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CONTAGIOUS CANCER

The evolution of a killer

By David Quammen

During the early months of 1996, not long before Easter, an amateur wildlife photographer named Christo Baars made his way to the Australian island-state of Tasmania, where he set up camp in an old airport shack within the boundaries of Mount William National Park. Baars's purpose, as on previous visits, was to photograph Tasmanian devils, piglet-size marsupials unique to the island's temperate forests and moors. Because devils are nocturnal, Baars equipped his blind with a cot, a couple of car batteries, and several strong spotlights. For bait he used road-kill kangaroos. Then he settled in to wait.

The devil, known to science as *Sarcophilus harrisii*, lives mostly by scavenging and sometimes by predation. It will eat, in addition to kangaroo meat, chickens, fish, frogs, kelp maggots, lambs, rats, snakes, wallabies, and the occasional rubber boot. It can consume nearly half its own body weight in under an hour, and yet—with its black fur and its trundling gait—it looks like an underfed bear cub. Fossil evidence shows that devils inhabited all of Australia until about 500 years ago, when competition with dingoes and other factors caused them to die out everywhere but in Tasmania, which dingoes had yet to colonize. More recently, Tasmanian stockmen and farmers have persecuted devils with the same ferocity directed elsewhere at wolves and coyotes. The devils' reproductive rate, opportunistic habits, and tolerance for human proximity, however, have allowed localized populations to persist or recover, and at the time of Baars's 1996 visit, their total number was probably around 150,000.

On his earlier visits, Baars had seen at least ten devils every night, and they were quick to adjust to his presence. They would walk into his blind, into his tent, into his kitchen, and he could recognize returning individuals by the distinctively shaped white patches on their chests. This

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Illustrations by Danijel Zezelj

trip was different. On the first night, his bait failed to attract a single devil, and the second night was only a little better. He thought at first that maybe the stockmen and farmers had finally succeeded in wiping them out. Then he spotted a devil with a weird facial lump. It was an ugly mass, rounded and bulging, like a huge boil, or a tumor. Baars took photographs. More devils wandered in, at least one of them with a similar growth, and Baars took more pictures. This was no longer wildlife photography of the picturesque sort; it was, or anyway soon would become, forensic documentation.

Back in Hobart, Tasmania's capital, Baars showed his pictures to Nick Mooney, a veteran officer of Tasmania's Parks and Wildlife Service who has dealt with the devil and its enemies for decades. Mooney had never seen anything like this. The lumps looked tumorous, yes—but what sort of tumor? Mooney consulted a pathologist, who suggested that the devils might be afflicted with lymphosarcoma, a kind of lymphatic cancer, maybe caused by a virus passed to the devils from feral cats. Such a virus might also be passed from devil to devil, triggering cancer in each.

CANCERS EVOLVE. AND ONE WAY THEY CAN EVOLVE IS TOWARD THE CAPACITY TO BE TRANSMITTED BETWEEN INDIVIDUALS

More evidence of contagion began to accumulate. Three years after Baars shot his photographs, a biologist named Menna Jones took note of a single tumor-bearing animal, something she had not seen before. Then, in 2001, at her study site along Tasmania's eastern coast, her traps yielded three more devils with ulcerated tumors. That really got her attention. She euthanized the animals and brought them to a lab, where they became the first victims to be autopsied by a veterinary pathologist. The "tumors" (until then the term had been only a guess or a metaphor) did seem to be cancerous malignancies, but not of the sort expected from a lymphosarcoma-triggering virus. This peculiarity raised more questions than it answered. Tasmanian devils in captivity were known to be quite susceptible to cancer, at least in some circumstances, possibly involving exposure to carcinogens. But the idea that the cancer itself was contagious seemed beyond the realm of possibility. And yet, during the following year, Menna Jones charted the spread of the problem across northern Tasmania. Nick Mooney, meanwhile, had done some further trapping himself. At a site in the northern midlands, he captured twenty-three devils, seven of which had horrible tumors. Shocked and puzzled, he remembered the Baars photos from years earlier.

Further trapping (more than a hundred animals, of which 15 percent were infected) showed Mooney what Jones had also seen: that the tumors were consistently localized on faces, filling eye sockets, distending cheeks, making it difficult for the animals to see or to eat. Why faces? Maybe because devils suffer many facial and mouth injuries—from chewing on brittle bones, from fighting with one another over food and breeding rights, from the rough interactions between male and female when they mate. The bigger tumors were crumbly, like feta cheese. Could it be that tumor cells, broken off one animal, fell into the wounds of another, took hold there, and grew? This prospect seemed outlandish, but the evidence was leading inexorably to a strange and frightening new hypothesis: the cancer itself had somehow become contagious.

