Filled with Desire, Perceive Molecules

Roger Strand and Caroline Engen

Prologue: The Desire to Help

The Tao that can be named is not the Real Tao. This is one of the many translations of the opening sentence of *Tao Te Ching*, the masterpiece of ancient Chinese philosophy. The real world is richer than what can be expressed by human minds. The Universe is too vast; a single human being is too subtle to be fully put into words. In the Taoist tradition, as for mystics in the West and the East, the path to experience the richness of the Tao goes around and away from words: Wordless practice, silent meditation, the extinction of the ego. "Empty of desire, perceive mystery", *Tao Te Ching* reads. "Filled with desire, perceive manifestations."

Mystery is not the subject of modern science. As Niels Bohr said, the objective of science is to say what can be said about the world, nothing less, nothing more. Some scientists may express the desire to "know the mind of God"; by and large they get disappointed. Science describes the manifestations of the world, that is, how the world manifests *before* us, *for* us and by means of us and our cognitive, physical and emotional abilities.

Medicine was never embarrassed to admit the desire of its science: to help ill people by understanding disease. This noble desire has been crowned with success; it is the desire that made Richard Nixon declare war on cancer and René Descartes (1637) dream that "… we might free ourselves from countless diseases of body and

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of mind, and perhaps even from the infirmity of old age, if we knew enough about their causes and about all the remedies that Nature has provided for us." In the centuries following Descartes, this dream was pursued with ever more sophisticated concepts and languages and ever sharper extensions of the human senses. Medicine got to know the organs; the tissues; the cells and finally the molecules. If we control the molecules, can we correct the body and control the disease? Can we eradicate disease? From the physiology of the nineteenth century and the beginnings of molecular medicine in the twentieth, the slogan of early twenty-first century is that of precision medicine, of tailoring nanometre technologies to the molecular make-up of every individual patient.

Mary Shelley had her well-intended but ill-fated Doctor Frankenstein advise the readers "[…] never to allow passion or a transitory desire to disturb his tranquillity. I do not think that the pursuit of knowledge is an exception to this rule." (1993, chap. 4) On the whole this young woman's advice was ignored and dismissed as ignorant and unscientific. To the extent they were tolerated in academia, the practices of reflexivity and extinction of the ego were relegated to the soft sciences: philosophy, social anthropology, nursing science and the like. In science, *real* science, not the sort that Sir Rutherford once dismissed as stamp collecting, the higher the precision, the stronger the passion, tending towards the total imperative. In medicine, the imperative was to help: We have to help the patients, we have to act, we must never give up. Disease is intolerable, death is defeat.

This chapter tells a story about a science filled with a desire that enables it to perceive molecules. Its protagonists are the cancer scientists. They are courageous and persistent, as admirable as the heroes of the Greek tragedies, in their pursuit of heroic deeds with sharp tools and precise names. But what happens when the discrepancy between the Tao and its name shows itself? Is it too early in the story yet for the heroes to meet their downfall that will evoke fear and pity in us who are their spectators? Perhaps the story takes a turn to reveal other heroes, those who patiently ingest the molecules of desire and allow their bodies to be named a surgical and molecular battleground – heroes with whom we can empathize as they thrive and suffer while molecular soldiers fight for remission and the Tao, from the depths of its dark valleys, may decide otherwise.

Acute Myeloid Leukaemia

Heaven and Earth are not kind.
The ten thousand things are straw dogs to them. (Lao-Tzu: Tao Te Ching, Chapter 5)

Occasionally individual stories are shifted by abrupt, incomprehensible and devastating events, like the sudden and unexpected presentation of a life-threatening condition. Accounts of this are a source of great terror, and among the events most dreaded is that of being diagnosed with cancer (Vrinten et al. 2014). The perception of cancer as a source of horror is composite and involves interpretation of many

dimensions of the disease, including the nature of cancer as a "stealthy, indestructible, indiscriminate killer", the toxicity and atrocities of cancer therapies, as well as death (Vrinten et al. 2016; Agustina et al. 2018; Murphy et al. 2018). As Peyton Rous articulated in his Nobel Prize Lecture in 1966, "The Challenge to Man of the Neoplastic Cell", "Tumors destroy man in an unique and appalling way, as flesh of his own flesh, which has somehow been rendered proliferative, rampant, predatory, and ungovernable" (Rous 1967).

