OLLI 492: Human Immune System

Session 7: April 20th Summary and Observations

Chapter 5: Fever, Stress and the Power of the Mind

Davis begins this chapter by describing an observation he made (but did not follow-up on) early in his career; namely, that cancer cells when heated are more efficiently destroyed. This gives him a segue into the main topic of the chapter, the effect of stress on the immune system. "…heat can induce some types of cancer cells to exhibit at their surface '**stress-inducible proteins**', so-called because cells display these proteins when they are in a state of stress. Not stressed in the everyday sense of the word but cells undergo what is called a stress response when they are damaged by, for example, exposure to high temperature, toxins or UV light. Protein molecules become misshaped by heat while UV light can break up a cell's genetic material, and if a cell has these problems it will put up at its surface protein molecules which are not found on healthy cells. These proteins act as a hallmark of cells that are damaged and when Natural Killer cells detect them on a cell, they attack it."

"But heat is not used to treat cancer routinely. A reason for this is that the relationship between heat, stress-inducible proteins, inflammation and cancer has turned out to be **far more complex** than anyone could have known at the time I performed my own heat experiment."

Davis goes on to describe some of this complexity: "… while our immune system can often suppress or destroy cancer, it can also do the opposite, and there are at least two ways in which cancers can benefit from an immune response, problems that may then be made worse by heat. First, many cancer cells co-opt features of immune cells – by expressing sets of protein molecules used by immune cells – so that they themselves respond to cytokines and other secretions produced during inflammation. This allows cancer cells to hijack the cues immune cells use to multiply and move around the body, so that they too grow, expand and spread. Second, solid tumours sometimes benefit from local inflammation because this can increase the tumour's supply of nutrients and oxygen. In fact, immune cells can be so beneficial to cancer cells that instead of evading an immune attack, some tumours secrete protein molecules specifically to attract immune cells to live inside them. These tumours often secrete hormones to alter the nature of the immune response at the site of the tumour, switching off the immune cells' capability to attack while maintaining a tumour-promoting local inflammation. A tumour that maintains a local inflammation is sometimes thought of as a wound that never heals."

A further complication: "… secretions from tumour cells can, in some circumstances, switch off an immune attack and in other situations amplify the attack."

The body's natural way of producing heat is through fever. Davis notes that "… though, the fact that all warm-blooded animals are able to raise their core body temperature during an infection – which we call a **fever** – indicates that this ability must provide a hugely important survival advantage, especially as it requires a lot of energy; an increase in body temperature of 1°C requires an increase in the body's metabolism of around 10–12%. ….This means that at least some of the chemical and biological processes causing a reptile or fish to seek a warmer habitat during an infection are similar to those within us during a fever. Even plants might be capable of something akin to a fever, as the temperature of bean-plant leaves can increase during a fungal infection."

Continuing with his consideration of fever, he notes that: "Raising temperature helps the body fight infections in all kinds of ways, affecting germs directly and increasing the activity of our immune system. Most germs that afflict us have evolved to thrive at normal body temperature.

As a result, the replication rate of a virus, for example, decreases 200-fold when the temperature is increased to 40–41°C (104°F). A fever also helps the immune system by increasing the number of immune cells entering the bloodstream from bone marrow, where they are produced. As a result of this, and because heat also causes immune cells to make receptor proteins which direct them to sites of inflammation, a fever increases the flow of immune cells to where they're needed. Once the cells are in the right place, all kinds of immune-cell activity can be boosted by an increase in temperature: macrophages are better at engulfing bacteria; B cells produce more antibodies; dendritic cells, those discovered by Steinman, are better at switching on T cells, and so on. But like everything to do with the immune system, the process can overshoot." Davis provides a few examples of potential negative effects of fever.

Davis next gives us a look at the remarkable set of processes which produce a fever. "The trigger for the body to raise its temperature – in us and probably all animals – is the detection of telltale signs of germs by the immune system's pattern-recognition receptors…. When these receptors lock onto, for example, the outside coat of bacteria or a virus, an immune response begins and as part of this response, cytokines are secreted."