Under ordinary circumstances, cancer is an individuated phenomenon. Its onset is determined partly by genetics, partly by environment, partly by entropy, partly by the remorseless tick-tock of time, and (almost) never by the transmission of some tumorous essence. It arises from within (usually) rather than being imposed from without. It pinpoints single victims (usually) rather than spreading through populations. Cancer might be triggered by a carcinogenic chemical, but it isn't itself poisoning. It might be triggered by a virus, but it isn't fundamentally viral. Cancer differs also from heart disease and cirrhosis and the other lethal forms of physiological breakdown; uncontrolled cell reproduction, not organ dilapidation, is the problem.

Such uncontrolled reproduction begins when a single cell accumulates enough mutations to activate certain growth-promoting genes (scientists call them oncogenes) and to inactivate certain protections (tumor suppressor genes) that are built into the genetic program of every animal and plant. The cell ignores instructions to limit its self-replication, and soon it becomes many cells, all of them similarly demented, all bent on self-replication, all heedless of duty and proportion and the larger weal of the organism. That first cell is (almost always) a cell of the victim's own body. So cancer is reinvented from scratch on a case-by-case basis, and this individuation, this personalization, may be one of the reasons that it seems so frightening and solitary. But what makes it even more solitary for its victims is the idea, secretly comforting to others, that cancer is never contagious. That idea is axiomatic, at least in the popular consciousness. *Cancer is not an infectious disease*. And the axiom is (usually) correct. But there are exceptions. Those exceptions point toward a broader reality that scientists have begun to explore: Cancers, like species, evolve. And one way they

can evolve is toward the capacity to be transmitted between individuals.

Devil tumor isn't the only form of cancer ever to achieve such a feat. Other cases have occurred and are still occurring. The most notable is Canine Transmissible Venereal Tumor (CTVT), also called Sticker's sarcoma, a sexually transmitted malignancy in dogs. Again, this is not merely an infectious virus that tends to induce cancer. The tumor cells themselves are transmitted during sexual contact. CTVT is widespread (though not common) and has been claiming dogs around the world at least since a Russian veterinarian named M. A. Novinsky first noted it in 1876. The distinctively altered chromosome patterns shared by the cells of CTVT show the cancer's lineal continuity, its identity across space and through time. Tumor cells in Dog B, Dog C, Dog D, and Dog Z are more closely related to one another than those cells are to the dogs they respectively inhabit. In other words, CTVT can be conceptualized as a single creature, a parasite (and not a *species* of parasite, but an *individual*), which has managed to spread itself out among millions of different dogs. Research by molecular geneticists suggests the tumor originated in a wolf, or maybe an East Asian dog, somewhere between 200 and 2,500 years ago, which means that CTVT is probably the oldest continuous lineage of mammal cells presently living on Earth. The dogs may be young, but the tumor is ancient.

Unlike devil tumor—now known as Devil Facial Tumor Disease, or DFTD—CTVT is generally not fatal. It can be cured with veterinary surgery or chemotherapy. In many cases, even without treatment, the dog's immune system eventually recognizes the CTVT as alien, attacks it, and clears it away, just as our own immune systems eventually rid us of warts.

The case of the Syrian hamster is more complicated. This tumor arose around 1960, when researchers at the National Cancer Institute, in Bethesda, Maryland, performed an experiment in which they harvested a naturally occurring sarcoma from one hamster and injected those cells (as cancer scientists often do) into healthy animals. When the injected hamsters developed malignancies, more cells were harvested. Each such inoculation-and-harvest cycle is called a passage. The experiment involved a dozen such passages, and over time the tumor began to change. It had evolved. The later generations, unlike the first, represented a sort of super tumor, capable of getting from hamster to hamster without benefit of a needle. The researchers caged ten healthy hamsters together with ten cancerous hamsters and found that nine of the healthy animals acquired tumors through social contact. The hamster tumor had leapt between animals—or anyway, it had been smeared, spat, bitten, and dribbled between them. (The tenth hamster got cannibalized before it could sicken.) In a related experiment, the tumor even passed between two hamsters separated by a wire screen. The scientists had in effect created a laboratory precursor of what would eventually afflict Tasmanian devils in the wild: a Frankenstein malignancy, a leaping tumor, which could conceivably kill off not just individuals but an entire species.

Early last summer I went to Tasmania, where I met Menna Jones for an excursion to the Forestier Peninsula, a long hook of land that juts southeastward into the Tasman Sea. Jones supervises an experimental trapping program aimed at ridding the peninsula of tumor disease or, at least, determining whether that goal is achievable. The Forestier is a good place for such trials because the peninsula (and its lower extension, a second lobe called the Tasman Peninsula) is connected to the rest of Tasmania by only a narrow neck—just a two-lane bridge across a canal. If the disease could

be eradicated from the entire peninsula, by removing all sick animals and leaving the healthy ones, Forestier and Tasman might be protected from re-infection by a devil-proof barrier across the bridge; and if that worked, the protected population could rebound quickly. The Forestier Peninsula, full of good habitat, might become a vital refuge for the species. Those measures might even validate a method—defense by tourniquet—that could be used on some of Tasmania's other peninsular arms.