Acute myeloid leukaemia – AML – a rare and aggressive haematological malignancy, exemplifies the terror of cancer. Annually, the disease is assigned as cause of some 150,000 deaths world-wide (GBD 2015 Mortality and Causes of Death Collaborators 2016). Originating and expanding from myeloid progenitor cells of the hematopoietic system, the disease usually presents itself by rapidly progressing symptoms, like fatigue, weakness, dizziness, shortness of breath and fever (Estey and Dohner 2006; Dohner et al. 2015; Short et al. 2018). It is not uncommon that the symptoms of AML initially are interpreted as a common viral infection, and in such cases suspicion of a more serious condition may arise abruptly and unexpectedly as the doctor is presented with blood sample results, often demonstrating aberrant blood cell counts. At the time of diagnosis approximately half of patients are in relatively good condition (Juliusson et al. 2009), but if left untreated, the condition typically advances quickly, resulting in bone marrow failure and ultimately death, often within weeks from initial presentation of signs and symptoms (Oran and Weisdorf 2012). The outcome in AML can, however, be improved by therapeutic intervention. The aggressiveness of the condition warrants rapid clarification of treatment goals and initiation of therapy, often commenced only a day or two after diagnosis. Current treatment options include chemotherapy-based regimens, hematopoietic stem cell transplantation, and targeted treatment. These regimens are severe and in many cases with little objective hope of success, while introducing their own risks of suffering and death from adverse effects. Accordingly, more lenient disease stabilizing treatment plans and supportive care are still real options (Dohner et al. 2017).

The diagnosis of AML, a lethal condition requiring potentially lethal treatment, thus, represents a true shock and horror story. It is not unreasonable to perceive the disease as a malicious enemy that attacks suddenly and without provocation. As such, AML is a medical emergency in which the patient's world is set in rapid and whirling motion.

Innocently thrown into this horror, who could be more worthy of help than the AML patient? Confronted with the naked and intense suffering of AML, futility becomes unbearable and physicians' and nurses' desire to help become an imperative: We have to help them. We *must* help them. The moral force of this imperative has led to extensive research on AML and decades of trying almost any therapy. And whereas Lao-Tzu and Mary Shelley warned against excessive desire, the strength of the desire to help AML patients could itself be seen as a sign of a human civilization that is willing and able to go at almost any length to protect and care for its frailest members, a part of humanity driven by compassion in the midst of a world also driven by darker and violent desires. Indeed, despite cancers of the blood being

relatively rare, the discipline of haemato-oncology has been at the forefront of cancer research and oncological practice from the early 1950s. The first randomized comparative clinical trial was performed in patients treated for leukaemia (Frei et al. 1958), and the treatment of cancers of the blood has been at the forefront of oncological therapeutic development. Chemo-therapeutics, combinational regimes (Chabner and Roberts 2005), adaptive cell- and immune-therapy (Singh and McGuirk 2016) as well as gene-therapy (Rosenbaum 2017) were all of them first explored in leukaemia.

Yet, the AML diagnosis remains a death sentence to most who receive it. While treatment outcomes have improved, the overall five-year survival is still in the order of 25%. Some patients are regarded as cured, in the sense that there is remission and no relapse is observed until death from other causes. In the case of relapsed AML, however, prognosis is so poor that a case of long survival was officially deemed a miracle by the Vatican Church and used as evidence in the canonization of the Canadian "Mother of Universal Charity", Marie Marguerite d'Youville. In the case of AML, the helpers can feel the same urgency as was expressed by President Nixon when he declared war on cancer in 1971:

> … The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal. (Nixon 1971, 53)

Urgency, desperation and also the sense of scandal that is implied in Nixon's statement. How can it be that Science split the atom and took man to the moon, and yet fail to find the cure for a trivial blood disease? Doctors must help these innocent suffering patients, but fundamentally and perhaps more importantly, Man has to tame and conquer this malicious expression of brute Nature, and it has to be conquered with Rutherford's Science, that is, by finding its precise causes and contravening them. "Human knowledge and human power come to the same thing, for where the cause is not known, the effect cannot be produced," Francis Bacon ([1620] 1994, 43) said.

