopsy. It seemed like a coin toss — some docs thought I had a recurrence and others did not. I was literally yelling and crying when I was wheeled into surgery, I was an absolute nutcase. It's the only time during my whole cancer experience that I was truly out of control. The thought that my fate would be decided while I was asleep was just too much to handle and I wasn't ready to go through treatment again. Thankfully I just had a benign reactive lymph node. My recurrence scare made me realize that I had put too much pressure on myself to succeed at school and life in general — a phenomenon called 'survivor's guilt.' It seemed like I hadn't learned my lesson from cancer — that one should live so that you could die tomorrow without regrets. After the scare I changed my attitude. I still tried to set ambitious goals, but kept my expectations low. With this new attitude I became a much happier person.

My college graduation was a true celebration for myself and my family. It wasn't about the degree, it was about being alive and healthy enough to receive the degree. Because of my recurrence scare and the stress of college, I was not sure what I wanted to do after graduation. My natural strengths were in math and the physical sciences and I enjoyed these subjects immensely. I had started to seriously consider medicine, but I was wary of making such a big career decision based on the fact that I had cancer. I eventually decided that the purpose of my work was more important than the process of doing it. Much of my ability to take the positive out of my cancer experience was a result of the supportive care I

received from my health care providers. I wanted to help patients in the same way my doctors had helped me. When I enrolled in Michigan's Medical Scientist Training Program, I was very aware of how cancer had affected my life.

Several of my close friends thought I was silly to enter medicine — they said medical school would 'do me in,' but I did not believe them. Turns out they were close to the truth — medical school has been much tougher than I expected. I was surprised by the rigidity of the curriculum and the emphasis placed on multiple-choice questions. When my classmates crowded around an answer sheet to a quiz I often wondered if they would show the same interest when they were examining future blood results that would significantly impact their patients' lives. Not even once as a patient did I wish that my doctors were more 'knowledgeable.' Numerous times, however, I wished they could have made better connections with their patients. In fact, when I was receiving treatment, I remember being asked to talk with a fellow patient who was considering refusing chemotherapy and radiation. Despite the overwhelming facts I have been asked to learn (and have already forgotten), my biggest concerns remain. Would I be able to convey the information I have learned to my future patients in a meaningful, empathetic manner? Will I be able to properly support a patient I met who said he would jump off the Golden Gate bridge before he would get treatment for a cancer recurrence? As a pre-clinical student I often reflected on the number of times I heard the word 'disease' versus 'patient.' In my future patient interactions, I certainly hope that there is a lot more to patient care besides the science of their pathologic condition.

A scary aspect of my medical training is that I have seen how easy it is to dehumanize medicine. Last month, a friend from junior high figuratively woke me up. He wanted to talk about his malignant brain tumor. I initially felt penalized for being the 'fellow cancer survivor' that had to take time out of my day to talk with him. But a few minutes into our conversation, I started to remember how scary it was to be a patient and I knew that my conversation would be the most important thing I did that day. When I recounted this story to another cancer survivor she replied, "first you acted like a doctor and then you acted like a survivor." My friend passed away a couple weeks later — I certainly hope that I gave him support when he needed it most.

To combat my tendency to forget what it was like to be a patient, I have participated in a support group for young adult cancer survivors. At the support group meetings I am reminded of the little things that can make a big difference in patients' lives. I am continually amazed at how much one can learn from talking to other patients and the variety of feeling each one experiences. The conversations also serve as a healthy reminder that my perception of health may differ from those whom I may care for. It's tough to predict how cancer will affect my future patient interactions, but I hope that it will help me to be an optimistic realist. I'll make sure that I enjoy life because I know it will give me more positive energy to share with my patients. Most importantly, I will do my best to make sure my patients are my top priority and will work to suppress anything that interferes with this — nobody deserves less.

If there is one thing cancer has given me, it is renewed passion for life. Thanks to the efforts of my health care team, my family, and the community at large, I have been given a second chance at life. It's a debt that I'll never be able to repay directly, but I am determined to make the most of the opportunities that come my way. When I was diagnosed my oncologist assured me that cancer would become a positive learning experience. I could not agree with him more. I would not wish cancer on anyone, but I am a much better person because of it.

Conquering Breast Cancer: One Patient's Journey

by Supreetinder Kaur Rangi Bauer

Mary Lou Bauer was diagnosed with breast cancer in August 2002 at the age of 64. She has been married to the Rev. David G. Bauer for almost 40 years and is the mother of Susan, John, and Charlie. She shared her story with me on May 20, 2003. The following is an excerpt of our conversation:

SRB: Tell us about your experience with cancer, from your diagnosis to the present.

MLB: The diagnosis was made early in August. I had had my annual physical exam with my primary care physician, whose procedure is to see the patient and then to say, "Now it's time for this and this and this test." That exam was in July. When I went back for the repeat visit he said, "The mammogram shows clear, but I don't think it is. I want you to see a surgeon."

So I had an appointment with a surgeon the following day. He asked why I was there, and I went through the procedure that my primary care physician had said, "There is a lump or there is a thickening or there is something that is different this year than there was last year." So that surgeon said, "I would like to see you again in ten days, or if you would like to, you can wait until you move to your new home." That was a move that was going to take place in September, and I said "No, I would like to see you as soon as possible," which was ten days later. When the surgeon examined me the second time, he said, "Well, there is something there because I can express fluid from your breast." I'm talking about my left breast. He said, "So, there's a procedure that would insert dye to show where the blockage is. My palpation of the area shows that it's in the 1 to 2 o'clock position, if your breast were a clock. So there's that procedure. We could do a biopsy, that's the second, and the third option is to do nothing." And I said, "The third option isn't a possibility. The first option, you're telling me that you already know where the troubled spot is, so it seems like biopsy."

So the biopsy was scheduled for August 26. The option was given to me did I want to stay under anesthesia while he had the frozen section analyzed, and I said, "Just keep me under until you hear from the lab," which he did. The frozen section at the lab indicated that it was clear. I went in eight days later to have the stitches removed and to hear the consultation with the doctor, and he said, "Well, the complete analysis of the tissue sample shows that there are cancer changes present." So again he presented about two or three options and I chose for him to do a partial mastectomy and a lymphadenectomy.

That surgery was scheduled for Wednesday, Sept. 11 ... that surgery took me a while to recover from. The drain was inserted in such a way that I was to drain the area, and each time I did it was extremely painful. So I called the doctor's office and asked him, "Should I be taking a pain pill about an hour before I do this procedure?" And he said, "Come right in." What he did at that point was to remove the drain so that I was much more comfortable. I returned for a visit about ten days later ... I went to him on Friday, Sept. 20, and he said, "Well, in analyzing the tissue that was removed in the partial mastectomy, the cancer cells were extremely close to the perimeter of what was removed. There were no cancer cells found in the lymph nodes but it was just very close in the tissue from the breast itself. So you have the option of waiting until you get to your new home before having radiation or chemotherapy or medication or surgery, after you consult with a specialist or two or three."

At that point, we talked to Frederick C. Bauer, a retired pathologist (and my husband's older brother), and he listened to the whole situation and then suggested that I talk to his son, Richard C. Bauer, who is a practicing pathologist, which I did ... and he was extremely careful in listening. He is probably one of the more careful listeners that I've encountered, and in fact my husband was on the phone too, because at no time did I feel that I was doing this alone. My husband was in the examining room whenever the surgeon consulted with us so I didn't really have to remember everything and tell him. He was hearing information for the first time, as was I.

So, anyway, Dr. Richard Bauer, when he listened to the whole thing, said, "Well, each of the options has a very good recovery record and it really depends on what is comfortable for the patient, the patient's age, medical

history, and personal preference, and what you choose will be good, once you think about all the options. If you choose surgery, it is very possible that sometime in the future you would have additional surgery." So, we thought about this over the weekend. We were going to be moving on Tuesday the 24th, and on Saturday I had two friends come to the house to help me pack. One of the women said, "You know, I had a mastectomy 25 years ago and I drove 30 miles away to Moline, Ill., for radiation. And I taught school during the day and then I'd get in the car and I would drive the 30 miles and I've had no problems." Sunday, two more friends came to help me and one of the women had had a mastectomy ten years before. I really felt that these people had been placed in my way to sort of let me know that this was a very common occurrence. I had not ever realized that either one of them had had a mastectomy. I think we probably called Dr. Bauer again on Sunday, and Monday went in to talk to the surgeon, who went over the report from the biopsy on Aug. 26 and the report of the partial mastectomy on Sept. 11. And (I) said — well, "we" said, and I say "we" because Dave and I seem to be of one mind of what to do — that, "All right, we would like to have you do surgery," and at that point the movers were coming the next day to pack, and we said, "as soon as you have an opening."

So the surgeon's nurse made a call and the surgeon moved some of his appointments the following day and I had surgery at 10 o'clock. So, we completed the move, and I returned to the doctor's office the next week and he removed the stitches. What he had done in the surgery was really packed my left side so that the drain was going into the dressing because we were moving 180 miles away and he said, "Well, this is not the best possible procedure, but you will be more comfortable." So, when I saw him then on Oct. 1 he removed the stitches. He thought everything was clean and clear. He said he had taken as much tissue as he possibly could and that the tissue that was removed was extremely close to the surface of the skin. And I laughed. I weighed at the time of the surgery from about 122 to about 125. Maybe by the third surgery I was down to, I don't know, 119 or 120, and I'm just under five feet five, so I'm average to slim build. And my bra size is a 34B so when he said he had to scrape and he was very close to the surface to the skin, yes, I could understand because there's not a lot of tissue to remove. So, anyway, one of the funny things is that a couple whom we know, had known about five years at that time, the wife of the couple is rather stout, and round, and so is her husband, but he said to his wife, "Well, if Mary Lou is going to have a mastectomy, what in the world are they taking off?" Anyway, that is my life. So, the doctor then said, "I would imagine that you should have an oncologist or you need to consult with someone in your new home because you're moving to Champagne-Urbana, Ill."

We had been given the names of three specialists by a new acquaintance, and one of the oncologists is named Dr. J. And so when the surgeon in Moline said, "Well, who would you like to have an appointment with?" and I asked him if he knew anybody personally and he said "No, I don't," I said "Well I have these three names." So we chose for him to contact Dr. J. I saw her in the middle of October and she looked at the reports and did a physical exam of me and thought she detected no lumps on my right side. She looked at the surgical scar. She said, "Well, things look like they're in good shape and I think we're going to have a very long and very healthy relationship. But I would like to see you after three months." I saw her again in January and again in April, so I have seen her a total of three times and she seems to think I'm doing fine. She said the last time, "Oh, you're doing fine, keep it up," both of us knowing that it's not anything that I do or don't do, cancer just happens.

I suppose I was really edgy about the whole thing. In fact, when I first heard my primary care physician say, "But I don't think your mammogram is right and I want you to see a surgeon," I really froze because breast cancer is what my mother had and from what she died when she was 72 years old. So, that's been my experience.

SRB: How has having cancer changed your life?

MLB: I think not taking a day for granted, or realizing that I cannot put off indefinitely saying something to a person that I would like them to know, or not putting off indefinitely a trip or a project. It's very important to take the time to be present and enjoy the moment.

SRB: What would you like to share with others who have been diagnosed with cancer?

MLB: Probably find out who else has gone through this and talk with them, and finding out "The fears that I have are ones that someone else has had too and I'm not really odd, I'm not really strange, I'm not really a person with little faith or a bad person by thinking catastrophically." It's just being able to say, "What did you do ... how did it hit you ... how did you find out?" and then hearing their story.

SRB: Were you comfortable with the way that your doctor told you that you may have breast cancer? Do you wish he had said anything differently?

MLB: My primary care physician seems to be a person who cuts right to the heart of the matter; he does not mince words. And when he said to me, "Your mammogram shows it's fine but I don't think it is," I'm glad he said what he did, and then he said, "and I want you to see a surgeon." So I was grateful that he had sent me to a surgeon and didn't say, "Well, we'll just keep track of this for three months or so and we'll see what you're doing." I really appreciated his sending me to a surgeon immediately. And I'm just grateful ... that at the physical exam when he palpated my breast tissue, he could detect somewhat of a change that was not apparent in the mammogram at all. So, what do I wish he'd said differently? Nothing. I'm grateful for what he did say.

SRB: Did you have any indication before that particular examination with your primary care physician that you may have breast cancer?

MLB: No, I didn't. Whenever I go for the annual physical exam I remember that my mother died of breast cancer. And yet, I do keep the yearly (mammogram) exam because you know the ostrich technique does not work in preventive medicine.

SRB: In addition to the yearly mammograms, did you perform breast self-examinations regularly?

MLB: No, I'm very poor about that. I don't as a rule. In 1968 when I was 31 years old I had had a fibroid adenoma on my right breast and I discovered that on my own. And it was removed when my second child was about 4 months old. I had the operation so I had to stop nursing. Not that I've learned from that and done breast self-examinations on my own ever. Who knows why?

SRB: It seems that you were scared of developing cancer since your mother had died of it and you detected something once, so I wonder if there are any particular reasons why you didn't perform regular breast self-exams.

MLB: No. When I had detected something in 1968 my mother was alive and she had not detected cancer. She died in 1980. I have a cousin on my maternal side who died of cancer at the age of 36 and she had found a lump when she did a self-examination. I don't know.

Oh there was something else, earlier in the summer. I was standing in front of the mirror at my dresser. I don't really stand in front of the mirror naked and look at me very often ... I was standing in front of the mirror just getting dressed and Dave said, "Look at me, look directly at me." And he said, "Are your breasts the same shape?" He thought he detected a different shape on my left side. I don't know whether he really did, because I didn't stand and look at me even then. I think partly (it's) my age, I am 65, and when I was growing up people didn't love their bodies as much as the language in the 70's and the 80's seemed to encourage .... I grew up saying, "I'm okay ... I'm fine, so let's get on with earning a living or doing a job or getting on with it. Enough of this introspection and navel inspection and that kind of thing."