Jones, who is a brisk, cordial woman with a mane of brown hair, picked me up in an official state Land Cruiser, and as she drove she described the effects seen so far. Her field people had culled more than a hundred devils within the past four months, she said, and though the size of the Forestier population seemed to be holding steady, the demographics had changed. Mature adults, the four- and five-year-olds, were being lost, and so three-year-olds, adolescents, were accounting for most of the parenthood. The biting associated with breeding brings fatal disease, and the disease kills fast—sex equals death, a bad equation for any species. "We think extinction is a possibility within twenty-five years," Jones said.

We crossed the little bridge onto the peninsula and, after a short drive through rolling hills of eucalyptus forest, rendezvoused with the trapping crew. The chief trapper was a young woman named Chrissy Pukk, Estonian by descent, Aussie by manner, wearing a pair of blue coveralls, a dangling surgical mask, and a leather bush hat. She had been trapping devils here for three years. Jones and I tagged along as Pukk and two volunteers worked a line of forty traps placed throughout the forest. The catch rate was high, and most of the captured devils had been caught previously and injected with small electronic inserts for identification. These devils came in on a regular basis, as if the traps were soup kitchens, and Pukk recognized many of them on sight. She and only she handled the animals, cooing to them calmingly while she took their measurements, checked their body condition, and, most crucially, examined their faces for injuries and signs of tumor. One devil, a robust male Pukk called Captain Bligh, showed wounds from a recent mating session: broken teeth, a torn nose, a half-healed cut below his jaw, and a suppurating pink hole on the top of his snout, deep enough that it might have been made by a melon scoop. But he seemed to be clean of tumor. "He's just a brawler," Pukk said. She released him, and he skittered off into the brush.

"You see a lot of old friends come and go," Pukk told me as she examined another animal. For instance, there was one she had caught the day before, a male called Noddy. She had last trapped him less than a week earlier, noted inflamed whisker roots, and released him; but in the brief passage of days, those inflammations had become tumors, and now Noddy was awaiting his fate in a holding trap.

Colette Harmsen, a veterinarian who had made the long drive south from Tasmania's Animal Health Laboratory at Mount Pleasant, was there to euthanize and autopsy any animal Pukk found unfit for release. She wore her black hair cut short, her jeans torn at the knee, a lacey black dress over the jeans, a black T-shirt reading SAVE TASSIE'S FORESTS over the dress, and, over it all, a pale blue disposable surgical smock. She was waiting at her pickup truck along with her pit bull, Lily, and her pet rat, CC, when Pukk arrived to deliver the unfortunate Noddy. Pukk and her crew returned to the trap line, Menna Jones went back to Hobart, and I stayed to watch Harmsen work. I had never seen anyone cut open a Tasmanian devil.

Her working slab was the tailgate of her pickup, spread with a clean burlap sack; her scalpels, syringes, and other tools came from a portable

kit. First she anesthetized Noddy with gas. Then, after drawing blood samples from deep in his heart, she injected him with something called Lethabarb, which killed him. She measured his carcass, inspected his face, and then sliced an olive-size lump off his right cheek just below the eye. She showed me the lump's interior: a pea-size core of pale tissue surrounded by normal pink flesh. She put a chunk of it into a vial; that would go to a lab up at Mount Pleasant, she said, to be grown for chromosome typing. From the left side of the face, among the whiskers, Harmsen cut another tumor. Noddy lay limp on the burlap, both cheeks sliced away, like a halibut. When she slit open his belly and found an abundance of healthy yellow fat, she sighed. "He was in good condition." The disease hadn't progressed far. There was no sign of metastasis. But the protocols of the trapping program on Forestier don't include therapeutic surgery and chemo. Harmsen put a bit of Noddy's liver, a bit of his spleen, and a bit of his kidney into formalin. Those samples, too, would go back to Mount Pleasant for analysis. She wrapped the rest of Noddy in his burlap shroud, put him in a plastic garbage bag, and sealed that with tape. He would be incinerated. Then she cleaned up, fastidiously, to eliminate the chance that tumor cells might pass from her tailgate or her tools to another animal.

The phenomenon of transmissible tumors isn't confined to canines, Tasmanian devils, and Syrian hamsters. There have been human cases, too. Forty years ago a team of physicians led by Edward F. Scanlon reported, in the journal *Cancer*, that they had "decided to transplant small pieces of tumor from a cancer patient into a healthy donor, on a well informed volunteer basis, in the hope of gaining a little better understanding of cancer immunity," which they thought might help in treating the patient. The patient was a fifty-year-old woman with advanced melanoma; the "donor" was her healthy eighty-year-old mother, who had agreed to receive a bit of the tumor by surgical transplant. One day after the transplant procedure, the daughter died suddenly from a perforated bowel. Scanlon's report neglects to explain why the experiment wasn't promptly terminated—why they didn't dive back in surgically to undo what had been done to the mother. Instead, three weeks were allowed to pass, at which point the mother had developed a tumor indistinguishable from her daughter's. Now it was too late for surgery. This cancer moved fast. It metastasized, and the mother died about fifteen months later, with tumors in her lungs, ribs, lymph nodes, and diaphragm.