The history of bone marrow transplantation is perhaps the most striking display of how much was considered to be at stake in Nixon's war, and how the desire to help was blended into persistence and commitment to show that what ought to work, indeed could work. To stay with Francis Bacon (1620), what Man can and ought to do, is to dominate and "penetrate the more secret and remote parts of Nature". Edward Donnell Thomas performed the first experiments with bone marrow transplants from donors to patients in 1957 and was awarded the Nobel Prize for his accomplishments in 1990. All the patients in the initial experiment died. A review in 1977 showed that among the first 100 patients to receive this treatment, three quarters died the first year, most of them because of the complications following the intervention. Yet, in the end persistence was crowned with success, or at least this is how the official story goes. Currently, only around 20% of AML patients subjected to allogeneic stem cell transplantation die from adverse effects, in part due to refinement of procedure and support and in part due to a better selection of

the patients (Styczynski et al. 2020). These refinements are part of the explanation why overall survival for AML has somewhat improved.

A similar story can be told for the molecular level. Novel compounds have been developed and put into use. Yet, long-term survival rates in AML remain poor (Talati and Sweet 2018), for a variety of reasons: The cancer frequently adapts to the drug and develops drug resistance; or the cancer goes into remission but after a while, there is relapse; or the toxicity of the drugs impairs the patient or even causes death (Yeung and Radich 2017). Molecular studies of AML suggest ever new compounds and treatment regimens to be tested, and sometimes outcomes are improved for some subgroup of patients (Talati and Sweet 2018). On the whole, however, AML remains a horror to the patients and their carers and a scandal for Science.

Filled with Desire, Find the Molecule

Trying to control the world?
I see you won't succeed.
The world is a spiritual vessel
and cannot be controlled.
Those who control, fail.
Those who grasp, lose. (Lao-Tzu: Tao Te Ching, Chapter 29)

For the Taoist, the failure to tame and conquer AML comes as little surprise. Humans do not control the world. The desire for a cure does not imply the possibility of a cure, neither in logical or practical terms. It is a fundamentally modern, European and perhaps secular conception that desire implies existence, grounded in the belief that human imagination and ingenuity is omnipotent and limitless. The ancient Greeks called such beliefs *hybris* and explained the problem in the myth of Icarus.

And yet, sometimes Science appears to deliver the Silver Bullet. Chronic myeloid leukaemia – CML –, the less severe brother of AML, became one of the prominent success stories of molecular targeted therapy. Molecules known as tyrosine kinase inhibitors became game changers in the history of CML. With the drug *imatinib*, known under its brand name Gleevec, CML patients on the whole no longer die from their leukaemia and show the same overall survival rates as the general population (Deininger et al. 2005). For CML, imatinib became the silver bullet but also one of the first proofs-in-principle that the Art of oncology can become Science in Rutherford's sense. According to current scientific understanding, CML is nothing more than the result of a single mutation in blood cells. The mutation causes the cells to produce a protein, BCR-ABL fusion protein (Deininger et al. 2005), that is the phenotypic cause of the disease. Imatinib contravenes in the damage caused by BCR-ABL, and thus the disease is conquered.

Imatinib is not the only silver bullet in cancer medicine. The invention of immune checkpoint inhibitors to stop cancer cells defending against the immune system is a similar victory of molecular ingenuity (Demaria et al. 2019). New drugs such as

ipilimumab, nivolumab and *pembrolizumab* do not only prolong life but also seem to induce durable remissions in a subset of patients with advanced malignant melanoma (skin cancer) who otherwise would have had very poor prognosis (Herrscher and Robert 2020). Likewise, the antibodies *pertuzumab* and *traztuzumab* dramatically improved outcomes for women with HER2-positive breast cancer in the scientifically most satisfactory way: They are monoclonal antibodies that bind to the HER2 receptor and thereby interfere in signalling pathways that are involved in the growth and division of cancer cells (Slamon et al. 2001). Not only do these drugs work; for many cancer researchers they are proof that they indeed are on the way to dominate and penetrate Nature in the innermost parts, as Sir Francis Bacon so picturesquely formulated it.