SRB: How well do you feel the doctor explained all the options available to you?

MLB: I thought the surgeon was very clear. When he explained the procedure the first time I said, "Could you tell my husband this?" And he said, "Oh, yes, he can come right in." So, he was very clear, and at no time did I feel that he was really plugging, "Now, if you have surgery, we've got 110% recovery on that!" He was very clear that there were three options, and maybe even four if you took a combination of one and three, and option five was if you took option two and three. So he was very clear about what my choices were.

SRB: How difficult was it to make a decision?

MLB: Oh, it took me a while, like three days. And I guess it was difficult each time. When I had the first operation, which was the biopsy, he walked into the room reading the report and said, "Well, there's no new proof, and it looks like, oh, wait, there is cancer." So the only thing that I could say I wish was that, you know, he had read it all before... I had thought it was all right, you know, so for a half a minute, I thought, "Oooh great!" And then he said, "No, there is cancer present or you have cancer changes present." So I was somewhat startled right then. But that was the only thing, and that's probably not a big deal.

SRB: You just wish he'd waited half a second.

MLB: Maybe he did that on purpose, to come in and say "No new growth" so that I would be at ease and begin breathing, because who knows when I had stopped breathing, waiting to hear what he had to say?

SRB: Tell us about your experience with your oncologist.

MLB: The oncologist ... whose patient I am seems to have a really fine reputation here in Champagne-Urbana. She is a real upbeat person who looks directly at me and listens. Last time she said, "Oh, you're great, now go home and tell your family how great you are." When I saw her the first time she said, "I think you're doing fine." And she looked at me and said, "You look disappointed." And I said, "Well, I thought maybe you're going to say I should be considering a second mastectomy." And she said, "Oh, I don't think we're there." She had given me a prescription for a prosthesis. This was in October .... When I saw her (at) the end of April she said, "Well, you haven't gotten a prosthesis yet. Why not? You're worth it." Maybe, I'm thinking, with a nurse having said to me, "Well, you know, don't be surprised if you don't have to have a mastectomy on the right side within a year." And there was someone else who indicated that that often is the case. I don't know whether I'm thinking, "When am I going to have a second mastectomy?" I really don't know why I haven't gotten a prosthesis.

SRB: What kind of support from your family and friends was most helpful?

MLB: Dave was there in the consultation room. He listened. Occasionally he asked a follow-up question when I couldn't seem to think of ... the next logical question. I think letting me wrestle with what would be best. He was in on the conversation when we talked to Dr. Fred Bauer and then to Dr. Richard Bauer and took the time to listen to lengthy explanations. He (Dave) was one to think surgery was something that seemed the most logical for me at my age, and Dave supported me in that decision. He said, "You are certainly more than your bosom measurements, so if that changes, you are still the same person." I called the three children to tell them that I was going to have surgery and why. Susan came for the second surgery and I think that was very helpful, because then I knew that she was with Dave at home. Phone calls, you know, how are you doing, but it wasn't lengthy phone calls. People would say, "I've thought about you and you are in my prayers and in my heart," and that was very touching.

SRB: What resources were most helpful to you? For example, literature or spiritual. Did your doctor recommend any books to you?

MLB: No, there were no books recommended. I think my prayer was to find the help that was needed. And I really think that some people were placed in my path. I have a friend who calls this ... she calls it a "God moment." For instance, the day before the partial mastectomy we were at a (church) meeting, and a man seated next to my husband said, "What are your plans for retirement?" And Dave told him, and then said, "Tomorrow my wife has surgery; she is going to have a partial mastectomy." And this man said, "I am a retired pathologist, but I substitute in Champagne-Urbana and two other communities. If you need the name of a radiologist or some oncologist I'll be glad to give you those." And Dave said, "Please do." That man then gave us the names of three people for whom he had worked and whose work he felt was superb. Dr. J was at the top of that list. And then, what was most helpful, I think, was other people saying, like the two teams of women who came to help pack, saying that they had had a mastectomy. And it's sort of like, you know, my experience, my mother had had a mastectomy and then died about two years later, my cousin had had a mastectomy and died a year and half later. I was meeting women who had survived ten years and 25 years. So what was most helpful? Meeting people who had survived. Also, I think Dave being very calm. You know, one doesn't pray for eternal life, because nobody lives forever. Praying for stamina and courage to make decisions that are right. I guess that's it.

A Chimera Among Us: A Review of Macklin Smith's *Transplant*

by Margaret M. Sadoff

Transplant

By Macklin Smith

Shaman Drum Books, 2003

It is Saturday, February 15th, 2003, and I am on my way to Shaman Drum to hear Macklin Smith read from his new book *Transplant*. Smith is an Associate Professor of English at the University of Michigan. While it is not so remarkable that an English professor has penned a book, the subject matter is indeed remarkable as well as extremely personal. Smith's collection of poems and musings take the reader along on his strange yet seemingly soulful journey from his diagnosis of leukemia during a routine checkup to his eventual remission. I had neither read the book nor heard of it before tonight's reading, but having read a handful of other "survivor stories" I expected an emotional and dramatic rendering of one person's angst in the midst of impending doom. What I found instead was a refreshing, self-effacing man who seemed overwhelmed by the standing-room only crowd.

Transplant is not the first book to be written about cancer and surely, sadly, it will not be the last. But it does hold the distinction of being the first book published by Shaman Drum Books. As Smith reads from the pages there is laughter, and not just chuckles of recognition but full-on belly laughter. Can a book about cancer be funny? Sarcastic? Irreverent? Yes, apparently, it can. And it can be equally moving and powerful. As I listen to Smith's story and his anecdotes interjected between stories, I can't help thinking how random, it seems, that illness finds us. Here is an educated, healthy, active person with no apparent history of disease, stricken in his prime and forced to re-evaluate his life all the while juggling life and death treatment decisions. This is the stuff human experience is made of —naked and raw, simple and surreal, tragic and comic.

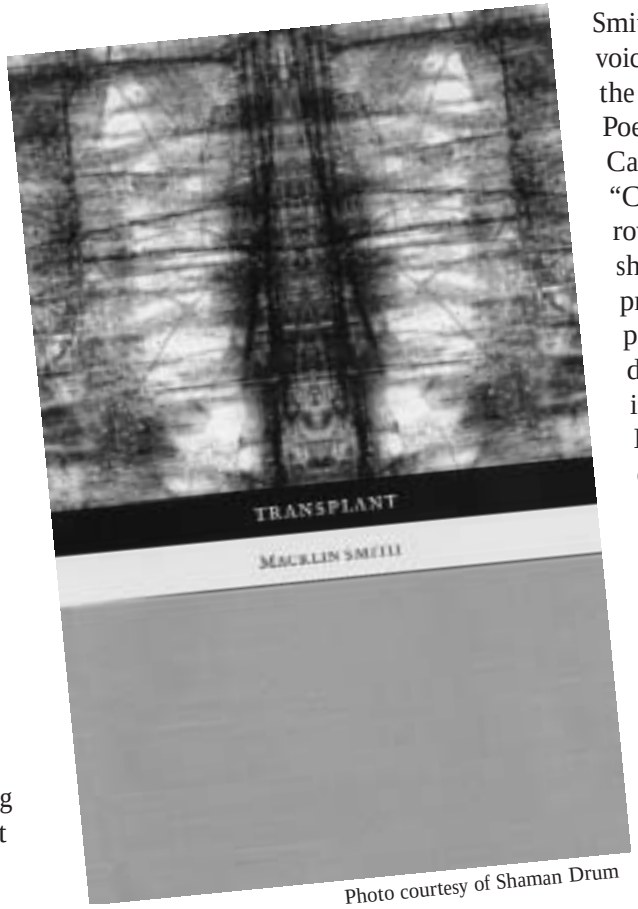

Photo courtesy of Shaman Drum

In the section entitled DIAGNOSIS, Smith struggles with the "why" of his diagnosis. In his most abbreviated poem, "Call and Response," composed of two short, stark lines, he writes simply "Why me? Why not." From its simplicity emerges a deep abyss of emotion. The poem's simplicity, however, is cleverly offset by the use of lengthy footnotes that serve to mine the emotion left unspoken in the text. And here, as throughout, there is humor. As he contemplates the various treatment options available to him and their associated odds ratios, Smith finds himself worrying about finances which prompts him to write a whimsical ode to M-CARE in one passage. Smith continues to unfold his unique voice from a patient's perspective in the section entitled HOSPITAL. Poems such as "The Hickman Catheter," "Busulfan," and "Cytoxan" give the reader a front row seat to the sometimes unpretty show that leukemia can be. Smith provides us with scene settings in painstaking and plain-language detail. One of my personal favorites is a poem titled "In Perspective." In it, Smith juxtaposes the vastness of space with the banality of a tuna salad sandwich, perhaps to show us that even in our greatness, the living of life is rooted in simple everyday pleasures.

Smith is an avid birder, scholar and connoisseur of all things literary and his love of birds and of nature shines through in much of his work. Whether watching the lilacs grow in his garden as if for the very first

time, walking his dog Sadie, or appreciating his wife Lynette the way one appreciates a fine piece of art, Smith returns, in the section entitled HOME, to the business of living. He returns, not with a vengeance, but with a newborn eye and a sweet appreciation for the new life granted him by God, medicine, and his matched, unrelated bone marrow donor. After his successful transplant, Smith is transformed (using his own term) into a chimera — his blood and bone cells, and all the cells to which they give rise, encoded by his donor's DNA. If your genes make you who you are, at least partially, then how does one redefine oneself in light of housing someone else's code? Smith ponders this in his poem "Dear Dean," in which he addresses his donor and wonders whether he too is experiencing some sort of odd communion — two strangers, now brothers in genome, joined inexplicably by millions of tiny double helices.

Transplant is a book of readily accessible poetry for all who are interested in the human experience. Smith, like other survivors, has emerged on the other side with a deepened respect for life and the miracle of living. He has also emerged with a huge dose of positivity that spills over onto the listeners as the evening's reading progresses. There is a school of higher thought that suggests that all the suffering and strife of the world is due to the fact that we are all of one being that has been split, and that suffering comes from our inability to recapitulate the whole. In sharing his donor's DNA, Smith is perhaps one step closer to completing that whole. In sharing his experience with us, perhaps we are one step closer to feeling that same sense of communion with nature and humanity.

Procedures: Beyond "See One, Do One, Teach One"

by Neal Elkin

My fascination with procedures dates back to the night I presented to the old University Hospital ER with acute shortness of breath. I remember very clearly the resident who, without warning, enthusiastically plunged a needle into my wrist, eager to send off an arterial blood gas (ABG). More than 20 years later, I still remember that pain in the depths of my arm.

As a recent University of Michigan medical school graduate and new house officer in emergency medicine, I'm now in a position to be the resident on the giving end of procedures. My short term goal is to learn the most efficient and least painful method of getting the job done, with patient comfort and communication being a high priority. My long term goal is to learn to teach how to do a procedure effectively, so I can pass the knowledge on to upcoming generations of medical students.

"See one, do one, teach one" is the algorithm we've all been taught. I'd like to offer some thoughts on each of those steps.

"See One"

The emergency department is an excellent place to begin to "see one." During my third-year Emergency Department (ED) rotation at the University Hospital, we spent an entire 8-hour shift observing and doing procedures with the nurses and technicians. It was fun to talk to these undisputed experts in getting rapid EKGs, placing IVs, and doing ABGs. They know they're good and they love the recognition. As they explain the details, you know their approach is definitely the correct way to get the job done. In fact, when a healthcare professional explains how to do a procedure and why, my advice to med students is act like you just received the gospel and leave it at that.

Trauma and codes rushed into the ED offer a special opportunity to observe experts at work. During these times, you can really appreciate the difficulty of placing IVs in a dehydrated patient with diabetic ketoacidosis, drawing blood on the patient with no pulse, and giving medications to the child who is seizing. This is an ideal time to watch how procedures can be lifesaving in the team effort to stabilize a patient. It's also a good time to observe how many staff use gloves, masks, and shields for protection.

In a more relaxed circumstance such as ambulatory surgery, it's fun to watch staff who can quickly place an IV in a patient who was scared to death, demonstrating that all their anxiety was unnecessary. Conversely, it's painful to watch an experienced nurse tunneling unsuccessfully for the recalcitrant vein in an obese patient who doesn't have a wisp of blue anywhere. Procedures on children are probably the most difficult to watch because most of them cannot conceptualize why a painful procedure is necessary in order to get better. The screaming definitely adds an unnerving dimension to the whole process.

Observing someone else do a procedure can also benefit the patient. During my internal medicine rotation, for example, I remember our team watching a new intern perform a lumbar puncture. It's good we were there. As the intern started to introduce a large gauge needle into the patient's back, the attending gently reminded him to stop and use the lidocaine first.

After watching a number of procedures, it becomes clear that there are different points of view about pain control. Consider the use of lidocaine as a numbing medication for the insertion of IV lines, for example. I never saw it used in the ED, but at the ambulatory surgery department of St. Joe's Hospital it was always used before placing IV lines.

"Do One"

Before we advance to this phase, it would be best to pause and to read about the procedure first. This offers the opportunity to go over the steps in detail, and may even include something important that your instructor forgot to mention. It's also crucial to understand the possible complications of a procedure before jumping in head first. It not only helps you learn how to ask for informed consent, but makes you more careful when you do the procedure itself.

Teaching effectively how to do a procedure takes special talent, and few health care professionals are really good at it. Some staff members are reluctant to let you try at all. Maybe that's because it slows them down, or

because they're worried you'll screw up and someone will sue them. Whatever the reason, at suburban hospitals especially, you really have to be aggressive about letting everyone know that you want to do procedures.

Once you're ready for action, inform the patient that you're a student still learning and give them the option to refuse your services without pressure. I was once in a situation in which the patient knew I was a student and clearly did not want me placing his IV. My instructor, however, was pressuring me to do it anyway. I'm glad I deferred to the patient's wishes and let the technician do it. The patient was relieved.