The case of the daughter–mother transplant and the case of the Syrian hamsters have one common element: the original sources of the tumor and the recipients were genetically very similar. If the genome of one individual closely resembles the genome of another (as children resemble their parents, and as inbred animals resemble one another), the immune system of a recipient may not detect the foreignness of transplanted cells. The hamsters were highly inbred (intentionally, for experimental control) and therefore not very individuated from one another as far as their immune systems could discern. The mother and daughter were also genetically similar—as similar as two people can be without being identical twins. Lack of normal immune response, because of such closeness, goes some way toward explaining why those tumors survived transference between individuals.

THE PHENOMENON OF TRANSMISSIBLE TUMORS ISN'T CONFINED TO TASMANIAN DEVILS. THERE HAVE BEEN HUMAN CASES

Low immune response also figures in two other situations in which tumor transmission is known to occur: pregnancy and organ transplant. A mother sometimes passes cancer cells to her fetus in the womb. And a transplanted organ sometimes carries tiny tumors into the recipient, vitiating the benefits of receiving a life-saving liver or kidney from someone else. Cases of both kinds are very rare, and they involve some inherent or arranged compatibility between the original victim of the tumor and the secondary victim, plus an immune system that is either compromised (by immuno-suppressive drugs, in the organ recipient) or immature (in the fetus).

Other cases are less easily explained. In 1986, two researchers from the National Institutes of Health reported that a laboratory worker, a healthy nineteen-year-old woman, had accidentally jabbed herself with a syringe carrying colon-cancer cells; a colonic tumor grew in her hand, but she was rescued by surgery. More recently, a fifty-three-year-old surgeon cut his left palm while removing a malignancy from a patient's abdomen, and five months later he found himself with a palm tumor, one that genetically matched the patient's tumor. His immune system responded, creating an inflammation around the tumor, but the response was insufficient and the tumor kept growing. Why? How? It wasn't supposed to be

able to do that. Again, though, surgery delivered a full cure. And then there's Henri Vadon. He was a medical student in the 1920s who poked his left hand with a syringe after drawing liquid from the mastectomy wound of a woman being treated for breast cancer. Vadon, too, developed a hand tumor. Three years later, he died of metastasized cancer because neither the surgical techniques of his era nor his own immune system could save him.

The tumor that I had watched Colette Harmsen harvest from Noddy's face would be examined at the Mount Pleasant labs by Anne-Maree Pearse and her assistant Kate Swift. Pearse is a former parasitologist, now working in cell biology, and she has a special interest in the genetics of Devil Facial Tumor Disease. She and Swift were the researchers who, in 2006, published a dramatic report in the British journal *Nature* that, with eight paragraphs of text and a single photographic image, had answered the lingering question about whether DFTD is a genuinely transmissible cancer.

Pearse came out of retirement (she had turned to running a flower farm) in response to the scientific conundrum of DFTD. A back injury has forced the use of a cane on her, but she is vigorous when describing her research. Although she was originally trained as an entomologist, her work with fleas drew her into the world of parasitology, and from there it was just a few more steps into oncology and the study of lymphomas among the devil and its close marsupial relatives. "Somehow my whole life was preparing me for this," she said when I visited her lab at Mount Pleasant. She added, almost appreciatively: "This disease." Pearse tends to think, as she put it, "outside the square"—a useful trait in the case of DFTD, she said, because the disease isn't behaving like anything heretofore known. "It's a parasitic cancer," she told me. "The devil's the host."

For the 2006 study, Pearse and Swift examined chromosome structure in tumor cells from eleven different devils. They found that the tumor chromosomes were abnormal (misshapen, some missing, some added) compared with those from healthy devil cells, but that the tumor chromosomes, from one cell or another, from one tumor or another, were abnormal in *all the same ways*. You could see that comparison graphically in the photo in *Nature*: fourteen nice sausages matched against thirteen variously mangled ones. Those thirteen chromosomes, wrote Pearse and Swift, had undergone "a complex rearrangement that is identical for every animal studied." The mangling was unmistakable evidence. It appeared in each tumor, but not elsewhere in each animal. "In light of this remarkable finding and of the known fighting behavior of the devils," Pearse and Swift wrote, "we propose that the disease is transmitted by allograft"—tissue transplant—"whereby an infectious cell line is passed directly between the animals through bites they inflict on one another."

Pearse and Swift had proved that DFTD is a highly infectious form of cancer, its transmission made possible by, among other factors, the habit of mutual face-biting. When I visited Menna Jones, she expressed the same idea: "It's a piece of devil tissue that behaves like a parasite." Jones was using the word "parasite" in its strict biological sense, meaning: any organism that lives on or within another kind of organism, extracting benefit for itself and causing harm to the other. The first rule of a successful parasite is, Don't kill your host—or at least, Don't kill one host until you've had time to leap aboard another. DFTD, passing quickly from devil to devil, killing them all but not quite so quickly, follows that rule.