The desire to help and to cure is visible not only in the volume and ferocity of cancer research but also in the theoretical structure of scientific knowledge. The prominent causal theories are those that are mechanistic and lend themselves to immediate translation into technological practice (such as Somatic Mutation Theory). Other attempts at theorizing, such as the much cited "Hallmarks of Cancer" are not even causal in the mechanistic sense but rather inventories of sites for practical interventions. Alternative types of theorization such as Tissue-Oriented Field Theory (Sonnenschein and Soto 2000) or approaches inspired by evolutionary biology might have more biological merit but in practical cancer research there is little patience with them. The first question in the cancer research seminar will invariably be: So how can this help improve clinical practice? Time is running out, the patients are dying and there is no place for philosophising.

The problem, however, is that the silver bullets have been so rare, and the cases where they work are also rare. What works for skin cancer does not work for colon or prostate cancer. What works for CML, does not work for AML. There are numerous attempts at finding *the* mutation that causes AML, and they find different answers. The situation resembles that of rationalism after Descartes: The rationalists all agreed that what is self-evident, must be true. The problem is that they all disagreed on what is self-evident. With AML, some mutations are common, but not ubiquitous; there are really many of them; and none of them seem to work as a site for a molecular silver bullet (Dohner et al. 2017).

AML Is a Name

The Tao that can be named is not the real Tao.
Names can name no lasting name.

Nameless: the origin of heaven and earth
Naming: the mother of ten thousand things. (Lao-Tzu: Tao Te Ching, Chapter 1)

The desire to cure with molecules is rationalist in nature; it is an instance of what has been called the Cartesian Dream (Schei and Strand 2015). Such desires can be fulfilled if, and only if, reality and knowledge can be brought into the appropriate

level of correspondence. To employ a cartographic metaphor: either the terrain has to be as simple as the map, or, alternatively, the terrain has to be changed so as to become as simple as the map, for instance by the use of bulldozers, lobotomy or other complexity-reducing technologies. As in the case of cancer; by cutting, burning and poisoning.

Sometimes, in the history of cancer, the terrain has emerged, seemingly, simple enough for the man-made map. That is, simple enough for scientists and physicians to fulfil their goal of improving outcome through precise and rational molecular approaches, for instance in the case of CML. The close relationship between clinical manifestations, morphological characteristics, the BCR-ABL fusion protein and response to targeted therapy led to the acceptance of a linear causal narrative of CML, a story in which the translocation is the ultimate cause of the disease. This story gradually grew so strong and compelling as to shape not only how CML was to be perceived, but also how cancer in general was to be explored and described, and how development of cancer therapy was to be pursued. More often, however, the intricacy of the gradually materialising landscape, of cancer at large, and individual tumours at small, has proven much more challenging to both map and navigate. Indeed, 20 years past the great success of imatinib and CML, this individual story by far remains the best example of precision oncology and its potential.

AML is one of the many diseases for which the ambition of precision oncology has struggled to become fulfilled. With time, and by force of evolving technologies, knowledge, and practices, the magnification of the AML landscape has gradually increased by changing the lenses through which the disease has been characterised and understood, gradually shifting from a clinical and macro-anatomical characterisation, to a focus on cells and morphology, and ultimately to one with emphasis on portrayal of molecular features and mechanisms.