Before doing the procedure, it's key to set up all the equipment logically and to double check that you've gotten everything. If time allows, the student should assemble all the materials. This allows time to think through what you need for the procedure and why.

Keep in mind that patients aren't the only vehicle for learning procedures. We also have each other and the grocery meat department. As a member of the Emergency Medicine Interest Group (EMIG) last year, I helped students learn suturing techniques and I organized a hands-on workshop using new portable ultrasound devices. Workshops are a great way to become comfortable with a procedure in an environment where malpractice isn't an issue.

"Teach One"

I am really looking forward to the time when I can teach in the hospital setting, because I know what works best for me. I think it's important for the teacher to display confidence that the learner will succeed, while being careful not to pressure a student if they don't feel ready. The instructor should not be panting over the student during the attempt to do a procedure, and neither student nor teacher should pressure the patient to agree if they're not comfortable. It's also not a good idea to expect a student to learn under extreme time pressure, or to penalize a student for taking time to do the job right.

Far more than three simple actions, I interpret "see one, do one, teach one" to mean "see many, talk about it, read about it, know the complications, attend workshops, inform the patient, get their permission, assemble the materials, do it under supervision, become proficient, and finally teach it the way you'd like to be taught."

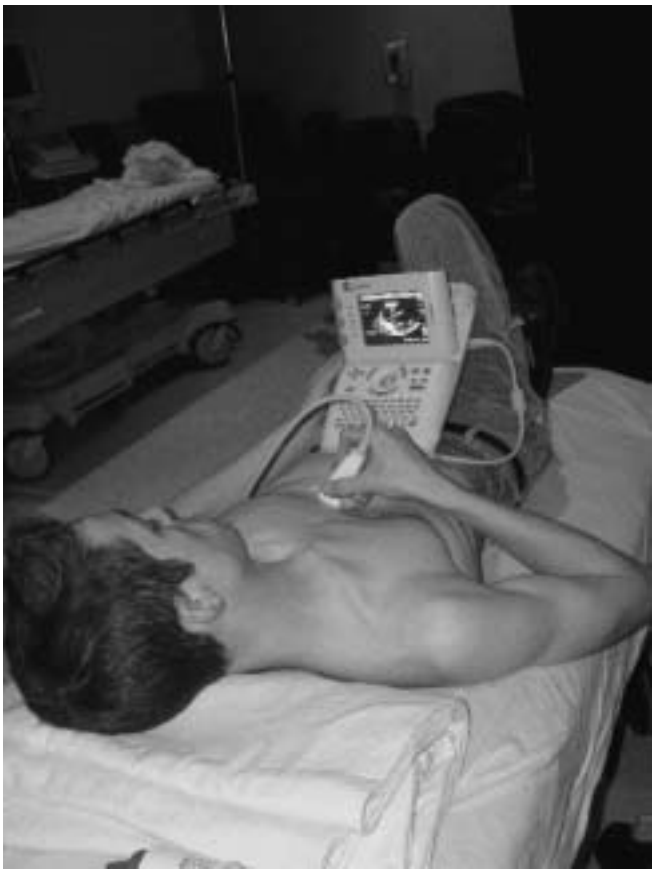

Photo by Neal Elkin

A medical student practices using a new portable ultrasound device on himself during an EMIG workshop.

The Midnight Blood Draw

by Eric Achtyes

Although I have never served in the military myself, my father was in the U.S. Marine Corps when he was in his twenties. His experience affected him deeply, and continues to define who he is today. For example, he keeps his shoe polish in an old ammunition box, and he has a 'U.S. Marine Corps' sticker plastered to the roof of the truck he uses to run his painting business. He also enjoys listening to old records with such military classics as 'The Halls of Montezuma' on them, and he avidly reads historical accounts of a variety of battles and wars. Always, when the national anthem is played, he removes his hat, places it across his heart, and sings loudly.

Perhaps because of my father's example and experience, I too am developing a deeper appreciation for the men and women who have served our country in wartime conflicts — regardless of whether I agree with the political reasons for them being there.

While I cannot claim to understand all the ways in which combat affects our military men and women, there are a few things that I have learned about the sacrifices they have made. One night, when I was on call at the local Veterans Affairs Hospital, I had the opportunity to learn vicariously through the life of one former soldier. It was one o'clock in the morning and I had been sleeping in a chair in a staff room when my pager went off. I was a third-year medical student and the intern with whom I was working wanted me to draw blood from a patient for a set of electrolytes. Weary but willing, I got up, gathered the necessary equipment and set out to find my man.

On the fifth floor I found the correct room number. After a quick knock, I opened the door. The room was black, so I tiptoed over to the light above the sink and turned it on. Bright light flooded the room, an unwelcome intrusion into the quiet darkness. Despite the brightness, the target of my blood draw snored on, oblivious to my presence. Padding to the bedside, I tapped Jerry's arm and shook him gently. He was a big man and it took some effort to wake him from his sleep. Suddenly he jolted upright, eyes darting around to see who, or what, had awakened him at this awful hour.

"I need to draw your blood," I said, mustering a weak smile. "Got any good veins for me?" Clearly, Jerry did not have a lot of easily accessible veins as a generous layer of subcutaneous fat buried most of them.

"This arm has the best ones, " he said, holding up his right arm. I noticed many little bruises from previous needle pokes and an IV already occupying one of the few accessible veins.

"How 'bout we try this arm instead?" I said pointing to the left. He assented, grumbling that he had once endured nineteen needle sticks to have blood successfully drawn. That occasion had included attempts by medical students, nurses, and finally the doctors themselves. Hoping it would not take as long nor as many needle sticks, I fastened the tourniquet snuggly above his left elbow.

I palpated without success for the median antecubital vein, which often crosses prominently in the fold of the elbow. Then, having seen some of the more experienced phlebotomists stab

Photos by Chithra R. Perumalswami

blindly for deeper veins in the forearm, I decided to try my luck. I felt what my fingertips told me was a vein, even though I could not see it, swabbed the skin clean with an alcohol wipe, and pushed in the needle. Jerry didn't even flinch. Since there was no flash of blood telling me I had been successful, I withdrew the needle a little, re-angled the tip, and stabbed again. Still no luck. After several more attempts to locate the elusive vein, I withdrew the needle completely, placing a bandage over the tiny hole.

"I'm sorry about that," I said. "We'll have to try another place."

"You get five pokes, and then we have to get someone in here who knows what they're doing," Jerry's tired voice told me.

"Okay," I said, "but the real pros, the phlebotomists, aren't here at night."

With a look of annoyance on his face, Jerry sighed in understanding.

Trying to put him at ease, I asked Jerry to tell me about himself. He began by saying that he lived in a small town nearby and that he had been in and out of hospitals for years with failing health. I noticed for the first time his motorized wheelchair parked in the shadows next to the bed. He shared with me the frustration of being disabled and of watching his wife try to support their family by working all day managing a small produce store.

"There is no one to take me anywhere to get things done because my wife is so busy at work," he told me.

I nodded understanding while puzzling over a smaller vein in his wrist. I said a little prayer that I would actually find this one and avoid needlessly poking the poor man again. Thankfully, this time there was a flash, and the blood slowly trickled into the syringe.

A moment later I said, "We've got all we need," depositing the precious blood into the labeled specimen tube for safekeeping. Walking over to the sink to wash my hands, I asked Jerry what division of the service he had been in.

"Army," he said.

"Did you see any active duty?" I asked, remembering how thankful my own father was that he had served in the military during the time in between the Korean and the Vietnam wars, therefore not participating in actual combat.

"Yes," he replied, "in Southeast Asia."

"You look too young to have served in Korea. It must have been Vietnam then," I said.

He nodded saying that he had initially gone to serve as an advisor to the South Vietnamese, but later ended up running 'intelligence' missions into North Vietnamese territory. "I never understood what I was doing on intelligence missions since I wasn't too smart," he joked. He said he was too big to squeeze into the tiny holes and tunnels that the Viet Cong had dug to hold their weapons and stores, but he had friends who had to explore them. It was very frightening because deadly traps often awaited them on the inside. Additionally, he continued to explain, in the countryside, you never knew who or where your enemy was. On one occasion, a peaceful-looking farmer working in his fields suddenly brandished an automatic weapon and began shooting at him and his fellow soldiers. Living in constant fear for their lives, some of the men were pushed past their breaking point, leading them to participate in atrocities too horrible to repeat.

"These were good family men with wives and children back home," he told me.

"War is a horrible, horrible thing," was all I could think to say.

Admittedly a pacifist, I have a hard time understanding what motivates our leaders to justify war when it tears men, women, children and families apart on both sides of the conflict. Are 'promoting democratic freedoms,' or 'defending America's interests,' such as oil, really acceptable reasons to do what we've done to Jerry and his family-or for that matter to the Vietnamese families who were also brutalized by the war? In my mind, there is a very fine line between defending the weak from a bully and becoming one yourself. We mustn't deceive ourselves. Prudent self-interest can easily turn into a prideful, ruthless selfishness that disregards the rights of others to self-governance and self-determination.

"Is there anyone you can talk to about your experiences?" I asked.

"No," he said, "I don't talk about this stuff with anyone. No one wants to listen to me talk anyway. You're the first person I've ever told about these things."

A bit shocked I asked, "What about your wife?"

"She's too busy and tired," he said, "but you seemed like an easy person to talk to."

Humbled, I said, "Well, it's the least we can do for those who have served our country the way you have. Good night, Jerry. We'll see you in the morning."

While I don't believe we should make excuses for the behavior of soldiers who act inappropriately during wartime, I was beginning to understand some of the stresses men and women like Jerry and his fellow soldiers experienced in their struggle to survive and to perform their duty. I couldn't help but wonder if, placed under the same stresses, I too would succumb to the psychological pressure and regress to patterns of otherwise unthinkable violence. Jerry made me question myself and wonder, "There but by the grace of God... go I?"

On that night, my patient Jerry became my teacher. Despite my clumsiness cannulating veins, I learned about the struggles and the hardships he faced. I began to grapple with the question of who really is to blame for the atrocities of war: the serviceman or woman, the pressure and the stress, the politicians? And I came to understand something that my dad has been trying to teach me by his example all these years. No one wants to be placed in the types of situations that war places you in, and quite frankly, we don't know how we would behave given those types of pressures and stresses. Therefore, we ought to extend to our service men and women a measure of grace and understanding for what they have endured on our behalf. They deserve our care and respect, whether that is through tending to their physical ailments or by lending a listening, empathetic ear. Sometimes, as I learned on a 'routine' midnight blood draw, the latter can do as much as the former for true healing.

Medical Students for Cuba

by Tammy Chang

Medical students take their education very seriously, because we want to be the best doctors we can possibly be. But a good education means more than studying hard and acing exams. So many experiences outside of school shape the people we are and contribute to our medical education.

This past spring, my fellow classmates and I founded an organization that would allow medical students to broaden our knowledge of international health issues. We called it "Medical Students For Cuba" (MSFC). Although medical school presents us with an enormous amount of information, we recognized that a first-hand international exchange to learn about healthcare systems outside of the US would be invaluable to our training as future physicians and healthcare policy makers. Not only that, it would provide an opportunity for us to donate much needed supplies to a country that has well-trained healthcare workers but limited resources. Many members of our group were the leaders of other student organizations at the University of Michigan, dedicating much time to improving healthcare conditions at home. Their work included everything from organizing the free Hope clinic in Ypsilanti to drafting proposals for the American Medical Association. However, MSFC allowed us to extend these efforts to the global community.

Cuba, Colombia, Chile and Costa Rica, are the Latin American countries with the best health systems according to the WHO World Health 2000 report. The United States ranked 37th despite being the country that spends the most money on its health system. Cuba's ranking can be put into even greater perspective when one takes into account the forty-year embargo placed on Cuba by the United States — an embargo that has all but choked the food supply in Cuba. Regardless of the political situation, MSFC determined that there was much to be learned from a universal healthcare system such as the one in Cuba. We had the opportunity to observe the advantages and disadvantages of their system, as well as the ways in which a high quality of healthcare was made possible with very limited resources.

Prior to leaving for Havana, our group members acquired over one thousand pounds of medical, recreational, and school supplies to be donated to the facilities we would visit. The facilities included local neighborhood clinics, city-wide polyclinics, and hospitals, as well as an AIDS Sanitorium located outside of the city of Havana. Although it was clear when we arrived that our donations were greatly needed and would be put to good use, we were pleasantly surprised that the combination of our presence and our hope of continued friendship was the major focus of the healthcare workers in each of the clinics we visited. Often our donations were quickly put aside, while the director of each facility would enthusiastically guide us on a tour and answer any question we posed regarding not only their work in healthcare, but also the state of healthcare in Cuba. This feeling of genuine camaraderie was made apparent in a thank-you letter we received from the director of the Hogar de Leonor Perez Maternity Clinic, which stated, "More than the donations, we thank you for your honesty and sincerity. Through the willingness of each of our countries to be friends and improve relations, you help us to strengthen and to assist in our continuous struggle for a better world."

Along with visiting government-run facilities, we also had the good fortune of meeting Father Fernando de la Vega of Montserrate Church in Havana, who runs several support groups, including one for people who are HIV positive. Every Thursday, Father Fernando and members of his church make dinner and provide educational seminars for HIV-positive community members. These people come to learn about ways to deal with their disease on a day-to-day basis and to gain medical care from the

physician involved in the program. For many this is the only time they can address psychological, physical, and emotional issues, as they also receive medicines, food, and supplies to treat their illness. The importance of this form of nontraditional care opened my eyes to the many ways in which healthcare can be provided.