How does any parasite, whether it is a species or merely a tumor, acquire the attributes and tactics necessary for survival, reproduction, and continuing success? The answer is simple but not obvious: evolution.

Cancer and evolution have traditionally been considered separately by different scientists with different interests using different methods. You could graduate from medical school, you could follow that with a Ph.D. in cell biology or molecular genetics, you could become a respected oncologist or a well-funded cancer researcher, without ever having read Darwin. You could do it, in fact, without having studied much evolutionary biology at all. Many cell and molecular biologists tended even to scorn evolutionary biology as a "merely descriptive" enterprise, lacking the rigor, quantifiability, and explanatory power of their disciplines. There were exceptions to this disconnect, cancer scientists who even during the early days thought in evolutionary terms, but those scientists had little influence.

In recent decades, however, the situation has changed, as molecular genetics and evolutionary biology have converged on some shared questions. One signal act of synthesis occurred in 1976 when a leukemia researcher named Peter Nowell published a theoretical paper in *Science* titled "The Clonal Evolution of Tumor Cell Populations." Nowell proposed what was then a novel idea: that the biological events occurring when cells progress from normal to pre-cancerous to cancerous represent a form of evolution by natural selection. As with the evolution of species, he suggested, the evolution of malignant tumors requires two conditions: genetic diversity among the individuals of a population and competition among those individuals for limited resources. Genetic diversity within one mass of pre-cancerous cells comes from mutations—copying errors and other forms of

change—that yield variants as the cells reproduce. That is, in the very act of replicating themselves (sometimes inaccurately), the cells diversify into a population encompassing some small genetic differences between one cell and another. Each variant cell then replicates itself true to type, constituting a clonal lineage (a lineage of accurate copies), until the next mutation creates a new variant. The fittest variants survive and proliferate. By this means, the genetic character of the cell population gradually changes, and with such change comes adaptation, a better fit to environmental circumstances. What constitutes "the fittest" among clonal lineages within a pre-cancerous growth? Those that can reproduce fastest. Those that can resist chemotherapy. Those that can metastasize and therefore escape the surgeon's knife.

Nowell's hypothesis about tumor evolution became widely known and accepted within certain circles of cancer research. (Among other researchers, it wasn't adamantly disputed but merely ignored.) Those circles have more recently produced a lot of rich theorizing, and a smaller amount of empirical work, supporting Nowell and carrying his idea forward. A culmination of sorts occurred in 2000, when the cancer geneticist Robert Weinberg, discoverer of the first human oncogene and the first tumor suppressor gene, published a concise paper titled "The Hallmarks of Cancer." Weinberg and his coauthor, Douglas Hanahan, described six "acquired capabilities," such as endless self-replication, the ignoring of antigrowth signals, the invasion of neighboring tissues, and the refusal to die, that collectively characterize cancer cells. How are those capabilities acquired? By mutations and other genetic changes, giving cells with one such trait or another competitive advantage over normal cells. Hanahan and Weinberg added that "tumor development proceeds via a process formally analogous to Darwinian evolution." With this cautious phrasing, they gave authoritative endorsement to the idea that Peter Nowell had proposed: Cancers, like species, evolve.

THE MOST BASIC QUESTION WAS: DID TUMORS BECOME MALIGNANT THROUGH EVOLUTION BY NATURAL SELECTION?

In 1998 a young researcher named Carlo Maley began looking for a way to study the evolution of cancer. Educated at Oxford and MIT as an evolutionary biologist and a computer modeler, Maley had no training in medicine and not much in molecular biology. During a postgraduate fellowship, though, he became interested in infectious disease. He figured that if evolution was cool, then coevolution—wherein both parasite and host are evolving—would be doubly cool. Then he stumbled across a description of cancer as an evolving disease. He read that Sir Walter Bodmer, a British geneticist and the former director of the Imperial Cancer Research Fund, had urged his cancer-research colleagues to "think evolution, evolution, evolution" when they considered tumor cells. Maley typed "evolution and cancer" into a search engine for the scientific literature, which turned up very little. He did learn of Nowell's hypothesis, but that was just theory. He was groping. He had done plenty of theoretical modeling, but for this task he needed the desperate realities, and the data, of clinical oncology.

And then, at a workshop in Seattle, Maley met Brian Reid, an experienced cancer researcher studying something called Barrett's esophagus, a pre-cancerous condition of the lower throat. They hit it off. Reid had the right clinical situation but wasn't deeply versed in evolutionary biology; Maley had the right background. They agreed to collaborate.