In the case of CML, molecular characterisation led to therapeutic progress. The molecular characterisation of AML resulted instead in disintegration of the disease category. While a single genetic aberrancy characterises the clinical and morphological phenotype of CML, AML comprises multiple chromosomal rearrangements and more than 30 individual genes have been shown to be repeatedly mutated. In most cases more than one genetic variant is identified, and recurring mutational patterns suggest that several mutated gene-products may work together in leukemogenesis (Cancer Genome Atlas Research Network 2013; Metzeler et al. 2016; Tyner et al. 2018). The name of AML is currently understood to refer to a collective, a heterogenous collection of various acute blood cancers, grouped together by similar cytomorphological and clinical characteristics and the same type of causal story. According to this story, AML develops as the result of the manifestation and gradual dominance of a novel aberrant cell population. This cell population is still assumed to descend from a simple principle: It is thought to have resulted from a single haematopoietic stem or progenitor cell which has accumulated the sufficient set (and sequence) of somatic mutations to have become a cancer cell (with properties such as differentiation block, autonomous proliferation and immortality). Several observations, however, suggest that even this narrative is overly simplistic. Indeed, tumour evolution is a characteristic of AML disease trajectories. Across time, the

cytogenetic characteristics and molecular patterns of recurrently mutated genes in AML show increasing complexity as the disease progresses. Furthermore, postulated causal factors, such as certain cytogenetic aberrancies or particular single gene variants, are sometimes lost through individual AML disease courses (Garson et al. 1989; Kern et al. 2002; Renneville et al. 2008; Ding et al. 2012; Welch et al. 2012; Hirsch et al. 2016; Dovey et al. 2017). Further, metaphase karyotyping, inferred cell population size by variant allele fraction patterns, single cell sequencing analysis as well as engraftment studies have demonstrated that individual AML samples frequently comprise numerous genotypically diverse cell populations (Welch et al. 2012; Bochtler et al. 2013; Cancer Genome Atlas Research Network 2013; Klco et al. 2014; Paguirigan et al. 2015; Vick et al. 2015; Shlush et al. 2017; Wang et al. 2017; Baron et al. 2018; Potter et al. 2018; van Galen et al. 2019). Moreover, treatment with targeted therapy is frequently followed by rapid emergence of alternate cell populations, characterised by mutations in unrelated genes (McMahon et al. 2019; Zhang et al. 2019). Several observations further suggest that gene variants may translate into phenotypic variation as a function of differentiation and that mutations and subsequent gene products may confer variable qualities dependent on individual context and connectivity (Sato et al. 2011; Yang et al. 2014; Karjalainen et al. 2017; Sung et al. 2019).

We have listed these molecular complexities to show that a simple, rationalist and reductionist account of AML is not merely challenged by complex phenomena at higher organisational levels, such as the life-world of the patients, his or her family, society and so on. For all diseases, also for those that are successfully treated with molecular silver bullets, the complexities of the life-world exist. CML patients survive with their Gleevec but the challenges of their quality of life are not at all trivial. Still, Gleevec works in line with its intention and well enough for it to be called a silver bullet and for the patients to be sufficiently well described by the name of CML. AML, however, is different. As mentioned above, AML emerged as a name for a condition discovered in the clinic and characterised in terms of its tissues and cells. As the Tao Te Ching reads, naming is the mother of the ten thousand things, and the naming of AML delineated the clinical, anatomical and cytological thing called by that name. By force of the desire to dominate and penetrate the innermost part of AML, however, the naming continued with ever more names, parts, mutations and aberrations until it became clear, at least for the prepared mind, that on the molecular level there is no one well-defined thing to be called AML. Rather, AML refers to a collective of conditions that are best understood and described as evolving processes of leukaemia where stability and constancy are only to be found at the clinical and anatomical level. At the cellular and molecular level, the Tao that can be named is not the real Tao. What is to be found, is heterogenous, dynamic and relational flux where casual contributions can be traced from several levels of biological organization. Ultimately, AML may best be understood as a disease of systems and cells rather than one of genes and molecules. Or at least, that is how AML may be best understood by our protagonists so far, the medical researchers.

Once again, it seems, that the story that has been told with medical researchers and health personnel as the protagonists, as the active subjects that observe and act upon their passive, suffering objects that suitably are called *patients*. How is AML to be understood for those who receive the diagnosis? What are their desires and how do they shape the manifestations of AML and its natural history?