Many of us felt a combination of profound sad-ness and hope during our visit. It was apparent that healthcare, education, and the arts are areas in which the Cuban government has had success. Sadly, it was also apparent that the daily necessities of living, such as food and basic medical supplies, are where the Cuban government has failed. And from our perspective, the conditions in Cuba are only getting worse. It was terrible to see the shortages, but it also gave us hope to know that through our relationships, we can work together to improve the lives of the people there. We continue to gather supplies to be shipped to our contacts in Cuba. Even if they aid just one person, we feel that our efforts are worthwhile. Now that we have returned, I realize that the primary impact of our trip was not our donations, but rather our genuine efforts and concern for the people in Cuba.

We have forged lasting and strong relationships and we intend to continue our efforts to help in all the ways that we can. What we have learned about their healthcare system reinforces the fact that there are complexities that we are only beginning to realize. They involve politics, economics, and cultural differences. These are the same issues that we will face here in the US as we work to improve healthcare. But it is comforting to know that even as medical students we can make a difference, both now and most definitely in the future.

All photography in this article by Joseph W. Dougherty

House of Mourning

by Howard Liu

> ***"It is better to go to a house of mourning than to go to a house of feasting, because that is the end of every man, and the living takes it to heart."*** Ecclesiastes 7:2

"Go watch your patient die," my resident told me as I stood in the intensive care unit (ICU)with my clipboard dangling in my hands. I was post-call and flustered, having slept an hour after two late admissions. It was time for rounds, time to present my new admissions and get home. But with those words, my day took a sudden turn. The routine was shattered, and I was to learn more about life than I would in a thousand rounds.

Bill* was a 74-year-old man with end-stage chronic obstructive pulmonary disease (COPD). He was eight days out from a surgery for an amputation of his left leg above the knee (AKA) and surgery had passed him to medicine for failure to wean from the ventilator. Being my first ICU patient, I was excited and intimidated by this man with so many medical problems. At the Veterans Hospital, he was a "VA special," a patient for whom one could fill in a blank for every organ system.

Although initially fragile, my patient had turned things around. He began to regain consciousness and his respiratory status improved. "Extubate him," my ICU attending commanded that morning. It was my first extubation, and I pulled the ET tube out in a shower of mucus as the respiratory therapist (RT) gave the man his nebulizers. My intern and I pounded on his back and the man filled his lungs with air. He gasped and sputtered as I had seen newborns gasp after emerging from the darkness into the world. We suctioned his throat just as I had suctioned babies on obstetrics. And finally, we cheered as the pulse ox read 93% and I felt an ownership in this man's rejuvenation, his rebirth.

But then things changed. Suddenly, the numbers began to slide, slowly descending into the valley of hypoxia. "Go get the respiratory tech!" I yelled at the nurse, and she nodded and ran. The pulmonary fellow stepped in, whipping out her stethoscope and listening for lung sounds as the sats dropped to the mid 70's. "He's not moving air," she murmured as the RT switched the mask to a nonrebreather at 100% O2. As the man struggled to breath, he looked right into my eyes and began to mouth some words. I leaned closer and focused on his cracked, desperate lips. "Let me go," he whispered over and over. "Let me go."

The attending echoed those words and I looked up, not even noticing his presence. Dr. Adams was a serious man who liked his unit rounds precise and polished. He had a booming voice and I had never heard him speak so softly. He leaned closer to the man and said, "Bill, do you mean what you're saying? Do you want us to let you die?" Bill wheezed heavily and then nodded. Our attending beckoned us out of the room.

"What is this man's code status?" My intern stepped in, "I've been talking to his daughter, and he was DNR/DNI.** He was intubated for the AKA but was so sedated afterward that he wasn't able to communicate with us. According to his daughter, he never wanted to be intubated in the first place." At these words, my attending nodded. "Start round-the-clock Albuterol/Atrovent and give him 120 of Solumedrol. I'll talk to his daughter to make sure that's what he really wants." He turned to me, "Go to the waiting room and see if he has any family. This man is dying."

I was in shock as I stumbled to the waiting room. Bill had been doing so well this morning! The waiting room was empty and I returned to the bedside. Not knowing what to do, I stood by my patient as he drew painful labored breaths. I watched his sternocleidomastoid jump into sharp relief and sink back into his neck. My resident popped his head in and stated, "the family's on the way and will be here in 10 minutes." And then I cast my medical training aside and reached for Bill's hand.

He surprised me by squeezing back and smiling under his mask. As I watched this old man struggle to breath it reminded me of my grandfather, who had passed away in my senior year of college. I had stood by a similar bed when Grandpa had struggled to smile, frail after a short battle with pneumonia. Old wounds reopened as I realized that here was another child's grandpa, leaving the world, never to return. I felt my eyes mist over and almost began to cry. But I'm

ashamed to say that I couldn't. I was simply too proud to let my attending see my humanity.

The family arrived and I turned to the door. Two middle-aged men, a woman and two young kids hovered in the doorway. I gazed at them and imagined the conversation in their hearts. "Is this man hooked to ten thousand lines really Grandpa? Can this be the same guy who said grace at Thanksgiving, told such corny jokes, and always pinched my cheeks and laughed?"

They entered the room and I watched Bill's eyes glow in joy. The men were his son and son-in-law, and the woman was his daughter. They shuffled forward and awkwardly took his hand. The son was stoic, standing upright and stroking his father's head. The daughter was emotional, weeping and kissing his hand. I saw Bill take their hands and painfully lift them to his lips, only to be blocked by his mask.

During this time I stood at the foot of the bed. I had let go of my patient's hand but wanted to stay by his side. I didn't know what to do. Should I leave and give the family some privacy? Or should I stay and comfort them? Paralyzed with indecision, I stayed. I saw the grandchildren fearfully step forward, gazing at their parents' faces for guidance. Then the granddaughter took Bill's hand and said, "I love you Grandpa." It was a beautiful moment and Bill simply beamed.

But throughout this scene, the ugly aspects of medicine grated on my soul. Every few seconds, an alarm on the ventilator would beep as Bill's BP climbed over 200 or his saturation dipped below 90%. And then, my attending and intern came back in. While the family was weeping and speaking tenderly to Bill, I heard their voices loud in the background. "So, what do you think caused this guy to go downhill so rapidly?" "Well, with end stage COPD and pulmonary edema, there are several ways to ...." I turned and gazed at them in horror. How could they intrude on such a sacred time, a man's last hours on earth, with their crass pathophysiology lecture? I flushed angrily and wanted to shout, "For God's sakes, get out! Give this man some peace in his last moments!"

But I didn't shout, I simply stood silent and watched. Later, I was shocked again when I overheard a conversation between my chief resident and the intern. "Are you going to do an autopsy on this guy?" "I didn't think it was a good time to ask." "You should always get permission for an autopsy. There's so much good learning. Have you ever done one? They're awesome!"

The rest of the day passed in a haze. At some point, the son emerged from the room and said that Bill was asking, "how long is this going to take?" We turned on the morphine and switched to comfort care. And my intern switched the mask to a nasal canula, to allow the man to talk and breathe more freely in his final hours. When I finally left that afternoon, I said good-bye to the family and shook hands with Bill one last time. "It's been a pleasure taking care of you."

As I trudged out to my car, my mind was filled with questions. Why was Bill intubated, when he was DNI? Was this a good death? Did this man have dignity in his last hours?

I paused in deep introspection as I started the engine. The sun gleamed on the snow as the hospital disappeared on my rearview mirror.

Footnotes:

* The names of the characters in this story have been changed to preserve anonymity.

** DNR/DNI is an abbreviation for Do Not Resuscitate/Do Not Intubate.

Giant Strides for Small Science, an interview with Martin Philbert, PhD

by Margaret M. Sadoff

Nanotechnology can be defined as "the art of manipulating materials on an atomic or molecular scale" to create new materials with novel properties.[1] The applications for use of this technology are as vast as nanoparticles are small. Carbon tubes that are 100 times stronger than steel, faster and smaller computers, stain-resistant fabrics, cancer screening and detection — all are examples of what can be achieved with nanoscale inventions.[2] In January 2000, the National Science Foundation created the National Nanotechnology Initiative in order to strengthen and encourage interdisciplinary research and education in this rapidly emerging field.[3] The FY 2003 Presidential budget included a request for $710 million for nanoscale science, engineering and technology research and development.[4] Of course, as with any newly emerging scientific endeavor, there is concern for the unknowable, unforeseeable consequences that may accompany these advances.[5] There is no denying, however, that if nanotechnology lives up to its promise, the rewards will be great and far-reaching. They will also have the potential to impact nearly every aspect of our daily lives.

Dr. Martin Philbert, PhD

Imagine a world in which tiny machines are engineered to enter the human body and repair damage or even cure disease. That's just what Isaac Asimov did in his 1966 novel, *Fantastic Voyage*. In the book, Asimov created the Proteus, a miniaturized submarine that journeys into a brilliant scientist's brain to destroy a life-threatening blood clot. Set against the backdrop of the Cold War, *Fantastic Voyage* is a remarkably prescient piece of science fiction. Nearly 40 years after its first publishing, the story continues in a collaborative research effort spanning the fields of neuroscience, engineering, structural biology and medicine. Today, several University of Michigan researchers have pushed Isaac Asimov's creative vision into the realm of clinical reality.

I sat down with Dr. Martin Philbert, Co-Principal Investigator of the UM initiative that is funded by a National Cancer Institute Unconventional Innovations Program Grant, to discuss the use of nanotechnology in biological systems.

Can you describe the technology that you and your colleagues have developed and how it is used in your research?

My lab uses nanoprobes as real-time, intracellular sensing devices in the study of neurons and other cells. We have been working with Co-Principal Investigator, Raoul Kopelman, Ph.D., the Kasimir Fajans Collegiate Professor of Chemistry, Physics and Applied Physics, since 1996 to develop and refine these probes. The nanosensors or "PEBBLEs" (for Probes Encapsulated By Biologically Localized Embedding) are comprised of a biocompatible matrix that encapsulates a fluorescent dye indicator. Upon laser activation, the indicator emits light and allows us to determine the precise location of sensors within the cell.

How do you get the PEBBLEs to enter cells?

PEBBLEs range from 20 to 200 nanometers in diameter — small enough to be rendered invisible to the cell. They are delivered via gene guns or liposomes, or they can be microinjected into cells *in vitro*. In this way, we can determine the precise position and location of sensors and measure various functions of mitochondria, the nucleus and other organelles within a single cell.

What makes PEBBLEs superior to other techniques for sensing intracellular activity?

PEBBLEs have several important properties that make them ideal biological sensors. First, a good sensor must be minimally invasive. PEBBLEs are much more than biologically inert—the surface can be cloaked and hidden from the system. So they overcome the major obstacle of classic intracellular dye techniques. Utilizing

a "stealth technology" strategy, PEBBLEs enter the cell or tissue without disturbing the system. Second, PEBBLEs allow us to separate the biological processes in the cell from the chemical components of the device. In our system, fluorescent indicators are fully encapsulated within the PEBBLEs so they cannot leach into the cell and change the cellular environment. In other words, the presence of PEBBLEs does not change the biology of the cell and the biology of the cell does not affect the chemical indicator buried within the PEBBLE. So we know that the biological phenomena we are observing is real rather than merely an artifact of altered cellular chemistry.

This technology has obvious indications for use as a therapeutic tool in addition to a sensing device. Can you explain how that would work?

In addition to its ability to sense the cell's environment, the technology provides a way to detect, repair or remediate problems as well. And most importantly, these functions can be engineered into the same dynamic platform. As far as detection goes, PEBBLEs can be introduced by intravascular injection, enabling us to detect plasma concentrations of many things — sodium, calcium, glucose, reactive oxygen species, and so on. In this way, the technology may have wide applications for clinical detection and diagnosis. Since multiple indicators can be used within a single PEBBLE simultaneously, this gets us closer than ever before to being able to detect the global environment within a single cell within a single snapshot in real-time. We have also had success in using gadolinium PEBBLEs to enhance the contrast of MRI. This allows us to detect very small tumors such as malignant gliomas, medullablastomas and other intracranial malignancies that may not be readily detectable with regular MR imaging techniques.

What about drug delivery?

As I mentioned previously, for sensing applications we want to be minimally invasive but as a therapeutic tool, PEBBLEs can be designed to be highly yet selectively toxic. Any targeting moiety can be attached to the surface so that, for instance, PEBBLEs could selectively detect and destroy cancer cells. The current therapeutic PEBBLEs contain ruthenium and deliver a "nanobomblet" — a lethal dose of singlet oxygen. Once attached to the cancer cell membrane (unlike sensor PEBBLEs, therapeutic PEBBLEs do not enter cells), a controlled oxidative burst destroys the membrane and ultimately the cell. Because the targeting moieties are designed to specifically target cancer cells, normal cells are spared. In addition, pinpointed laser activation provides further control, acting as a fail-safe on/off switch. Again, detection and destruction capability can be engineered into the same PEBBLE. For example, we can first view then selectively kill brain tumor cells simply by changing the wavelength of light. We only laser target those areas that are detected as having tumor cells.

So if targeted delivery and selective activation bypasses the liver and there is no metabolism, this seems to give an obvious advantage over traditional chemotherapeutic agents.

Yes, this kind of therapy provides a major advantage over classic therapy and its associated problems. For instance, we do not deal with the traditional dose-response problems of toxicity since by selectively targeting and destroying single cells, we reduce the total dose given and do not damage other cell types or organs. This may eliminate the side effects often seen with traditional chemotherapy such as hair loss, mucousitis, and GI distress. Also, we avoid the problems that chemotherapeutic agents pose with regard to metabolism and bioactivation since PEBBLEs are deactivated upon elimination from the body. This technology, therefore, maximizes the benefits of therapy and minimizes the adverse consequences associated with the toxic response.

How far away is this technology from clinical trials?

Pre-clinical trials are probably about one to two years away.

Do you think this technology will eventually replace chemo and radiation therapy?

More likely it will be used as an adjunct to traditional therapies.

Are there certain cancers that will respond more favorably, for example, solid tumors versus leukemias?