Reid and his colleagues possessed sixteen years of continuous data on Barrett's patients and a tissue bank going back to 1989. They knew which patients had developed esophageal cancer and which hadn't, and they could match those outcomes against what they had seen in cell cultures and genetic work from earlier in the patients' history. So they could ask evolutionary questions that were answerable from patterns in the data. The most basic question was: Did tumors become malignant through evolution by natural selection? The other big question was: Can doctors predict which pre-cancerous growths will turn malignant? Maley and Reid, along with additional collaborators, found that case histories of Barrett's esophagus tend to confirm Nowell's hypothesis. Cancerous tumors, like species, *do* evolve. And from the Barrett's data, predictions can be made. The higher the diversity of different cell variants within a pre-cancerous growth, the greater the likelihood that the growth will progress to malignancy. Why? Because of the basic Darwinian mechanism. Genetic diversity plus competitive struggle eliminates unfit individuals and leaves the well-adapted to reproduce.

Maley and Reid have more recently taken such thinking one step beyond evolution—into ecology. Along with Lauren M. F. Merlo (as first author) and John W. Pepper, they published a provocative paper titled "Cancer as an Evolutionary and Ecological Process," in which they discussed not just tumor evolution but also the ecological factors that form evolution's context, such as predation, parasitism, competition, dispersal, and colonization. Dispersal is travel by venturesome individuals, which in some cases allows species to colonize new habitats. Merlo, Maley, and their colleagues noted three ways in which the concept of dispersal is applicable to cancer:

small-scale cell movement within a tumor (not very important), invasion of neighboring tissues (important), and metastasis (fateful).

Reading that, I remembered Devil Facial Tumor Disease and wondered whether there might not be a fourth way: transmissibility. An infectious cancer is a successful disperser. It colonizes new habitat. DFTD seems to be dispersing and colonizing, much as pigeons disperse across oceans, colonizing new islands. This wasn't just evolution; it was evolutionary ecology.

I called one of the paper's coauthors, John W. Pepper, an evolutionary biologist at the University of Arizona, and asked whether I was stretching the notion too far. No, he said, you're not. If he could revise that paper again, Pepper told me, he would insert the idea that tumors evolve toward transmissibility.

Eight hundred million years ago there was no such thing as cancer. Virtually all living creatures were single-celled organisms, and the rule was *Every cell for itself!* Uncontrolled, undifferentiated cell growth wasn't abnormal. It was the program of all life on Earth.

Then, around 700 million years ago, things changed. Paleontologists call this event the Cambrian explosion. Complex multicellular animals, metazoans, appeared. And not just meta*zoans* but meta*phytes*, too—that is, multicellular plants. How did it happen? Very gradually, as single-cell creatures resembling bacteria or algae began to aggregate into colonial units and discover, by trial and error, how they could benefit from division of labor and specialization of shape and function. To enjoy those benefits, they had to set aside the old rule of absolute selfishness. They had to cooperate. They couldn't cheat against the interests of the collective entity. (Or anyway they *shouldn't* cheat, not very often; otherwise the benefits of collectivity wouldn't accrue.) Cooperation was a winning formula. Primitive multicellular creatures, roughly along the lines of jellyfish or sponges or slime molds, began to succeed, to grow, to occupy space, and to claim resources in ways that loner cells couldn't. You can see their imprints in the Burgess Shale: weird things like sci-fi vermin, pre-vertebrate, pre-insect, that seem to have been built out of bubble wrap and old Slinkys. They succeeded for a while, then gave way to still better designs. Multicellularity offered wide possibilities.

But uncontrolled cell replication didn't disappear entirely. Sometimes a single atavistic cell would ignore the collective imperative; it would revert to the old habit—proliferating wildly, disregarding all signals to stop. It would swell into a big, greedy lump of its own kind, and in so doing disrupt one or more of the necessary collective functions. That was cancer.

The risk of runaway cell replication remained a factor in the evolutionary process, even as multicellular creatures increased vastly in complexity, diversity, size, and dominance on our planet. And species responded to that risk just as they responded, incrementally and over long periods of time, to other such risks as predation or parasitism: by acquiring defenses. One such defense is the amazing ability of living cells to repair mutated DNA, putting the cell program back together properly after a mishap during cell replication. Another defense is *apoptosis*, a form of programming that tells a cell not to live forever. Another is cellular senescence, during which a cell continues to live but no longer is capable of replicating. Another is the distinction between stem cells and differentiated cells, which limits the number of cells responsible for cell-replacement activity and thereby reduces the risk of accumulated mutations. Another is the requirement for biochemical growth signals before a cell can begin to proliferate. Many of these defenses are controlled by tumor-suppressor genes, such as the one that produces a protein that prevents cells from replicating damaged DNA. Nobody knows just how many anti-cancer defenses exist within a given species (we humans seem to have more than mice do, and possibly not so many as whales), but we do know that they make our continuing lives possible.

Tumors, in the course of their own evolution from one normal cell to a cancerous malignancy, circumvent these natural defenses. They may also change in response to externally imposed defenses, such as surgery, chemotherapy, and radiation. The fittest cells, in Darwinian terms, are those that reproduce themselves most quickly and aggressively, resisting all signals to desist and all attempts to kill them. The victim (that is, the human or the Tasmanian devil or the Syrian hamster) suffers the consequences, having become the arena for an evolutionary struggle at a scale far different from that of its own struggle to survive. But the principles of the struggle are the same at each scale.