We have to recall once again that naming is the mother of the ten thousand things. We now know that untreated AML usually presents itself by symptoms such as fatigue, weakness, dizziness, shortness of breath and fever, which quickly escalates until death arrives. In the absence of diagnoses and doctors, the misfortune that struck could be anything, a corona virus for that matter. In 1976, the mummy of the Egyptian pharaoh Ramses II was subjected to scientific investigation and lesions characteristic of tuberculosis were discovered. Bruno Latour famously asked if Ramses II died from tuberculosis, and indeed what it could mean that he died from something that only was named much after his death. Unfortunately it seemed that the lesions had been caused on the mummy itself by a fungal infection; however, the philosophical puzzle remained. From the Taoist perspective, Ramses II and all other predecessors died but we do not exhaust the truth of their death by giving it an anachronistic label. Indeed, we may expect that the vast majority of people whom we now would regard as AML victims, had no ideas of AML and its horrors at all. They did not perceive them. They fell ill and died.

In a modern welfare state, however, part of the destiny of becoming afflicted with AML is to acquire the diagnosis and with it, the knowledge of how AML manifests itself. The category of AML patients is now real by the process that Ian Hacking explained with his doctrine of dynamic nominalism: People are called by a name, and the naming changes them. They now know that they have a horrible disease and that they are likely to die very soon.

Not too much is scientifically known about how it is to be an AML patient; most of the research projects have served to fulfil the desire to help by technological means. We wrote above that the "aggressiveness of the condition warrants rapid clarification of treatment goals and initiation of therapy, often commenced only a day or two after diagnosis." While this is generally true, it does not mean that all patients will receive therapy. Quite a few of them are quite old and with comorbidities. We shall return that point later. For now, however, let us focus on the relatively young AML patient, meaning, in his early sixties or younger, who believed that he was quite healthy and now is subjected to the shock of the diagnosis and the extreme urgency of action. Complex decisions are to be made in a state of shock, devastation and confusion. Patients frequently describe a feeling of being overwhelmed and struggling to process information and make informed decisions (LeBlanc et al. 2017). The decision-making process is characterized by a lack of shared interpretation of the situation where patients tend to grossly overestimate their chances of cure and one-year survival and underestimate the risk of dying from the treatment (Sekeres et al. 2004).

The disease as well as the treatment result in physical deterioration and loss of bodily strength and function. With a compromised body, it is a struggle to maintain social functions and meaningful activities. Many patients experience their

identities, relationships and worlds as threatened. It is not uncommon that patients suffering from AML experience psychological symptoms in line with those of anxiety disorders and depression (Tomaszewski et al. 2016; Deckert et al. 2018). More than 50 years ago, Kübler-Ross (1969) interviewed terminally ill individuals and named the stages of grief: denial, anger, bargaining, depression and, towards the end, acceptance. To this, we may add the sense of guilt that some cancer patients experience when they fail to mobilise the energy to "fight the disease" (Crawford et al. 2020).

To summarize, the course of AML is a matter of blood cells and bone marrows, of treatment choices and responses and of bodies that decay and die. More than that, however, it is a matter of travelling in landscapes of strong experiences and emotions, with shock, horror, fear and hope in the fore and middle ground. In our interpretation, then, our story has two sets of protagonists who meet each other in strong emotions and desires, under the name of AML. The patients, just being thrown off the cliff of apparent good health, are now suspended in desperate fears of instant suffering and death and equally desperate hopes that life can go on as before. The doctors and nurses want to help and must help. The first-hand solution for both is medical treatment. Perhaps it works, in the sense that the disease goes into remission or even is cured. Perhaps it does not work. In either case, it *might* work, and in this way the treatment already does two types of other work. It sustains the hope that the patient desperately needs and it releases the unbearable frustration into action for the doctor or nurse. They are doing something, they are doing the best they can, they are helping. A sense of meaning is produced. Hard work and expensive treatments confirm the dignity of a civilisation that spares no cost to try to protect its frailest. In an ironic twist of the plot, some of that cost has to be born by the patients themselves, if not financially in modern welfare states, by the suffering caused by adverse effects which even may be fatal. Still, regarding the modern project of medical science as heroic, these costs are also meaningful. Without the sacrifice of dozens and hundreds of patients who died because they received bone marrow transplantation, the technique would not have been developed into its current sophisticated form by which it cures thousands of patients.