We know this works with solid tumors and we think it will work for other cancers and disease processes as well. Obviously, each unique situation will require a slightly

different strategy. The beauty is that the platform is flexible enough to accommodate those various strategies.

What are the challenges to overcome with this technology?

One of the challenges with intravascular therapy will be our ability to keep the PEBBLEs in circulation long enough to get to the target. So there is still a good deal of fine-tuning to be done in terms of therapeutic delivery. But so far, *in vitro*, we haven't observed any negative consequences.

Other collaborators in this joint venture include:

Anne Marie Sastry, Ph.D., Associate Professor of Mechanical and Biomedical Engineering, University of Michigan School of Engineering. Dr. Sastry works on 3-D modeling of PEBBLE behavior within cells and studies how PEBBLEs distribute and interact with one another intracellularly.

Al Rehemtulla, Ph.D., Associate Professor of Radiation Oncology and Brian Ross, Ph.D., Professor of Radiology, University of Michigan, School of Medicine. Drs. Ross and Rehemtulla work on imaging and therapeutic modalities for translation to the clinic.

Jeffrey Anker, B.S., doctoral student, University of Michigan, Applied Physics Program. Mr. Anker is working on magnetic modulation of nanoprobes for the detection of low abundance ion binding events.

I wish to thank Dr. Martin Philbert for helpful editorial comments. Dr. Philbert is Associate Professor of Toxicology and Associate Chair for Research and Development in the Department of Environmental Health Sciences, School of Public Health, at the University of Michigan. He specializes in neurotoxicology and experimental neuropathology.

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Cell-based Immunotherapy of Cancer: New Directions in Tumor Immunology

by Michael S. Khodadoust

Immunotherapy represents an extremely promising alternative to traditional cancer therapy. Inducing an active anti-tumor immune response would utilize the specificity and potency of the immune system, yielding a treatment capable of eliminating the most resilient cancers without the toxicity associated with more conventional approaches. It is even conceivable that after rejection of a tumor, the immune system could then provide the patient with protection against a future relapse. This would represent a tremendous improvement in the current standard of care for many cancers.

The notion that the immune system could be used in cancer therapy arose out of early experiments where chemically induced tumors were transplanted into syngeneic mice. Although normal tissues were accepted by the recipient mouse, transplanted tumors were rejected.[1] These simple experiments demonstrated that the immune system was able to distinguish cancer cells from healthy cells and could effectively eliminate established tumors. Based on these and other findings, numerous cancer vaccine trials have been conducted. Thus far, however, these attempts have been largely unsuccessful.

More than fifty years after the conception of tumor immunology, the advancements in our understanding of immunology have led to radical new approaches to the treatment of cancer. Foremost among these advancements has been the identification of tumor associated antigens (TAAs). There are now numerous TAAs associated with a variety of cancers that are able to elicit a T-cell response. The discovery of these antigens not only provides targets for immunotherapy, but it also allows for the precise measurement of the immune response induced by treatment. A second major breakthrough in the field of immunology was the discovery of the central role that the dendritic cells (DCs) play in invoking an immune response. Consequently, DC-based vaccines have become a major focus of research. Progress has been made in several fields of immunotherapy, most notably monoclonal antibody therapy and cytokine therapy, but the increased understanding of the immune system has given rise to the next generation of cancer immunotherapy: the manipulation and delivery of functional immune cells designed to provide active anti-cancer immunity. Although extremely technically demanding, cellular immunotherapy represents one of the most promising anti-cancer treatments currently under investigation.

Dendritic Cell Vaccines

Dendritic cells are essential to the immune system because they are uniquely capable of priming both naïve CD4 helper T-cells and naïve CD8 cytotoxic T-cells. In cancer therapy, DCs are used to present tumor antigens to T-cells in the lymph nodes. DCs can be cultured with high yield from peripheral blood mononuclear cells or CD34+ progenitor cells, or alternatively can be collected from peripheral blood after mobilization by administration of FLT-3 (Fms-Like Tyrosine Kinase) ligand or G-CSF (Granulocyte Colony Stimulating Factor). TAAs can be delivered to the DCs in several forms, and then the DCs load these antigens onto MHC class I and II molecules. After loading of the antigen, the cells can be injected into the patient where they must home to the lymph node and then present their antigen to naïve T-cells.

Clinical trials with DC-based vaccines have been tolerated very well and have achieved moderate success. However, the trial designs involving DCs have been notoriously variable. Despite the large number of published DC trials, there is no consensus for the best population of DCs to use, the optimum antigen loading process, or the most effective route of administration. Most DC trials are designed with a focus on obtaining a clinical response, not optimizing the treatment, and as a result, this form of therapy has remained in a primitive stage.

The state of maturation of administered DCs is a key variable in DC-based vaccination. Cultured DCs are initially immature. They actively sample antigens from their environment, but do not express high levels of MHC molecules or essential costimulatory molecules required for T-cell activation. Therefore, immature DCs are poorly immunogenic, and have even been shown to make T-cells tolerant to presented antigen.[2] Although immature DCs have been used widely in trials with some success, their capacity to tolerize is a serious

concern.[3] In contrast, mature DCs are highly immunogenic, display appropriate antigen presentation markers, and express necessary chemokine receptors required to home to secondary lymphoid tissue. Interestingly, studies in rhesus macaques have shown that mature and immature DCs injected intradermally migrated to the draining lymph node with equal frequency.[4] Furthermore, recovered immature DCs had spontaneously matured during trafficking to the lymph node. However, another study in melanoma patients showed slightly more mature DCs reaching the lymph nodes than immature DCs.[5] Perhaps more importantly, the study demonstrated that mature DCs migrated into the T-cell regions of the lymph node, while immature DCs remained around the periphery, possibly limiting their ability to stimulate a T-cell response. The issue of maturation is further complicated by the finding that tumor lysates contain certain DCs maturation factors.[6] Thus, DCs loaded with tumor lysate can quickly mature even in the absence of other maturation stimuli. The question is not simply whether to use immature or mature DCs, but rather at what time point during the maturation process will injected DCs be most effective at trafficking to lymph nodes and priming T-cells. Clinical trials must be designed to determine the optimal state of maturation of therapeutic DCs.

Another unresolved issue in the conduct of DC based clinical trials is the method of administration. The most common routes of administration are intravenous, subcutaneous, intradermal, and intranodal. Presumably, the injected DC must traffic to lymph nodes to present their antigen. Although intravenous administration is a common route of administration in DCs trials, it seems unlikely that it can effectively deliver DCs to the lymph node. There is currently no evidence that monocyte-derived DCs can gain access to lymph nodes via the blood, but this route is still sometimes used in trials for this population of DCs. One trial involving this type of DC showed that intravenous injected DCs migrated to lungs, liver, spleen, and bone marrow, whereas intradermally injected DCs could be found in the regional lymphatics.[7] However, even subcutaneous or intradermal injections of DCs rarely succeed in delivering large numbers of DCs to the lymph nodes. For example, the previously mentioned de Vries et al. study[5] recovered only 1.8% of injected mature DCs and 0.3% of injected immature DCs from the draining lymph node. Intranodal injection has yielded better results, but is much more technically demanding and has not proven to be more effective in producing an immune response.[8] The poor migration of DCs to lymph nodes presents a major barrier to effective DC based immunotherapy.

A final major variable in the design of DC vaccinations is the form of antigen used to load the DCs. The use of peptides has several advantages. It allows for high loading efficiency of the antigen and greater control over the induced immune response. The peptides can be used in immune assays to precisely measure the number and quality of reactive T-cells. Additionally, compared to the use of whole cell lysates, peptides reduce the chances of the patient developing autoimmunity to other self-antigens present in the tumor lysate.[9] One major drawback to using peptides is that it requires the prior identification of TAAs specific to the cancer to be treated. Many peptides are also MHC allele specific as well. Thus, not only must the TAA be expressed on the tumor, it must also be compatible with the patient's MHC haplotype. Using whole protein or cell lysates allows the patients' own DCs to process and load compatible epitopes on their MHC molecules.

Another major concern with peptides is immune escape. It has been demonstrated that tumors can downregulate expression of targeted antigens to evade T-cell attack.[10] The use of only a single peptide antigen leaves the immune system vulnerable to this type of escape. It is also possible, though, that once an immune response to tumor cells has been initiated, the immune system may recognize other TAAs that it has not been vaccinated against on the dying tumor cells, a concept called epitope or determinate spreading. One recent study of 18 patients with either stage III or IV melanoma treated with peptide loaded DCs demonstrated that a single patient developed immune reactivity to other melanoma antigens in addition to the one to which he was immunized.[11] Notably, this was the only patient who achieved a complete response, implicating the importance of epitope spreading in achieving a clinical response. Unlike peptide based antigens, the use of whole cell tumor lysates does not require the prior identification of TAAs expressed by the cancer cells, and it is more likely to produce a T-cell response to multiple antigens, thereby limiting the possibility of immune escape. However, this also increases the likelihood that one of the antigens will be an important self-antigen. Other methods of delivering antigens to DCs are being tested as well.[12] Many of these methods allow for greater loading of antigens, but add complexity to an already technically demanding treatment.

Adoptive T-cell Immunotherapy

An alternative approach to DC therapy is adoptive transfer of CD8+ cytotoxic T-lymphocytes. This method bypasses the need for the body to initiate the immune response. Adoptive transfer of T-cells involves selecting or producing T-cells that are reactive to the cancer, expanding and manipulating them ex vivo, and then administrating them to the patient.

There are several different ways to produce a significantly large population of tumor-reactive T-cells. One is purifying and expanding tumor-infiltrating lymphocytes. Another approach involves collecting T-cells from the tumor-draining lymph nodes, and then selecting these for tumor-reactive cells. Alternatively, a tumor vaccine can be given at a remote site, and cells from the vaccine-primed lymph node can be selected. Highly reactive T-cell clones to specific tumor antigens can be selected and expanded through long-term culture in vitro.[13] A more experimental approach to rapidly producing large numbers of tumor specific T-cells is gene delivery of cloned T-cell receptor genes to peripheral blood T-cells. These transduced T-cells will all be specific for the antigen of interest.

The difficulty in adoptive T-cell therapy is not simply in producing sufficient quantities of tumor-specific T-cells, but also in maintaining them and their function in vivo. Adoptively transferred T-cells are rapidly eliminated following transfusion. In a study of 10 melanoma patients, on average one-half of infused T-cell clones were deleted after only 6.68 days.[14] Supplementation with IL-2 increased the median half-life of the cells to 16.92 days, but the reason for the rapid elimination of adoptively transferred cells is still unclear. The quality of persisting cytotoxic T-cells is as important as the quantity. The cytokine profile of the tumor-specific cells is a crucial factor in the elimination of tumor. For example, a high IFN-gamma to IL-10 ratio correlates with a positive outcome in renal cell cancer patients.[15] The development of culture conditions that optimally polarize CTLs to IFN-gamma secreting cells is an active field of research.

Immune Regulation of Anti-tumor Immunity

A growing concern in tumor immunology has been the role of immune regulation in suppressing anti-tumor responses. The resurgence of the much maligned T-regulatory cell (Treg) has led to speculation of their effect on the anti-tumor immune response. Treg cells suppress antigen-specific immune responses through cell-to-cell contact and secretion of suppressive cytokines such as TGF-beta and IL-10. Recent evidence now strongly implicates the CD4+/CD25+ population of Treg cells in the control of the anti-tumor response. Studies in humans and mice have found Treg cells localized inside tumors.[16,17] These cells were also shown to be producing IL-10 and TGF-beta.[17] Mice treated with anti-CD25 depleting antibodies prior to tumor challenge responded significantly better to adoptive T-cell therapy than non-depleted controls.[18] Additionally, transfer of CD25 depleted T-cells to nude and healthy mice conferred superior protection against subsequent tumor challenge than non-depleted cell populations.[18,19] Further evidence of the involvement of Treg cells in suppressing anti-tumor responses comes from a recent human clinical trial examining nonmyeloablative chemotherapy followed by adoptive tumor infiltrating lymphocyte transfer.[20] This treatment produced dramatic results in several patients with metastatic melanoma. Two of thirteen subjects had over 95% regression of cutaneous and subcutaneous melanoma lesions, while four other patients achieved partial responses, and another four displayed significant shrinkage in at least one metastatic mass. The transferred cells persisted and remained much longer than cells transferred in conventional adoptive therapy trials. This is most likely due to the elimination of Treg cells during the conditioning regimen, although it is possible that the lymphodepletion altered the homeostatic mechanisms of the patients, allowing for the persistence of the transferred cells. Bypassing the suppressive effects of Treg cells and other regulatory mechanisms of the immune system will be critical in the development of successful immunotherapy.

The field of cell-based cancer immunotherapy is still in its infancy. Perhaps the most remarkable aspect of this future therapy is that despite all of the unknowns surrounding the field, effective immune responses are relatively common, and clinical responses have been achieved in several clinical trials with patients who have failed all other treatments. With continued optimization of protocols and further understanding of the immune system, tumor immunotherapy has the potential to develop into the standard of care for cancer patients.