This process, whereby cells mutate, reproduce, and proliferate differentially within a body, is called somatic evolution. It stands as a counterpoint to organismic evolution (progressive changes at the scale of whole bodies within a population), and the opportunities for it to proceed are abundant. According to one count, at least 291 genes in the human body contribute, when damaged by mutation, toward somatic evolution.

Mutations occur when something goes wrong during cell replication. A cell replicates by copying its DNA (sometimes inaccurately), sorting the DNA into two identical parcels of chromosomes, then splitting into two new cells, each with its own chromosomes. This process is called mitosis. The goal is not to generate an ever-higher num-

ber of cells during a creature's adult lifetime but simply to replace old cells with new ones. Mitosis counterbalanced with apoptosis, cell death, should provide a constant supply. But each time a mitotic division occurs, there is some very small chance of mutation. And the many small chances add up. A human body contains about 30 trillion cells. The number of cell divisions that occur in a lifetime is far larger: 10,000 trillion. A disproportionately large share of those divisions occurs in epithelial cells, which serve as boundary layers or linings, such as the skin and the interior surface of the colon. That's why skin cancer and colon cancer are relatively common—more cell turnover, more chance of mutation and evolution.

How many mutations does it take for a malignancy to occur? Estimates range from three to twelve, in humans, depending on the form of cancer. Five or six is considered an operational average for purposes of discussion. Here's some good news: For a cell to acquire those five or six changes, at the usual rate of mutation, is highly, highly, highly unlikely. The odds are great against quintuple mutation in any given cell, making cancer seem impossible within a human lifespan. One form of mutation, however, can vastly increase the later rate of mutation, which gives the pre-cancerous cells many more chances to become malignant.

In the United States, about 40 percent of us will eventually get cancer bad enough to be diagnosed. And autopsies suggest that virtually all of us will be nurturing incipient thyroid cancer by the time we die. Among octogenarian and nonagenarian men, 80 percent carry prostate cancer when they go. Cancer is terrible, cancer is dramatic, but cancer isn't rare. In fact, it's nearly universal.

The biological mystery of how the Tasmanian devil's rogue tumor manages to establish itself in one animal after another is still unsolved. But a good hypothesis has been offered by an immunologist named Greg Woods at the University of Tasmania. Woods and his group studied immune reactions in *Sarcophilus harrisii*, which seem generally to be normal against ordinary sorts of infection. Against DFTD cells, though, no such reaction occurs. "The tumor is just not *seen* by the immune system, because it just looks too similar," Woods told me when I stopped by his lab. The devils have low genetic diversity, probably because they inhabit a small island, they colonized it originally by way of just a few founders, and they have passed through some tight population bottlenecks in the centuries since. They're not quite so alike one another as a bunch of inbred hamsters, but they're too alike for their own good in the current sad, anomalous circumstances. Their immune systems don't reject the tumor cells because, Woods suspects, in each animal the critical MHC genes (the major histocompatibility complex, which produces proteins crucial to immunological policing) are all virtually identical, and the devils' police cells can't distinguish "him" from "me."

Most of the DFTD team are, like Greg Woods and Anne-Maree Pearse, located in Hobart or Launceston. Most of the animals aren't. So, two days after the autopsy on Noddy, I drove back to the Forestier Peninsula for another round of trapping with Chrissy Pukk and her crew. It wasn't that I expected to learn any new angles on the science. I just wanted to see more Tasmanian devils.

This time, Pukk issued me my own pair of blue coveralls. As we set off along the trap line, she exuded the contentment of a joyously crude tomboy enjoying the best job in the world: trapping devils for the good of the species. The only downside was the necessity of issuing a death sentence to any animal with a trace of tumor. "You get attached to the individuals," she admitted. "But you've got to remember all the other individuals you can save if you take that animal out early on."

Wouldn't this be less difficult emotionally, I asked her, if you gave them *numbers* instead of names? She answered the question—saying she couldn't do her work properly if she wasn't emotionally invested, plus which, names were easier to remember—and then she continued to answer it throughout the day. These creatures, they all have their memorable eccentricities, their little histories, she explained. Some she could recognize almost by smell. You couldn't do *that* with numbers.

There were forty traps again today, and about a dozen trapped devils to process, all recaptures, previously tagged and named. Trap by trap, animal by animal, Pukk worked through the measurements and the facial exams, handling each devil firmly but with a steady touch that provoked no devilish squirming: Captain Bligh (looking glum, or maybe a little embarrassed at having been caught again so soon), Hipster, Isabel, Masikus (Estonian for "strawberry"), Miss Buzzy Bum (her rump had been full of burrs), Rudolph (thus called for a nose that had been rubbed raw), Sandman, Skipper, and many others. They may have been virtually indistinguishable in the terms by which immune systems operate, but Chrissy Pukk knew each devil at a glance.

