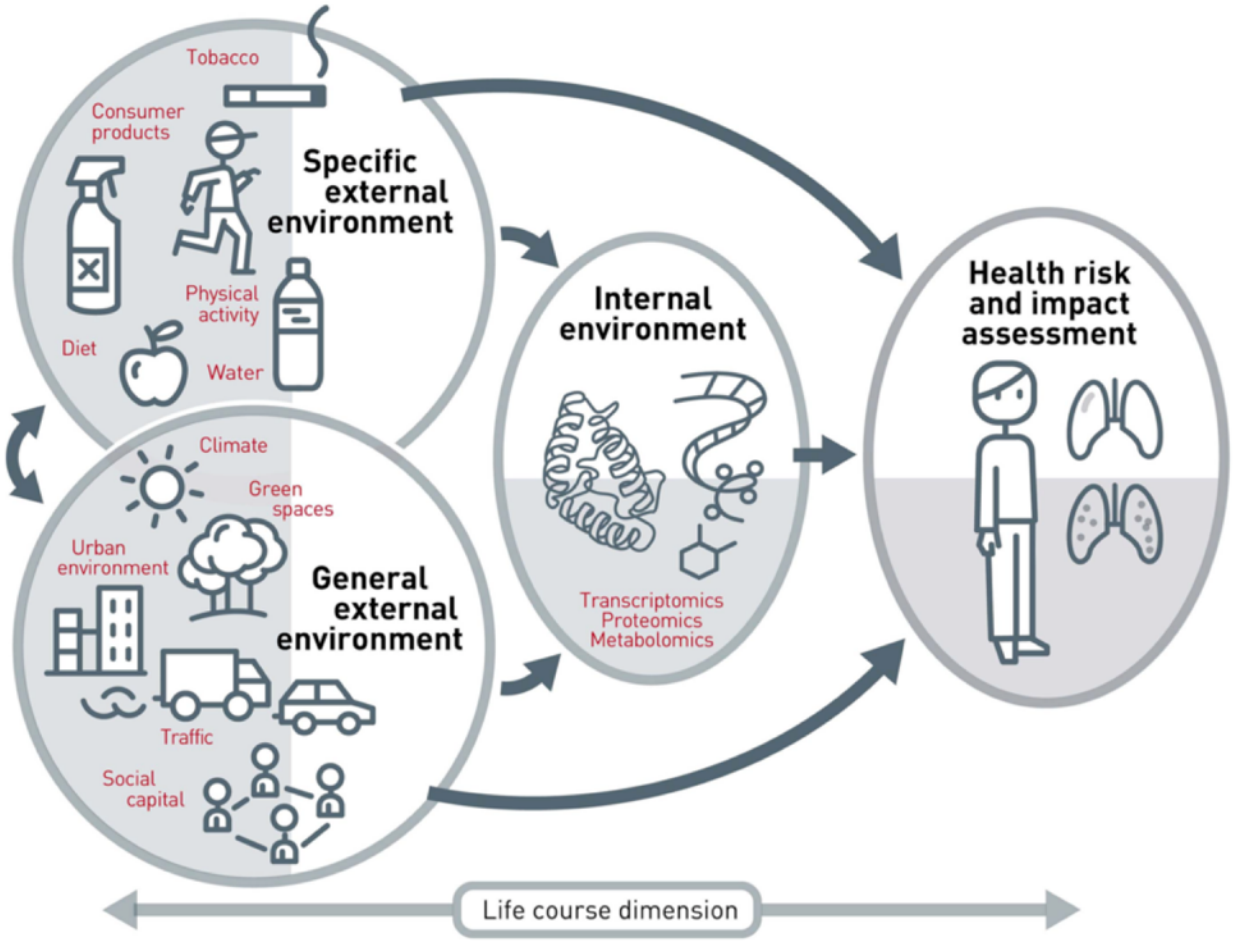
Future of Medicine - Part Two



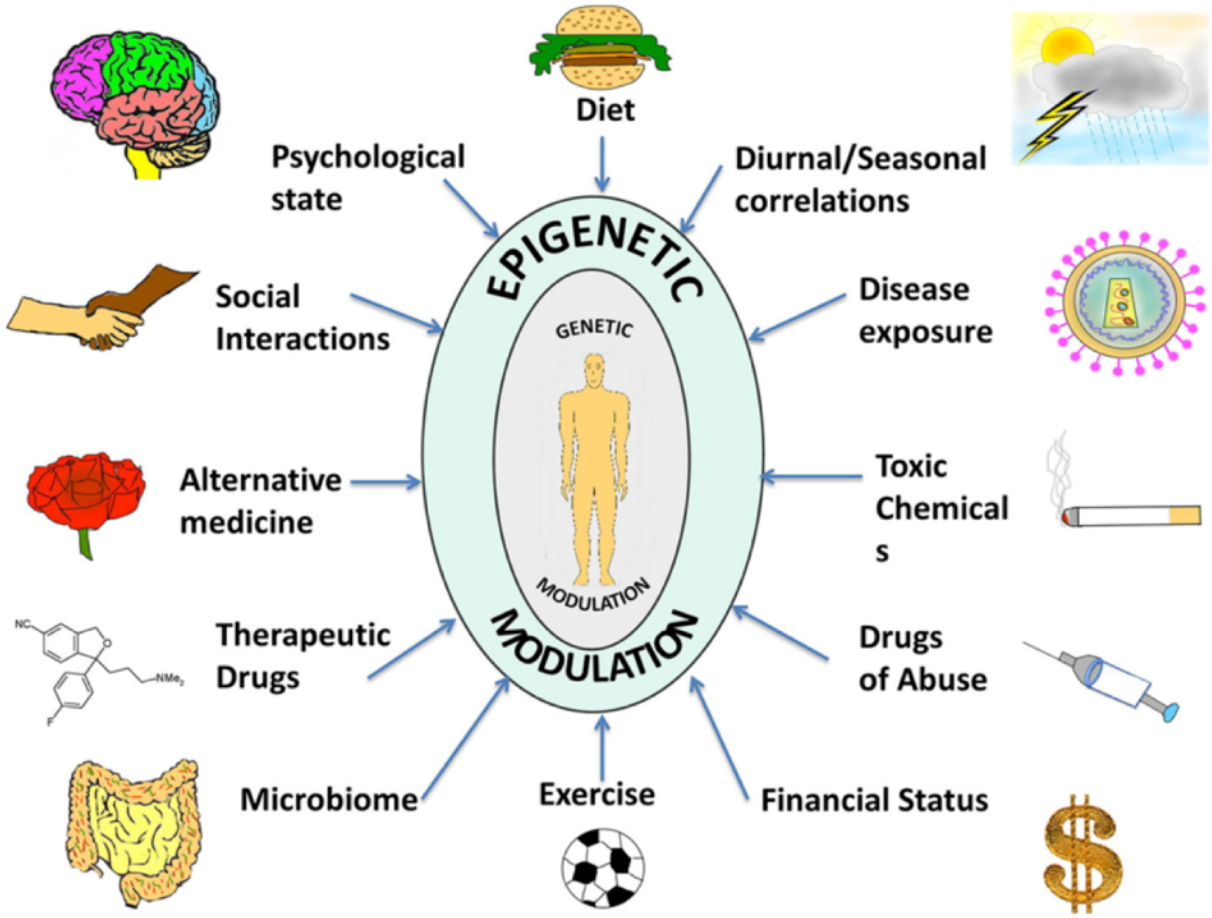
Further research divided the exposome into three categories. One is specific external, and this refers to things like diet, the water we drink, physical activity, and the personal and home care products that we use. Number two is the general external. These are the broader external influences like the overall environment that we live in, things like air pollution, social interaction, and climate. Then the third category is the specific internal. This is our metabolism, our hormones, our microbiome and metabolome, inflammation, oxidative stress, etc. These influences are key. In fact, we now understand that the exposome is the primary driver of disease. According to recent estimates by the World Health Organization, over 50 percent of mortality is related to just three factors of the exposome: air pollution, cigarette smoking, and diet.

At one point, it seemed like genetics would hold the key to human health and disease. The 20th century was really a heady period in terms of genetics. It was characterized by the discovery of DNA, the polymerase chain reaction, or PCR, method of amplifying and studying DNA, and then, of course, ultimately mapping the entire human genome. This led to an era of biological determinism, which was the idea that human health and even behavior was almost entirely controlled by genes, and it led to some pretty bold proclamations like this: “We now have the possibility of achieving all we ever hoped from from medicine.” That was from Lord Sainsbury, the UK Science Minister. Also,

"Mapping the human genome has been compared with putting a man on the moon, but I believe it is more than that. This is the outstanding achievement not only of our lifetime, but in terms of human history," and that was from Michael Dexter from the Wellcome Trust.