More than 150 years ago, Claude Bernard, one of the fathers of modern physiology, explained his concept of modern medicine: "By normal activity of its organic units, life exhibits a state of health; by abnormal manifestation of the same units, diseases are characterised; and finally through the organic environment modified by means of certain toxic or medicinal substances, therapeutics enables us to act on the organic units" (Bernard [1865] 1957, 65). For Bernard, this is what medicine *is*. It is the application of toxic substances in order to reinstate chemical equilibrium or homeostasis in the organic body. What we can see so clearly in the case of AML, where that homeostasis only rarely is to be achieved, is the poverty of Bernard's concept. Medicine is its own Tao that cannot be named, and part of it is that real people meet with the real fears, hopes and despair and produce a sense of meaning together. Medical research plays an ever stronger role in those meetings and negotiations, in part because it actually, sometimes, delivers improvements in treatment à la Bernard, that act directly at the molecular level. This is good in itself and it

sparks hope and fuels a positive process for the doctor-patient dyad. In part, however, research and above all clinical trials have their own value because they are future-oriented with a vision of progress and because they involve action. The more patients are inscribed into trials, the more is done for them: Not only are they receiving standard treatment but the extraordinary, with the latest and most exclusive promising drug, is being made available to them. In this way clinical trials are important sites of symbolic interaction and the creation of meaning.

Is all this good then? That question cannot be answered in the general and out of context. Where some see a human interaction that gives hope, others judge it as false hope created by false promises. Patients are known to systematically overestimate the benefit of the treatments that they accept to take and that the doctors so desperately need to give them. And behind the hospital scene there are the pharmaceutical companies and their shareholders who are creating huge profits for themselves on drugs that have modest clinical benefit in the usual sense and cause serious adverse effects.

Empty of Desire, Perceive Mystery

> Suddenly Master Lai grew ill. Gasping and wheezing, he lay at the point of death. His wife and children gathered around in a circle and began to cry. Master Li, who had come to ask how he was, said: "Shoo! Get back! Don't disturb the process of change!"
>
> Then he leaned against the doorway and talked to Master Lai. "How marvellous the Creator is! What is he going to make out of you next? Where is he going to send you? Will he make you into a rat's liver? Will he make you into a bug's arm?". (Zhuangzi: The Great and Venerable Teacher 2003)

Doctor Frankenstein, having been created by an English mind, came to recognise temperance as a major virtue and a yardstick by which passions and desires should be tested. Desire can be excessive at the expense of virtue and the good life. One interpretation of our story about AML medicine and research is that a particular desire to help, conditioned and constrained by the Cartesian and Baconian dreams of dominating, penetrating and controlling Nature, led, if not to excess, into a peculiar state of affairs where biomedical success has been scarce but where doctors, patients and researchers are dependent upon biomedical research to meet their emotional needs. To the extent such an interpretation can be said to be plausible, the ethical issues are multiple. From a deontological perspective, the entire enterprise, consisting of the research and innovation value chain from the research departments of pharmaceutical companies down to the individual patients, could be seen as immersed in dishonesty about the real potential of treatments. From a utilitarian view, the public expenditures on expensive cancer medicines would be seen as unjust and unfair. Finally, at the individual level the question remains if and when hope is to be maintained, and for what. Elisabeth Kübler-Ross, in her groundbreaking work on the stages of grief during terminal illness, described how the final

phase is that of acceptance where the patient's "circle of interest diminishes" (101). She noted:

> There are a few patients who fight to the end, who struggle and keep a hope that makes it almost impossible to reach this stage of acceptance. They are the ones who will say one day, "I just cannot make it anymore," the day they stop fighting, the fight is over. In other words, the harder they struggle to avoid the inevitable death, the more they try to deny it, the more difficult it will be for them to reach this final stage of acceptance with peace and dignity. The family and staff may consider these patients tough and strong, they may encourage the fight for life to the end, and they may implicitly communicate that accepting one's end is regarded as a cowardly giving up, as a deceit or, worse yet, a rejection of the family. (102)