Rudolph's condition gave her pause. He was a two-year-old, nicely grown since she had first trapped him, his red nose healed . . . but there was something on the edge of his right eye. A pink growth, no bigger than a caper. "Oh shit," she said. Tumor? Or maybe it was just a little wound, puffy and raw. She looked closely. She peered into his mouth. She palpated lymph nodes at the base of his jaw. The volunteers and I waited in silence. Evolution had shaped Rudolph for survival, and

evolution might take him away. It was all evolution: the yin of struggle and death, the yang of adaptation, DFTD versus *Sarcophilus harrisii*. The leaping tumor, well adapted for fast replication and transmissibility, has its own formidable impulse to survive. And no one could know at this point, not even Chrissy, whether it had already leapt into Rudolph.

"Okay," she said, sounding almost sure of her judgment, "I'm gonna give him the all clear." She released him and he ran.

At latest report, Devil Facial Tumor Disease has spread across 60 percent of Tasmania's land surface, and in some areas, especially where it got its earliest start, the devil population seems to have declined by as much as 90 percent. In November, the Tasmanian government classified the devil as "endangered." DFTD specialists differ strongly on how such a crisis should be met. One view is that suppressing the disease—trapping and euthanizing as many infected animals as possible and then establishing barriers, as on the Forestier Peninsula—is the best strategy. Another view is that the species, virtually doomed on mainland Tasmania, can better be saved by transplanting disease-free devils to a small offshore island. Still another view, maybe the boldest and most risky, is that doing nothing—allowing the disease to spread unchecked—might yield a small remnant population of survivors, with natural immunity to DFTD, who could repopulate Tasmania.

Weeks after my last outing with the trappers, back in the Northern Hemisphere and wanting a broader perspective—not just on the fate of the devils but on the evolution of cancer—I met Robert Weinberg at a stem-cell conference in Big Sky, Montana. Because it was a Sunday, with the first session not yet convened, and because he is a genial man, Weinberg gave me a two-hour tutorial in a boardroom of the ski lodge, fortifying some points by flipping through his own four-pound textbook, *The Biology of Cancer*, a copy of which I had lugged to our meeting like a student. He was incognito in a plaid Woolrich shirt. He'd be called on that evening to deliver the keynote address, but never mind, he was prepared.

"Infectious cancer is really an aberration," Weinberg told me, affirming what Greg Woods had said. "It's so bizarre. It has happened only rarely." Maybe it's possible only in cases where there's close physical contact between susceptible tissues. "That, right away, limits it to venereal tumors, or tumors that can be transmitted by biting." Weinberg knew that I'd walked in with a head full of Tasmanian devils.

Does this mean that cancer cells are harder to transmit than, say, virus particles? "Much," he said. "Cells are very *effete*. Very susceptible to dying in the outside world." They dry out, they wither, they don't remain viable when they're naked and alone. Bacteria can form spores. Viruses in their capsules can lie dormant. But cells from a metazoan? No. They're not packaged for transit.

And that's only one of two major constraints, Weinberg said. The second is that if cancer cells *do* pass from one body to another, they are instantly recognized as foreign and eliminated by the immune system. Each cell of any sort bears on its exterior a set of protuberant proteins that declare its identity; they might be thought of as its travel papers. These proteins are called antigens and are produced uniquely in each individual by the MHC (major histocompatibility complex) genes. If the travel papers of a cell are unacceptable (because the cell is an invader from some other body), the T cells (one type of immunological police cell) will attack and obliterate it. If the invader cell shows no papers at all, another kind of police cell (called NK cells) will bust it. Only if the antigens on the cell surface have been "downregulated" discreetly but not eliminated altogether can a foreign cell elude the immune system of a host. That's what Canine Transmissible Venereal Tumor seems to have done: downregulated its antigens. It shows fake travel papers—blurry, faded, but just good enough to get by.

Nice trick! How did CTVT do that? Although nobody knows exactly, the best hypothesis is evolution by natural selection—or by some process "formally analogous" to it.

Weinberg went on to explain that the process is a little more complicated than classic Darwinian selection. Darwin's version works by selection among genetic variations that differentiate one organism from another, and in sexually reproducing species those variations are heritable. But evolution in tumor lineages occurs by that sort of selection plus another sort—selection among *epigenetic* modifications of DNA. Epigenetic means outside the line of genetic inheritance: acquired by experience, by accident, by circumstance. Such secondary chemical changes to the molecule affect behavior, affect shape, and pass from one cell to another but do *not*, contrary to the analogy, pass from parent to offspring in sexual reproduction. These changes are peeled away in the process of meiosis (the formation of sperm and egg cells for sexual reproduction) but preserved in mitosis (the process of simple cell replication in the body). So cancerous cell reproduction brings such changes forward into the new cells, along with the fundamental genetic changes.

Does that mean tumors don't evolve? Certainly not. They do. "It's still Darwin," Weinberg said. "It's Darwin revised." ■