"As well as cytokines, the detection of germs by pattern-recognition receptors also triggers the production of the hormone prostaglandin E2…. during an immune response it is mainly produced by immune cells as well as other cells responding to the cytokines produced by immune cells. The production of cytokines and the hormone prostaglandin E2 is essentially how the immune system warns the brain of danger and triggers a fever. Aspirin reduces a fever by stopping prostaglandin E2 from being made."

"In a fever, these cytokines and hormones act on a region of the brain called the **hypothalamus**. In response, the hypothalamus signals for the body to produce another hormone, noradrenaline, which constricts blood vessels in the body's extremities and triggers brown fat cells to burn up energy and produce heat (the specialist job for this type of fat cell), as well as acetylcholine, which acts on muscles to cause shivering, for example, all of which serves to increase the body's temperature."

He goes on to describe the role of the hypothalamus in influencing our behaviors and emotions. Given the connection between the activity of the immune cells and the hypothalamus, he concludes that "… our immune system undoubtedly shapes our moods and feelings."

"Broadly, the immune system and our **nervous system** are in constant dialogue, each affecting the other through the body's flux of cytokines and hormones. Many hormones affect our immune system, including the sex hormones estrogen and testosterone, but it is stress hormones that have the greatest impact. We all know what stress is, though it's hard to define. It can be as all-encompassing as a fever or as fleeting as butterflies in the stomach. What is clear is that stress can have major effects on our health, because of its connection with the immune system. **Reducing stress may boost immunity**,"

While staying with the theme of stress and the immune system, Davis recounts the work of two researchers at the Mayo Clinic that produced a therapy for rheumatoid arthritis that is based on a hormone produced as a reaction to stress. I won't go into the details of the work of the physician Philip Hench and the biochemist Edward Kendall. Another example of dogged persistence and serendipity that led to the discovery of cortisol/cortisone; this substance proved effective in relieving the symptoms of rheumatoid arthritis. And led to a Nobel Prize for both researchers.

Davis continues: "We now know that among the hormones produced by our adrenal glands in response to stress, one that is especially significant to the immune system is cortisol. Cortisol works to prepare the human body for stressful situations by helping establish, for example, the body's fight-or-flight response: increasing our blood sugar levels and dilating blood vessels for muscles to prepare the body for immediate action. Importantly, cortisol also **quietens the immune system**, perhaps to prevent an inflammatory reaction switching on or overshooting when the body is under stress, and perhaps also because an immune reaction isn't of immediate importance in a fight-or-flight situation and energy is best used elsewhere. Overall, cortisol has an incredible impact on the human body, affecting the activity of around one in five of all 23,000 human genes."

Hench and Kendall's "Substance X… or, more precisely, the compound Merck managed to synthesise, was named cortisone (it is very closely related to cortisol; enzymes in the body can change one into the other). And it quickly became the most sought-after drug in history…. Even so, there was no detailed understanding of how it worked as a medicine. "

It soon became evident that cortisone was not a cure for rheumatoid arthritis; in fact there were serious side effects of prolonged usage at dosage levels required to treat rheumatoid arthritis. However, "It was found that cortisone could treat asthma (as well as some other diseases) at far lower doses than were required for the treatment of rheumatoid arthritis. Since then, cortisone and its derivatives – often just called steroids, the name for this class of compounds with similar chemical structure – have, year after year, been among the world's most widely prescribed medicines."

"Cortisol itself is also used as a medicine – in which case it is often referred to as hydrocortisone – for example, in a cream that can be applied to skin to reduce swelling or treat minor irritations. A synthetic chemical very similar to cortisol – dexamethasone – is about forty times more powerful in suppression of immune responses and is used in an enormous number of ways, to treat rheumatic inflammation, skin diseases, severe allergies and more. Other medicines similar to cortisol are used in preventer inhalers for asthma."

Davis concludes this part of the chapter with an account of the sad ending of the careers of Hench and Kendall after their discoveries and Nobel Prize.

Davis notes that the discovery of cortisol "… opened up the molecular basis for how our mind and body are connected." And stress is at the heart of this connection. He recounts the work of Hans Selye working at McGill University in Montreal. "Selye took stress to be 'the nonspecific response of the body to any demand'…. [But] Selye often emphasised that stress is not all bad; that it is also, he said, the spice of life."