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"Yotta-detection" and "Nano-destruction": Emerging innovations in the fight against cancer.

by Mahesh Shenai

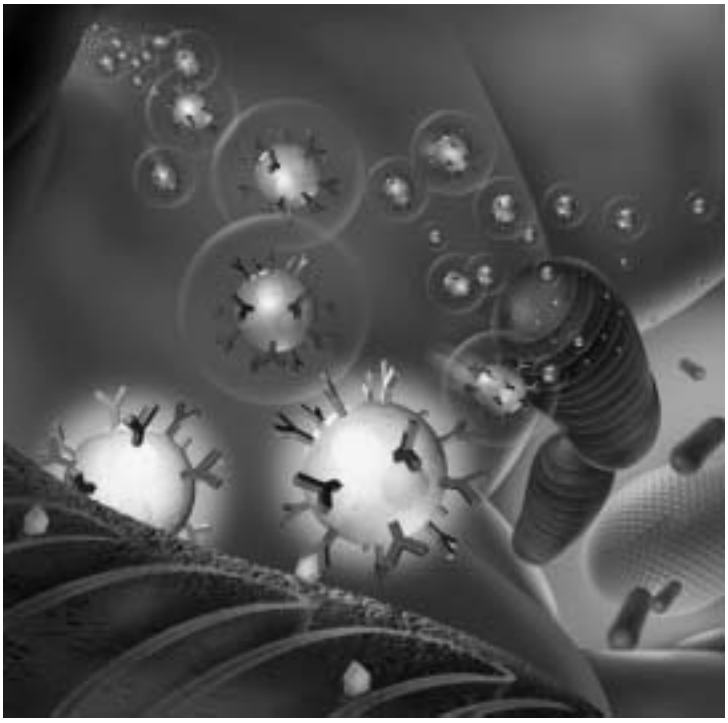

Illustration by Christopher Burke

Even before the term "cancer" was coined by Hippocrates (460-370 B.C.), the precise cause of cancer was an item for speculation. The ancient Egyptians blamed cancer on a single universal entity — the Gods. As time went by, the etiology of cancer remained mysterious, but the hypotheses became more mundane, implicating everything from excessive black bile and stomach worms (temporarily awarded the Nobel prize in 1926) to specific foods and contagions. Though some of these proposals were proven largely ridiculous, the ancient debate had matured from blaming an unequivocal godly force to acknowledging the diversity of etiologies. Today, our understanding of cancer etiology spans the magnitudes of the metric scale. On the largest scales, epidemiological studies have been able to isolate specific causes of cancer in millions of people. And on the smallest scales, rapid advancements in molecular biology have elucidated the contributions of numerous defects in the cell's genome and proteins (the nanoscale) to cancer causation. As a result, the random expedition for a single "magic bullet" cure that covers the entire spectrum of etiologies has transformed into a more focused search for novel *strategies* aimed at finding and characterizing tumors early, followed by targeted, customized therapy.

The numbers are clearly against us. With an estimated 100 trillion micron-sized cells comprising our body, each having 3 trillion base pairs, only one of potentially 10^{24} (yotta-) events needs to falter for human diseases, such as cancer, to ensue. Each event occurs stochastically in the sub-nanoworld of single molecules, incapable of being visualized by even our most powerful microscopy techniques. Detecting the event of cancerous transformation early and reliably is a numerically incomprehensible feat. Even if detected, the precise manipulation and destruction of these nanoevents seems more than impossible. Nevertheless, medical science is making tremendous progress in defeating these odds. Armed with a history of solid basic science research and new multidisciplinary strategies, novel medical imaging techniques have begun to identify the molecular appearance of cancer, while treatment strategies are now focused on targeting these molecular events.

Long before tumors appear as gross anatomical or symptomatic irregularities, cellular and molecular processes have already begun to go awry. Thus, while conventional imaging techniques (CT, MRI) have been invaluable in detecting cancerous lesions and directing their treatment, discovery and intervention is initiated relatively late in the metastatic progression timeline. However, novel imaging techniques are emerging on the horizon that emphasize the visualization of *functional*, sub-cellular processes instead of anatomic, macroscopic processes. As a result, physicians will be able to identify critical molecular defects and their potential for malignancy in order to vastly alter treatment strategies early in the course of disease. For example, positron-emission tomography (PET) uses engineered, process-targeted probes with radiolabeled isotopes that are detectable at pico- or femtomole/gram levels.[1] Exploiting the knowledge that glycolysis, DNA replication and other processes are dysregulated in cancer cells, these probes are designed to assay the levels of such targeted processes in real-time. Already, whole-body PET scans

have been applied to image ovarian, breast, prostate, and lung cancers, as well as Hodgkin's lymphoma and melanomas — but progress will depend on the development of novel probes that can differentiate between molecular classifications of cancer. Another innovation, *in vivo* near-infrared optical imaging, is a technique that also relies on versatile "smart" probes that can be detected with special scanners or endoscopic procedures.[2] Unlike the limited radioactive probes of PET, however, optical techniques could exploit an entire spectrum of fluorescent markers, potentially allowing the simultaneous monitoring of multiple molecular processes across several fluorescent channels. Optical imaging has been successfully used in animals, and is currently under study for its feasibility in humans. Both PET scanning and *in vivo* optical imaging hold tremendous promise in obtaining molecular signatures from evasive cancerous or pre-cancerous cells. Such specific knowledge would allow physicians to hone in on these delinquent cells with novel, molecular-guided chemotherapeutic missiles.

Numerous efficacious anti-tumor drugs exist, but their mechanisms depend on blocking cellular "housekeeping" processes such as DNA replication, cytoskeletal dynamics and other essential cellular processes. Consequently, these drugs destroy tumor cells, but inflict collateral damage on surrounding non-cancerous cells. Molecular-targeted anti-cancer drugs exist (Gleevec, Herceptin), but generally affect one mechanism in a cellular process and thus are limited to the treatment of cancers caused by a known single-defect. However, targeting information obtained from imaging and other protocols allows for the modular engineering of multifunctional nanodevices that seek the diverse "addresses" of suspect cells, deliver a local but lethal dose of chemotherapy, and then report its success in tumor destruction. One such nanodevice, the "dendrimer,"[3] is a synthetic nanoparticle containing numerous generic functional groups (10-1000) with the potential to attach to a variety of targeting agents, a battery of drugs, and specific reporter molecules, *simultaneously*, allowing for a powerful punch to a single cell. Pioneering research at the bench level is characterizing the synthesis and conjugation of these nanodevices, as well as their efficacy in the eradication of cancerous lesions.

As fundamental bench research is translated into clinically useful treatment strategies, the future of cancer detection and destruction is extremely optimistic. Further discovery and development will rely on multidisciplinary research that brings together the engineering and physical sciences with fundamental biological research towards a single anticancer goal. While the numbers are still clearly against us, we have the momentum of rapidly emerging engineering and biotechnology, to screen the potential yotta-events and eliminate errors with nanotechnology.

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The New Face of Chemotherapy: Designing Drugs for the Individual

by Kiarri Kershaw

"Imagine a day when you go into your doctor's office and, after a simple and rapid test of your DNA, your doctor changes her/his mind about a drug considered for you because your genetic test indicates that you could suffer a severe negative reaction to the medication." [1]

This quote, about pharmacogenomics, taken from the website of the National Center for Biotechnology Information, is what many believe to be the future of prescription drug therapy. Wouldn't it be great, as a patient, to know that the medicine you're about to take is going to be safe and effective? And as a physician, wouldn't it be nice to be able to ensure that your patient is not going to suffer from an adverse reaction to the medication that is commonly used for their illness? Individual variation in drug response can range from therapeutic failure to serious or even fatal adverse drug reactions (ADRs). A recent meta-analysis of 39 prospective studies from U.S. hospitals reported that 6.7% of patients have serious reactions and 0.32% have fatal adverse drug reactions. These fatal ADRs cause approximately 100,000 deaths per year in the United States.[2] This makes adverse drug reactions one of the leading causes of death. Can pharmacogenomics reduce this risk?

A central goal of pharmacogenomics is the prediction of drug response based on a patient's genetic profile. There is no simple way to determine how people will respond to a drug. Traditionally, pharmaceutical companies have used a "one size fits all" system, developing drugs that the "average" patient will respond to. This wouldn't be a problem if all drugs had wide therapeutic windows, meaning that they were effective over a wide range of doses. If this was the case, then it wouldn't matter as much that a particular drug was metabolized faster in one person than another. In reality, though, most drugs do not have wide therapeutic windows. Consequently, patients respond to treatments in a variety of ways: the medication can be ineffective for them; it can work fine; or it can cause toxicities, resulting in harmful side effects. Pharmacogenomics aims to consider all of the different genes that determine drug response and provide physicians with the knowledge they need to accurately prescribe effective medications to their patients.

With the publishing of the human genome sequence in 2001, it was found that there are about 10 million single nucleotide polymorphisms (SNPs) that account for all the genetic variation encoded in the human population. SNPs are variations in a particular nucleotide that occur in more than 1% of the population. Of the 10 million known SNPs, 60,000 exist in the coding regions of a person's DNA. These variations are the source of genetic predispositions to disease, response to chemicals and pharmaceuticals, as well as predictors of severity and progression of disease. They can also be used, theoretically, to determine a particular chemotherapy regimen for treatment purposes.

The discovery of SNPs has facilitated the use of genetic testing to predict drug response. It is no longer necessary to sequence each patient's genome, as interindividual variability in drug response will be represented in the 60,000 SNPs that are in the proximity of expressed genes. Although traditional gene sequencing technology is very slow and expensive, DNA microarrays can screen 10,000 SNPs in a matter of hours. Micro-arrays consist of a set arrangement of immobilized complementary DNA or oligonucleotide probes on a silicon chip. Once researchers have established that a certain SNP or group of SNPs is associated with a particular disease, they can use microarray technology to test an individual for that DNA disease-expression pattern, indicating disease susceptibility or drug sensitivity. This is done by taking the fluorescently labeled, genomic DNA of a patient and hybridizing it to an array loaded with probes for various SNPs. Spots on the microarray will fluoresce with greater intensity at SNPs that are specific to each patient, thereby determining whether they have or are at risk of a particular disease, as well as whether or not a certain chemotherapeutic will be effective or contraindicated in a particular patient. Microarrays have yet to be marketed as diagnostic tests, but there are several single SNP tests currently available. Myriad Genetics has developed a test called BRACA analysis that detects gene sequence variants in BRCA1 and BRCA2 genes that represent polymorphisms that are known markers of breast and ovarian cancer predisposition.[3] Having mutations in one of these genes puts a patient at higher risk of developing these cancers. Likewise, microarray

technology can be used to determine whether or not a certain chemotherapeutic will be effective in a patient.

Oncology is a field in which pharmacogenomics would be especially useful. Pharmacogenomics could be used to create more selective cancer treatments. According to the American Cancer Society, chemotherapy is one of the most effective methods we have for controlling and curing cancer. There are several factors involved in determining which drugs physicians choose to use for treatments, including type of cancer, stage of the cancer, patient age, patient's general state of health, and types of anticancer treatments given to the patient in the past. Chemotherapy drugs are also usually given in combination to create a more hostile environment for the cancer cells. Doctors must balance out dosages to be as effective as possible in killing cancer cells with only minimal side effects. Without knowing the genetic information of a patient, though, these doses can sometimes be unknowingly misbalanced and fatal. One example of this is among the thiopurine family of drugs, particularly 6-mercaptopurine. This prodrug is used to treat childhood acute lymphoblastic leukemia. Its activation requires the metabolism of thioguanine nucleotides, which enables mercaptopurine to exert its cytotoxicity and be catalyzed by multiple enzymes. It is activated by hypoxanthine phosphoribosyl transferase, but it can also be inactivated either via oxidation by xanthine oxidase or methylation by thiopurine methyltransferase (TPMT). The activity of TPMT is highly variable and polymorphic among individuals, and these disparities are associated with the therapeutic efficacy and toxicity of mercaptopurine. It has been found that TPMT-deficient patients are at very high risk of developing severe hematopoietic toxicity if treated with conventional drug doses. This seemingly minor genetic difference can prove fatal if not recognized prior to treatment. Prometheus Laboratories in San Diego markets a genetic screen for the aforementioned SNP, TPMT called PRO-PredictRx® TPMT.[4]

Does it all sound too good to be true? Genetic testing for single nucleotide polymorphisms like TPMT and BRCA1 are already being used routinely before prescribing chemotherapy treatments. But no new technology is without its flaws. Are there pitfalls to this form of testing? What are the economic and social implications of pharmacogenomics? Who will have access to these genomic tests, and who is going to pay for them? Should there be regulation of who can be screened and under what circumstances? How will that be determined? Today, such questions are being addressed by scientists representing a diverse number of specialties from anthropology to bioethics. There aren't a lot of conclusive answers to these questions yet, as the field of pharmacogenomics is still relatively new. However, there are some things we should all be thinking about. Everyone can agree that the most cost-effective therapy is the one that works the first time. The direct cost of genotyping the population should not be very expensive. The cost of testing patients is believed by some to start at around $10 for screens of single mutations and $250 for screens of multiple genetic polymorphisms.[5] Lab testing has traditionally been paid for by the individual or a third party (e.g., insurance company or the government), but these tests could conceivably be included in the market cost of the prescription drug. With the development of more pharmacogenomic tests to complement prescription drugs, the demand for screens will increase and the cost will increase with it. This has obvious implications for the cost of health care in general.

According to Dr. Muin Khoury and Dr. Jill Morris of the Centers for Disease Control, clinical and epidemiologic studies are needed to address a few key issues for pharmacogenomics to be successful. One is how much variation there is in drug response between individuals with different genotypes. Is a particular SNP causing toxicity in patients, or is the therapeutic window of the drug wide enough to accommodate a variety of drug responses? The size of the population that is affected by a variant gene sequence is another important issue. The cost of genotype testing could be too high, when compared to the benefit of preventing disease or prescribing a drug more accurately, if it only helps a minute fraction of the population. Finally, there are also imperfections in the testing system. Often, diseases are caused by multiple gene mutations combined with environmental factors. Testing only one gene mutation can result in the generation of false positives. Analyzing a collection of SNPs grouped together in the genome, known as haplotypes, would be the best screen, but these are more complex to develop. Regardless of the remaining uncertainties, the day when patients can go into the doctor's

office for a genotype screen is approaching and researchers in many disciplines are working together to predict and prepare for the social and economic impacts this new technology will have on our health care system.