From a secularised Occidental perspective the acceptance that Kübler-Ross describes could be seen as a sign of the passage from being to nothingness, of, in her words, a diminishing circle of interest. Also, from what we might call spiritual Oriental perspectives such as Taoist or Zen Buddhist thought, acceptance would be a matter of emptying desires and interests. Still, it would not be seen as something void of significance. Rather than resignation it could be a passage of liberty from the self into transcendence and mystery. This is how to interpret Master Li's intervention. He tries to prevent the relatives from trivialising this significant moment at the end of Master Lai's life.

Secular or spiritual, Western healthcare is also sensitive towards the dignity of peaceful death. Hospices for cancer patients have long traditions and supportive and palliative care play important roles in the stories that we did not tell earlier in this chapter. Indeed, we have so far portrayed the AML patient as a mostly healthy person thrown into shock but then we disregarded that most AML patients are very old. One rule of thumb is that it is meaningful to treat AML if the patient is less than 80 years old and otherwise healthy. That excludes the majority of AML patients, who die after a short course of disease and in the presence of palliative care. The ethical issues mentioned at the beginning of this section can accordingly be reframed as the dilemma of finding the appropriate cut-off for offering treatment.

The verses of Tao Te Ching might suggest sharp dichotomies between being full or empty of desire; between manifestations and mystery; and between resistance and acceptance. Sharp dichotomies are, however, neither logically necessary nor a historically correct interpretation of these philosophical sources. In the ancient Chinese thought to which the Tao Te Ching belongs, opposites are themselves recognised to be names, that is, imperfect renderings of the real world. Nothing is merely a simple question of black and white, as indicated by the typical symbol associated with yin and yang (Fig. 1):

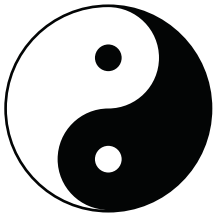

Fig. 1 A modern, simplified *tajitu,* symbolising the relationship between yin and yang

In this representation of the yin and the yang, there is always something black in the white and vice versa. This is not to say that all there is, are shades of grey. Rather, it is a message of ambiguity and complexity. It is possible to grieve and also suspend grief. One can experience tragedy and also acceptance.

The shades of grey, or rather differences by degrees, are also part of that complexity. In the received view of science it is often presented as the stance of disinterestedness and objectivity. Our story presents the science of AML as extremely passionate and driven by desires. We do not tell the story in this way to argue that it rather should become disinterested. Science cannot be disinterested. A wholly disinterested stance is mystical and not oriented towards words or action. Rather, as a matter of degrees, the science of cancer and of AML might benefit from relaxing just a bit from its urge to help, being slightly less medical and slightly more biological. Rather than spending all energy on "What molecules can help the patients?" one could ask the biological question "What is the function of cancer?" and perhaps learn a lot. And, as is well known in the sciences of nurses and other health professionals, one could learn a lot from the patients and their illness, if the illness is seen as something more than an enemy to be conquered or a deficiency to be removed. There is nothing new in this type of tactic; indeed, the history of physics and chemistry shows more than often that a temporary retreat from practical urgencies can give results that ultimately become highly applicable and useful.

Ultimately, however, these considerations will have to be made from within the practices that we have described. In Zhuangzi's story above, Master Li shooed the relatives away, apparently without hesitation, as if he knew the situation to the fullest, including the relatives' intentions. In that sense Master Li seemed to show quite strong opinions and desires himself. Of course we do not know what happened afterwards. Perhaps they threw him out. The stance true to the practice of telling such stories is neither that of the passionate scientist or the immutable mystic. Rather, we who present a Taoist perspective on AML position ourselves as the village fools. Our stories are tolerated, perhaps, and we may get to tell them to the end until we are told to leave. With some luck, they inspired some new desires, some new curiosities to explore the yin and yang, not only the yang, of AML.

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