Stress "…causes the adrenal glands, situated on top of our kidneys, to pump out hormones including cortisol. Cortisol's function is to prepare the body for a change in activity, and levels of cortisol in a person's blood don't only change with stress; they vary according to the time of day as well. Cortisol levels are highest in the morning, peaking around 7 to 8 a.m., and lowest at night. It's thought that the morning increase helps the body prepare for the change in activity of waking up. Still, cortisol levels change much more dramatically with stress, and in so doing they **dampen our immune system**. Cortisol does this by reducing the efficiency with which immune cells engulf germs, produce cytokines or kill diseased cells. This is fine for a brief time, but if stress persists, our immune system may stay **weakened**."

"There is evidence that people who are stressed for prolonged periods of time suffer worse from viral infections, take longer to heal wounds, and respond less well to vaccination. All kinds of stresses have been linked with diminished immune responses, from burnout at work to unemployment. Even natural disasters like a hurricane can alter the state of people's immune system."

Studying the effect of stress in humans is very complicated. There are multiple factors that cannot be controlled. Researchers turned to studying stress in mice, where the variables are easier to control. Result from mice studies: "This is strong evidence that stress and immunity are directly linked through cortisol levels."

Davis recounts studies on stress in humans, and the effect it has on the immune system. He concludes: "Overall, the bad effect of stress on health is probably the best-established link between lifestyle and the immune system."

He also recounts the effect of other emotions on the immune system, but notes: "While many emotions may impact the immune system, only the influence of stress is widely accepted, which then raises the question of whether or not practices that might reduce stress – from adult colouring books to psychoanalysis – could directly boost our immune defences."

He spends a great deal of time examining the studies on the effect on the immune system of practicing t'ai chi and mindfulness. These studies are often conducted on very small samples, and not controlled for other variables. There is no incentive to spend millions on controlled studies to prove that these practices, which cannot be patented, are effective in controlling stress and the immune system.

Davis sums up: "While the medical importance of cortisol, and its derivatives, is clear, there remains much more to be understood in how our body, brain and behaviour each affect one another. Evidently, our immune system is a realm of interaction not just between the body and other organisms but also between the body and the mind, and between our physical and mental well-being."

Chapter 6: Time and Space

In this chapter, Davis focuses on the temporal fluctuations of the activities of our genes, bodily functions, and behaviors, tuned to the 24 hour cycle of Earth's rotation. Our immune system is subject to the same forces. He notes: "The body's daily rhythm affects our well-being in all kinds of ways. "

Studies on immune reactions in mice point toward a dependency on time of day. Their immune systems react more strongly when they are at rest. "And roughly speaking, the same is true for us in that our immune system is stronger during our natural rest time, at night."

"One reason for this is that, as we saw in the previous chapter, the immune-suppressive hormone cortisol is kept low during the night…. [However]… the idea that the immune system is simply better or worse by day and night is too crude. Although it provides less of a sound bite, it would be more accurate to say that our immune system is in a different state depending whether it is day or night."

After considering, and rejecting, an evolutionary explanation for this phenomena, Davis suggests: "Another possible reason for our immune system behaving differently during the day

and night is simply that, as one scientist puts it, 'it has no choice'. 'The function of sleep,' researcher Till Roenneberg puts it, 'is to make us fit for being awake.' From this perspective, our immune system may not have evolved to respond differently by day and night for any particular benefit but as a side effect of the body's twenty-four-hour cycle which has evolved to optimise the body's use of energy. It is probably the current consensus that 10–15% of all our genes vary their activity by day and night, primarily to regulate the body's metabolism, and as a consequence of this, all of the body's processes are affected, including the immune system."

Davis goes on to recount the temporal variations that effect many diseases like asthma, gout, rheumatoid arthritis, etc. He even discusses the harmful effects of jet lag and night-shift work. He concludes: "… many disease symptoms vary according to the time of day or night but there's no simple rule how; each is affected differently."

"Our body's twenty-four-hour cycle is such an integral and influential aspect of our physiology that disruptions to it can be harmful."