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Human Papillomavirus as a Causative Factor in Head and Neck Cancer: Research from the University of Michigan Head and Neck Oncology Laboratory

by Erin McKean Lin, Thomas E. Carey, Carol R. Bradford

Human Papillomaviruses (HPV) are known causes of cervical and anogenital cancers and are associated with about 10% of cancers worldwide. Over the past 20 years, HPV has also been identified as a potential etiological factor in head and neck cancers.[1] Researchers at the University of Michigan Head and Neck Oncology laboratory have studied many aspects of HPV's potential role in head and neck squamous cell carcinoma (HNSCC), including epidemiology, detection of HPV DNA in fresh tumors and cell lines, gene expression, interaction with tumor suppressor genes, and determination of the state of viral DNA (integrated versus episomal) in HNSCC.

The earliest study from the University of Michigan suggested that HPV could have a role in the development of head and neck squamous cell carcinoma in immunosuppressed hosts.[2] Three transplant patients with HNSCC had histopathology suggestive of papillomavirus infection (koilocytosis with hyperkeratosis and parakeratosis). One 18 year-old female patient with no alcohol or tobacco history was found to have a lingual squamous cell carcinoma. A second patient was a 29 year-old woman diagnosed with a left tonsillar fossa and tongue-base tumor. Though she had a 25 pack-year history of tobacco, she was strikingly young to display this type of tumor. The last patient was a 53 year-old man with a considerable tobacco and alcohol consumption history, who had only a 7-month interval between transplantation and diagnosis of laryngeal cancer. This may suggest a potentially additive or synergistic effect of HPV with traditionally recognized risk factors for HNSCC.

Following these interesting observations, twenty-two HNSCC cell lines established at the University of Michigan, representing twenty tumors, were screened for the presence of HPV DNA.[3] Southern blot and polymerase chain reaction (PCR) analyses revealed only three HPV-positive cell lines (3/20 of tumors or 15%). One cell line from this group came from the tumor of another surprisingly young woman with laryngeal cancer. UM-SCC-23 contained HPV 31 sequences and was derived from an epiglottic cancer in a 36-year-old woman with both alcohol and tobacco exposure. Another young woman transplant patient with no history of alcohol and tobacco use was later found to have an HPV-positive lingual squamous cancer. Again, these results were suggestive of HPV as a cofactor in head and neck cancer. The prevalence of HPV in fresh tumors versus cell lines was quite different. Overall, using PCR, the prevalence of HPV DNA in HNSCC studied worldwide was estimated at 34.5%.[4,5] The lower prevalence in the University of Michigan cell lines may suggest a hit-and-run mechanism of carcinogenesis or it may simply reflect differences in screening techniques and probes utilized. Hybridization techniques traditionally have been gold standards for detection of HPV, yet PCR is more sensitive.

Ten years after the initial studies of HPV in head and neck cancer at the University of Michigan, researchers began to study HPV infection in "young" versus "old" HNSCC patients.[6] Fourteen "young" (<50 years old) and fourteen "old" (>50 years old) HNSCC patients were matched for tumor site. Four additional unmatched patients were also studied. Specimens were analyzed by PCR and Southern blot hybridization. Fifteen of thirty-two samples harbored HPV, with sixty-percent of those containing HPV type 16, a high-risk type. Tumors from 50% of the younger group were HPV-positive versus 44.4% from the older group. There was no significant difference noted. An unexpected observation from the study was the statistically significant improved survival rate among HPV-positive patients. This finding inspired later studies on prognostic factors.

Additional experiments at the University were performed to determine HPV's role in carcinogenesis in low-risk individuals .[7] Four tumors from nonsmoking, nondrinking women, ages 43 to 57 years were examined for the presence of HPV DNA. Cell cultures established for two of the four tumor specimens were also tested. Three of four fresh tumor specimens were HPV-positive using PCR with L1 primers, which are not specific for any particular HPV type. Established cell culture DNA from the fourth tumor was also found to harbor HPV DNA, suggesting a possible enrichment of cells containing HPV during the culturing process. HPV typing revealed four of four tumors positive for high-risk HPV type 16. Of note, three of four tumors were

lingual cancers, and the fourth specimen was of a tonsillar squamous cell carcinoma. This is consistent with the general acceptance that the tonsil and tongue base are the sites most commonly associated with HPV-related HNSCC.

Beyond examining cancerous lesions themselves, studies were performed on premalignant head and neck lesions, primarily inverted papillomas. The first study found that the presence of HPV predicted recurrence of inverted papilloma (IP), a locally aggressive lesion with the potential for progression to malignancy.[8] Of twenty-five patients with surgically-resected IP, thirteen recurred, all of which were previously identified as HPV-positive. Five IP specimens with dysplasia were HPV-positive, and all three patients in whom malignant transformation occurred were HPV-positive. All patients with HPV-negative specimens had no recurrences. A subsequent study examined HPV types involved in progression of inverted papilloma.[9] Overall, twenty of thirty-two IP specimens tested positive for HPV. Within this group, five of seven dysplastic IP specimens were HPV-positive, as were three of three synchronous specimens (IP adjacent to cancerous tissue). Additionally, four of seven metachronous carcinoma lesions (cancerous lesions without IP arising in a previously biopsy-proven IP site) were positive for HPV. IP specimens that were benign but HPV-positive contained either HPV type 6 or 11. The dysplastic lesions contained HPV 6, 11, or 18. Synchronous lesions contained HPV6, 11, or 16. Three of four metachronous lesions contained HPV-16, while the type of the fourth lesion was indeterminable. These results were generally consistent with what is known about HPV subtypes in anogenital lesions. More than 70 distinct types of HPV exist, and specific types have been linked to malignant lesions of the penis (HPV 16 and 18), vulva (HPV 16 and 18), uterine cervix (HPV 16 and 18), and larynx (HPV 6, 11, 16, 18, 30 and 33). Other types (e.g. HPV 6 and 11) are frequently associated with benign lesions. The papillomaviruses have thus been divided into high-risk and low-risk types, with the most frequently encountered high-risk oncogenic viruses being HPV 16, 18, 31, 33 and 35. However, detection of high-risk type HPV DNA in head and neck premalignant and malignant lesions does not itself prove causality. Expression of the HPV genome was thus studied in tissue from a nasal inverted papilloma and adjacent normal tissue in an immunosuppressed patient. Expression of E6 and E7, HPV oncoproteins, was found only in the IP tissue.[10]

Respiratory papillomas (RPs) are other premalignant lesions that were also studied for HPV presence, type, and correlation with progression to malignancy.[11] 82.4% of RP specimens were HPV-positive, with 9.8% of these positive for both high- and low-risk HPV types, 13.7% positive for high-risk HPV types alone, and 58.8% positive for only low-risk HPV types. Of four patients who went on to develop laryngeal carcinoma, one had both HPV type 16 and 18, one had HPV type 16, one tested positive for "high risk" HPV by hybrid capture analysis and for HPV type 6 by dot blot hybridization, and one tested positive only for HPV type 6. The two patients with tumors containing high-risk HPV had no alcohol and tobacco exposure, while the two with tumors containing low-risk HPV had exposure to both alcohol and tobacco. Again, data were consistent with current knowledge about HPV types. Infection with high-risk HPV types was associated with long-term risk of developing HNSCC, while infection with low-risk HPV types appeared to act in concert with other factors in the development of disease.

HPV DNA may remain episomal (in its circular dormant form within the cell) or may integrate into the host DNA. Integration in genital lesions eventually results in the increase of E6 and E7 transcripts, high-risk HPV oncoproteins, which inactivate the retinoblastoma (Rb) and p53 tumor suppressor gene functions and also activate eukaryotic cell division. Loss of p53 and pRb functions allows cell cycle deregulation and thus increased mutation and chromosomal instability. Additionally, activation of telomerase allows addition of terminal repeats to chromosome ends, a process that has been shown to be critical in immortalization of tumors. In genital lesions, HPV genomic DNA is most commonly found in an episomal state in precursor lesions, whereas high-risk HPV DNA is usually present in malignant lesions of the cervix in an integrated state. In HNSCC, the story may not be as clear cut. A low-risk HPV type was found to be integrated in a tonsillar carcinoma at the site of several putative tumor suppressor genes,[12] and a high-risk HPV type was found to be integrated in an oral HNSCC primary tumor and cell line with six loci.[13] Through efforts to identify additional HPV-positive HNSCC cell lines in the University of Michigan, UM-SCC-47 was found to be stably HPV-positive, presumably containing integrated HPV type 16 DNA.[14] UM-SCC-47 is currently being characterized by spectral karyotyping (SKY) and concurrent fluorescence in situ hybridization (FISH).[15] Preliminary results have revealed integration of HPV type 16 at one single locus of the pseudotetraploid,

highly rearranged UM-SCC-47 genome. The HPV DNA appears at the same locus in several subclones, and thus the integration appears to have likely occurred early in the malignant transformation of the tumor. This is suggestive of a causal role for HPV.

Perhaps the most important research regarding HPV in HNSCC involves its prognostic implications.[16] HNSCC with p53 tumor-suppressor mutations may have a worse prognosis, since the HPV E6 protein can complex with wild-type p53 and inactivate it. Single-strand conformational polymorphism (SSCP) and DNA sequencing were performed on thirty-two HNSCC specimens to determine p53 status of the tumors, and PCR and Southern blot hybridization were used to identify HPV-positive specimens. HPV DNA was detected in 46.9% of the specimens, with 60% of positive specimens containing HPV type 16 DNA. Eight of thirty-two specimens displayed nonsilent p53 mutations, with two specimens containing two separate mutations (a total of ten mutations). Six of the p53 nonsilent mutant specimens were from HPV-negative specimens, while only two were from HPV-positive tumors. This suggested a possible correlation between HPV-positive status and wild-type p53. Patients with tumors containing nonsilent p53 mutations (primarily HPV-negative) had a hazard ratio for death 4.48 times that for patients with tumors containing wild-type p53 (more likely HPV-positive). Furthermore, when comparing survival of patients with HPV-positive versus HPV-negative p53 wild-type-only tumors, there remained a survival advantage for patients with HPV-positive tumors. The overall best survival was seen in patients with HPV-positive, p53 wild-type tumors. Hypotheses for this advantage include early expression only of E6 allowing p53 function after tumorigenesis, interference by E6 of only one function of p53 (e.g. apoptosis versus transcriptional regulation), and incomplete p53 inactivation. In any case, these results, if confirmed with larger studies, could have great importance in prognosis and treatment choices offered to this subgroup of patients.

Conclusion

Research from the University of Michigan Head and Neck Oncology Laboratory has contributed significantly to the evidence implicating HPV as an etiologic factor in head and neck squamous cell carcinoma. Results have provided new information and ideas, and have also supported data from other laboratories and institutions. It has been shown that HPV may be a cofactor with tobacco and alcohol use in the progression of premalignant lesions, while HPV alone may be implicated as a causative agent in immunosuppressed patients. HPV may also be responsible for carcinogenesis in low-risk patients (e.g., young nonsmoking, nondrinking women), though there appears to be no difference in HPV infection between "young" and "old" HNSCC patients. HPV does appear to be most often associated with squamous cell cancers of the tonsils and tongue base, and certain types of HPV, especially HPV 16, 18, and 31 are more likely to be associated with malignant progression of head and neck lesions. Expression of high-risk viral proteins is also important in progression, and expression of the HPV genome may occur transiently or constitutively through stable integration. Integration is possibly a key transforming event in many tumors, causing disruption of viral E2 and increased oncogenic E6 and E7 transcripts and/or disrupting human tumor suppressor or cell cycle regulatory genes. While it is possible that HPV is merely a benign presence on oropharyngeal mucosa without any detrimental effects, its expression and correlation with recurrence and progression of premalignant lesions suggest otherwise. Additionally, HPV-positive tumors appear to have different outcomes, suggesting a central role. Patients with HPV-positive tumors survive longer than those with HPV-negative tumors, and HPV-positive, p53 wild-type tumors have the best survival. Thus HPV may cause a less aggressive form of HNSCC and perhaps even a distinct cancer type, responding to different treatments than other HNSCCs.

Research in the areas of transmission and HPV presence in early- versus late-stage tumors remains to be done. Complete genetic characterization of cell lines with integrated HPV DNA could help to better explain tumor behavior and determine specific prognostic indicators for individual patients. Integration studies are ongoing, and additional samples have been collected from low-risk patients for screening and further investigation. New data should provide further support for the role of HPV in head and neck carcinogenesis.

Finally, much excitement has been generated by the new HPV vaccine. It will be important to study the effects of the vaccine on prevalence of head and neck cancer in women and other subgroups who receive the vaccine. However, since it appears that only a select group of patients will receive the vaccine, information regarding its efficacy with head and neck cancer will be difficult to interpret. Those who are at risk for oropharyngeal HPV may not be in a high risk group for anogenital HPV and therefore may not be vaccinated. The profile of the patient at risk for oropharyngeal HPV is unknown, as is the mechanism of transmission. Thus,

unlike selecting groups at risk for HPV-associated cervical cancer, populations at risk for HPV-associated oropharyngeal cancer cannot be easily identified. Furthermore, HPV appears to be an important cofactor in HNSCC, not a primary causative agent in most cases. Thus, patients may still develop HNSCC with traditional risk factors, but they may develop the disease later in life (without the "first hit" of HPV to speed carcinogenesis). Therefore, an accurate picture of the effects of the vaccine will be difficult to determine. Certainly, this is an area to which researchers at the University of Michigan will pay close attention.

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Quality of Life: Another Look

by Julie Phillips

Photo by Kelly Birchmeier

I've been thinking about the words "quality of life" lately. What does it mean to have good quality of life, or poor quality of life? The way we, as future medical professionals, think about good and poor quality of life affects our daily interactions with patients. Our attitudes affect their attitudes and shape their decisions. Our beliefs about "quality of life" affect life and death, and the lives of children and parents and families.

I got into an argument with a resident during my third year of medical school about whether it would be better to have a child with cystic fibrosis or Down's Syndrome. He said CF, I said Down's. "They'll never be who they were meant to be," he argued. "They'll never become anything."

"But they won't live in pain." I shot back. "They won't spend all their time in the hospital and die young." At first I thought he was being incredibly narrow-minded. But now I wonder whether it was an argument that could be discussed at all.

My brother, David, has Down's syndrome. By external measures, his quality of life has limitations. He cannot perform any of the "instrumental activities of daily living" (IADLs) without supervision and prompting. (IADLs are a clinical tool to assess "whether the person can... manage his or her living environment independently or whether he or she is dependent on others."[1]) He reads very poorly and writes only with great effort. He did not graduate from high school. Twenty-three years old now, he will probably never live independently or have a job that requires more than physical labor. He does not drive. He lacks common sense. He does not have the maturity to sustain a romantic relationship, and it seems likely that he never will. If I did not know him, and was asked as a physician to describe his level of function, my voice would take a somber tone.

But think about "quality" — and take another look. David has a lot of leisure time. He spends a good deal of time exercising, and is more fit and strong than most people. He didn't struggle much with school, because he had no expectations. He puts little pressure on himself, never over-commits, and has few worries. He thinks if he's working twenty hours a week he's taken on too much, and needs to slow down. Not because he doesn't have boundless energy, but because there are other things he'd rather be doing. He generally goes to bed as early or as late as he chooses. He often sleeps late. He has no debt, and very few obligations.

He has a job washing dishes at Pizza Hut. The job has important benefits, in David's mind: occasional free pizza and a paycheck. He has many friends, whom he sees often - mostly people living in his neighborhood and athletes on his Special Olympics teams. He's outgoing and very funny.

Now consider a different life — my life. I can do all of the IADLs without a struggle. But my life lacks the balance of my brother's life. As a medical student, I work hard — well over 20 hours per week. I have less time to exercise, and am less fit. I see friends less often. Through my education I've amassed well over one hundred thousand dollars in debt. Although I'm three years older than David, I don't have a job yet. I overcommit and "stress out." I worry more.

I have had moments, during my medical school career, when I think my quality of life has been pretty poor. The winter months of M2 year, for example, when I was overwhelmed by the studying and it seemed like I never saw anyone socially, when the work seemed to stretch out before me like a dark road that would only get uglier beneath my feet — as if I was walking barefoot on gravel, barely tolerable after so many months, but would soon be walking on shards of glass. It seemed I had nothing to look forward to but more drudgery. I remember months of third year where never-ending tiredness had sunk into my bones. I would close my eyes for a moment, standing up in an elevator going up to the eighth floor. I had fantasies about going to sleep. When I did sleep, I dreamed about my pager going off.

It felt like I was constantly tagging along behind the team, not quite belonging. Never knowing as much as everyone else, wondering if I ever would... wondering if I would ever be good enough to practice medicine.

To examine the quality of my life, clearly and objectively, is somewhat painful. But in truth, I don't believe David's quality of life is better than mine. I believe that, except perhaps at the extremes, "quality of life" is a ridiculous term, something that can't be measured or assessed, let alone predicted by an outsider.

Because I am a medical student, training to be a physician, I have always driven myself hard. I sometimes forget that ambition is not the same as true quality of life, which may be better measured by happiness than by achievement. A child who will never have great aspirations — by my measure — may nonetheless have a life of the finest quality. My way is not the only way to build a life of high quality.

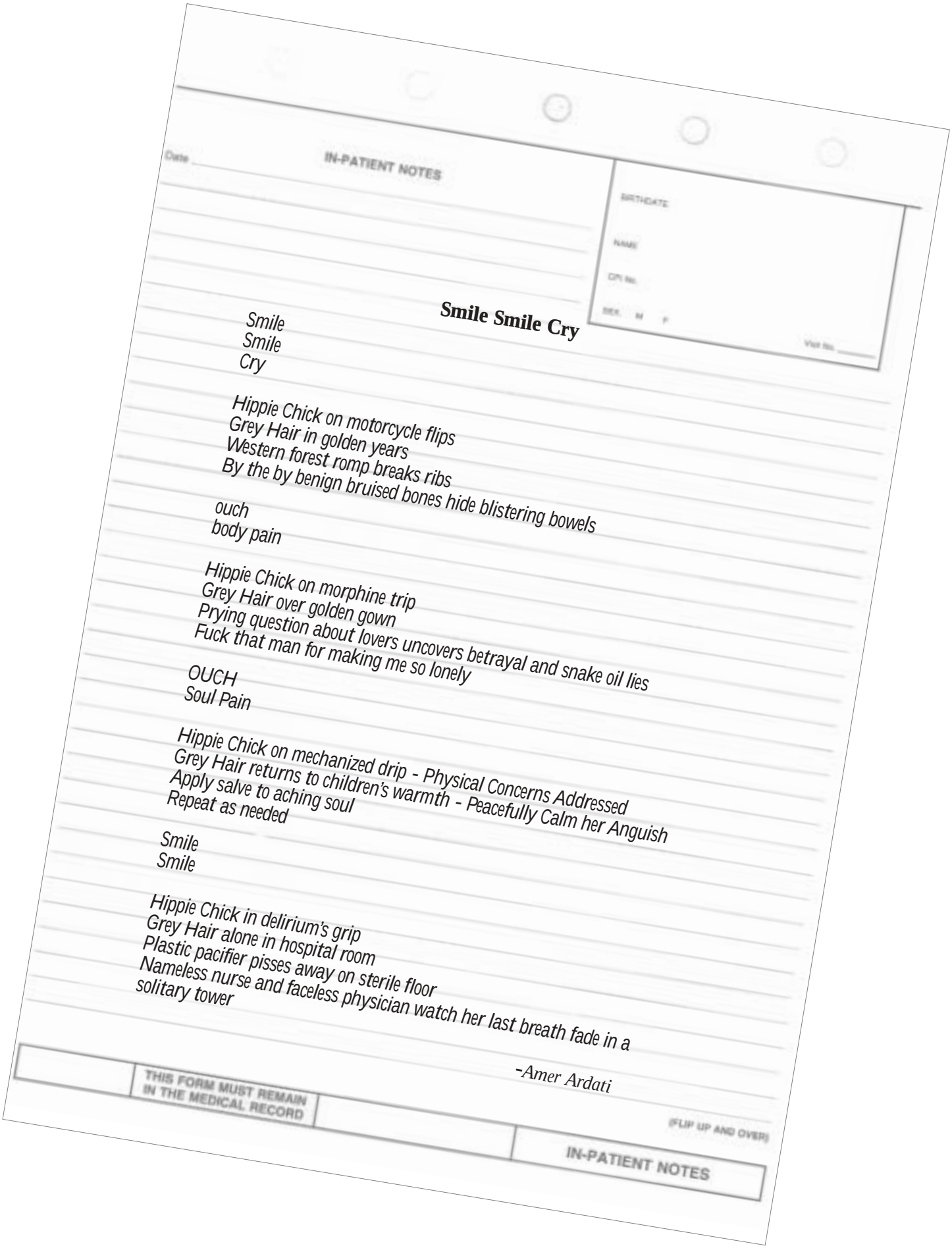
IADLs are a measure of whether a person is "dependent on others." When I am proud of my achievements, it is easy to forget the degree to which I, too, am dependent on others — including people like David. Grabbing breakfast in the cafeteria after a long night, I don't think about the person who washed my plate and cup — although I am certainly grateful for the coffee. More importantly, David makes me smile, and reminds me that happiness doesn't require any credentials.

"They'll never be who they were meant to be," asserted the resident, wrongly. Who is to say who someone is meant to become? None but God and that person. I don't despair because my cat doesn't bark or fetch. She was not meant to. Clearly, David is who he is meant to be — a happy, productive 23-year-old who has Down's syndrome. I guess I am who I am meant to be, although it doesn't always feel that way — seems like I'm still striving, but he's arrived. We all do the best we can, after all, with what we have. Those of us with great gifts are given more gifts — education, money, the love of friends and family. It is easy to look at what we plan to give back, and forget how much has been invested in us, and how much we owe.

Who can say whether a life is good? I still think mine is, despite ample evidence to the contrary. I asked David if his life was good. He said yes. And would it continue to be good, in the future? He thought so. His demeanor suggested that he thought these were silly questions. But they are questions that only he can answer.

References:

[1] Duthie. Practice of Geriatrics, 3rd ed. W.B. Saunders Company. 1998.


IN-PATIENT NOTES

Date

BIRTHDATE

NAME

CPI No.

SEX M F

Visit No.

Smile Smile Cry

Smile
Smile
Cry

Hippie Chick on motorcycle flips
Grey Hair in golden years
Western forest romp breaks ribs
By the by benign bruised bones hide blistering bowels

ouch
body pain

Hippie Chick on morphine trip
Grey Hair over golden gown
Prying question about lovers uncovers betrayal and snake oil lies
Fuck that man for making me so lonely

OUCH
Soul Pain

Hippie Chick on mechanized drip - Physical Concerns Addressed
Grey Hair returns to children's warmth - Peacefully Calm her Anguish
Apply salve to aching soul
Repeat as needed

Smile
Smile

Hippie Chick in delirium's grip
Grey Hair alone in hospital room
Plastic pacifier pisses away on sterile floor
Nameless nurse and faceless physician watch her last breath fade in a solitary tower

-Amer Ardati

THIS FORM MUST REMAIN IN THE MEDICAL RECORD

(FLIP UP AND OVER)

IN-PATIENT NOTES

Six months

Viral grenade kills tumor

the article states, full of promises

but my patient can't read, or at least not now

double vision and all

no escape in the library

no islands of dolphins

no mystery adventures

except the mystic webs of tumor infiltrating her brain

evading drugs, beams of radiation, and the surgeon's scalpel

but her hot pink hair smiles nonetheless.

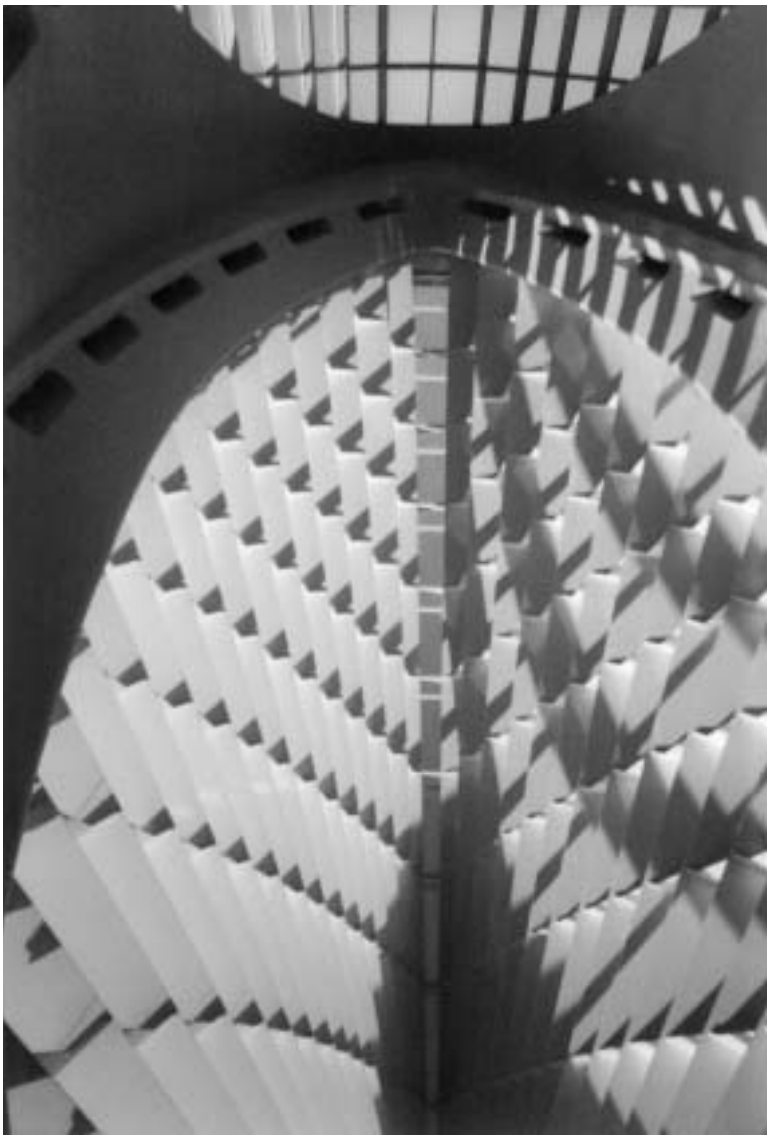


Photo by Sevanne Demirjian

The alien in her brain started

to bud exponentially

no children for her, post-radiation

no life insurance since the diagnosis

it's slow-growing, the scans show

maybe they can take it out because

she's right-handed and it's in the right part of her brain

but still no life insurance.

Five years? She asks me.

No, I said six months

Six years? She doesn't understand, her brain won't let her

Five months? No, I'm sorry,

Six months.

-Chithra R. Perumalswami

In the subway

With a large black garbage can behind
and a small white bucket in front
an old man in a goatee sits on a side-turned crate
belting out deep, sonorous tones of an old Spanish song
with robust sound and slow movement
he manages to carve out a tenuous space for himself
a melancholy Puerto Rican club
the dimness at his grandfather's legs
the limitless expanse of an ocean
veranda at
dusk
he
paints all
these
pictures
for the
steadily
growing
crowd
around him
but no one
pays
some don't
even stop
as they toss
garbage into
the can behind him
suddenly
almost imperceptibly
the air shifts and the voice blows out
like an unprotected flame
in the face of ever increasing wind and sound
the old man stoically holds on to
the song with his
guitar
it is only when the
screeches come
at the moment in
which the old
man is
completely
drowned out
that a large
majority of the
crowd bends
down to his
white bucket
as if to spite
the train

Photo by Joseph W. Daugherty

-Adam Possner

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1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide. N Engl J Med 1979;301:1382-5.

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