Davis next describes how this cycle is controlled. "The body's master clock, which acts as the conductor of the orchestra, is made up of around 20,000 nerve cells located in the hypothalamus at the base of the brain. This in turn takes its cue directly from our eyes." Experiments showed that our eyes convey more information to the brain/hypothalamus than just the way the world looks like. "Russell Foster, who made this discovery, then at Imperial College London, proposed that this meant there must be another type of cell in the eye, different to rods and cones, whose purpose was not to help form an image of the world but whose photoreceptors specialised in detecting simply **how much light** there is – **brightness** – for the purpose of controlling the body clock."

Foster was eventually proven right; the master clock is driven by the amount of brightness detected. "As Foster discovered, the hypothalamus clock takes cues from special cells in the eye, but this doesn't drive the body's rhythm all on its own. While the hypothalamus clock acts as conductor, harmonising the ensemble, the players – all the rest of our body's cells and tissues – are quite capable of keeping their own time, as their own genes and proteins wax and wane." And it is the disconnect between the master clock and the other "clocks" that can cause problems.

A perfect example of how these disconnects can affect a person's health is space travel. Davis spends a great deal of time describing the health issues faced by astronauts on the International Space Station. "The consequences of disrupting our body clock are especially evident when magnified by the extreme conditions of space. As the International Space Station whizzes around the earth at around 17,000 miles per hour, astronauts are in sunshine for forty-five minutes, then darkness for forty-five minutes; sixteen days whizzing by for every one of ours on earth."

Davis concludes that ".. we are not built for space. The human body has evolved to fit our environment. It is tuned to the level of gravity felt at the earth's surface, the twenty-four-hour cycle of day and night, the way we interact socially, and so on. If there is ever a realistic plan for humans to settle elsewhere in the solar system, our immune system and many other bodily systems will need to be tricked into thinking we haven't left home."

Davis sees potential in these outcomes: "Our understanding of the body's daily rhythm already opens up an opportunity – to do with the **timing of medication**. As symptoms of diseases and the activity of our immune system change during the day and night, it follows that medicines might best be given at specific times of the day."

"Timed delivery of medicines might be more widely important than current practice suggests, as fifty-six of the top hundred bestselling drugs in the USA, including all of the top seven, target the product of genes that change their activity with the time of day. Around half of these bestselling drugs stay active in the body for only a short time after being taken, so matching the time they are taken with when they will be most effective may well improve their performance."

Davis notes the difficulty with implementing timed administration of drugs: many people don't take their medications as prescribed. There is potential for new "programmable" delivery mechanisms, but he sees more potential in timed administration of vaccines.

A bigger issue than daily temporal fluctuations is the problem of ageing. "Our relationship with time is changing thanks to one of the greatest triumphs of humankind in the last century, perhaps in all history: our increased lifespans."

Davis notes that our bodies become weaker at fighting infections as we age. "It's not that our immune system simply becomes unresponsive as we age, because the elderly are also far more likely to suffer from autoimmune diseases, caused by unwanted immune responses. Rather, it seems that our immune system somehow goes awry as we age."

Davis describes some of the effects of ageing on our bodies: "No matter how much we rage against the dying of the light, ageing is inevitable – right down to the level of our constituent cells…. [Cell division slows down], cells from someone elderly… divide only around twenty times… Our genetic material is modified over time – chemicals can become attached to it, and the way the strands of DNA are folded up can also be altered – changing which genes are easily switched on or off. These processes underlie what is called epigenetics, the modification of genetically encoded traits by one's environment…. telomeres shorten each time a cell divides. We don't know if short telomeres are merely a mark of ageing, like grey hair, or are part of the process by which cells age. It is possible that telomeres work as a tally of how many times the cell has divided so that the cell knows when to stop."

"The situation is complicated by the fact that some cells can also increase the length of their telomeres, using an enzyme called telomerase. In fact, immune cells use this enzyme to stop their telomeres shortening when they multiply, as do cancer cells – likely a contributing factor in their apparent immortality – and drugs that stop telomerase from working show promise against cancer (although cancer cells can evolve resistance). There is also evidence that stress can influence telomerase activity, though this is perhaps not so surprising given the enormous number of effects stress has on the human body."

After describing the effects of ageing on our cells, genes, bodies, Davis asks: "…why does this happen, why do we age at all? "

After examining evolutionary and other explanations offered for why we age, Davis concludes: "Overall, we can describe a lot of what happens during ageing, at the level of what physically happens to our genes, cells and organs, but the fundamental question of why we age is still open. In all likelihood there is more than one correct answer."

Davis now gives us a broad overview of the aged immune system: "Returning to the immune system specifically, part of the problem we face in old age is that our bodies produce **fewer immune cells**. Different studies have come to slightly different conclusions as to which types of immune cell continue to be produced at a steady rate and which do not, but there is a decrease overall. One of the probable reasons for this is that bone-marrow stem cells, which

produce immune cells, lose their regenerative potential over time likely because of the accumulated damage to their DNA. Evidence for this comes from the fact that bone marrow from an older person is less efficient in establishing a new set of immune cells when used for transplantation to help a cancer patient. This is one reason why charities which recruit bone-marrow donors are especially keen to sign up younger people. In addition, immune cells in elderly people are poorer at detecting signs of disease and respond less efficiently to the protein molecules that direct them to a wound or the site of an infection. Although they are able to move just as fast as cells isolated from younger people, they are therefore less accurate in getting where they are needed."

"At the same time, signs of an active immune response – cytokines, clotting factors and other inflammatory molecules – are often found at higher levels in the blood of elderly people, even when there are no overt signs of infection. This phenomenon is sometimes called 'inflamm-ageing'. There are many reasons why a low level of background inflammation might persist in elderly people, such as there being an accumulation of damaged or senescent cells, but the effect is that the system is less able to discriminate between germs and the body's own cells and tissues, and is particularly weak at detecting germs that have never been encountered before. In broad-brush terms, it is easier for an immune reaction to be triggered in elderly people but, by the same token, the system is less stringent in responding appropriately."

Davis again urges a system wide view: "Effects arise not just from the ageing of immune cells but from the ageing of the system as a whole – a consequence of the system already having spent decades battling germs."

One important feature of our immune system may complicate the functioning of the immune system as we age, namely the creation and retention of memory immune cells that are produced after an infection. "Crucially, this means that older people have more of their immune cells devoted to battling previously encountered infections, leaving fewer immune cells available for the fight against new infections."

Another important component of our immune system, the thymus, changes as we age. "Unlike most organs… the thymus is at its largest in childhood. This is because our immune system develops most dramatically when we are young, each of us being born with only a temporary defence borrowed from our mother which must be replaced by our own immune system. From puberty onwards, the ability of the thymus to scrutinise newly made T cells begins to decline and the thymus itself shrinks in size. It was once thought that the thymus had shrunk so much by the time we reach old age that it no longer allowed for the development of new T cells at all – but we now know that this is not quite true. It does retain some activity. The thymus in elderly people probably works at something like 1–5% of its activity in childhood. It's as if the body has decided that after puberty, it now has most of the T cells it will need for the rest of life."

"Once T cells are seldom produced with brand-new receptors, the body's set of T cells is shaped by the particular suite of germs a person has been exposed to over their lifetime, so that the numbers of T cells able to fight those specific germs is increased. Other factors, perhaps including levels of exercise and stress, likely also shape the immune system as we age." Evidence that our immune system adapts to our experiences, and is not controlled by genetics, comes from studies of identical twins. "An international team of scientists led by Mark Davis (no relation) at Stanford University analysed the immune system of 105 sets of healthy twins in over 200 ways, including measuring the level of different immune cells in their blood and the ability of immune cells to secrete cytokines before and after participants were given a shot of flu vaccine."

"They found that most aspects of our immune system depend on non-heritable factors far more than on the inheritance of our genes. It has long been clear that some combination of

nature and nurture determines our health, but the fact that nurture plays such a large role in the configuration of our body's defence is surprising."

"Davis's analysis of twins also showed that the immune systems of younger identical twins were far more similar than those of older identical twins. The implication is that as we age, the individuality of our immune system increases. We become more, not less, of ourselves."

"This complexity – **everyone's unique history** – is one reason why it is especially hard to design medicines that work with the immune system in the elderly."

Davis concludes this chapter with an extended discussion of the concept of tailoring vaccine administration for the elderly to a particular time of day, and a "call to arms" to better understand the process of ageing.