Unfortunately, those promises didn't really pan out. The limitations of using genes to predict and prevent disease became apparent pretty early on. Ironically, Craig Venter, who was one of the first to sequence the human genome, was also one of the first to recognize its limitations when he said, "We simply don't have enough genes for this idea of biological determinism to work." We now know that genetics accounts for less than 10 percent of human disease and that the remaining causes are environmental, which is to say, they're related to the exposome. The majority of mutations of single genes, which we refer to as single-nucleotide polymorphisms, or SNPs, are highly prevalent. This means they occur frequently in the population. You might think they play a significant role because of that, but these SNPs also, for the most part, have low penetrance, which means they don't often manifest in clinical disease, and they will only do so in the presence of specific environmental exposures. This is to say that the mutation or polymorphism of a gene doesn't necessarily guarantee dysregulation of that gene.

Put another way, genes load the gun, but environment pulls the trigger.



This relationship between genes and environment is what's studied in the field of epigenetics, which literally means "on top of genetics." The simplest definition of epigenetics is changes in gene activity that don't involve alterations of the underlying genetic code, but still get passed on to at least one successive generation—and possibly two, according to recent research.

DNA was originally considered like a template or a mold, where you could pour raw genetic material into that mold a hundred different times and you would get a hundred identical copies. This is, of course, biological determinism, the idea that genes really run the show and environment has little to do with it. But we now know that's not the case. A better analogy between genes and environment would be a film or theater production. Genes are like the script, and then the cast, crew, costumes, director—everything that goes into making the production—is like the environment. If you consider ***Romeo and Juliet*** as an example, the script really hasn't changed since it was written by Shakespeare in the late 1500s, but it's been performed and produced in hundreds, if not thousands, of different ways. If a script is terrible, even a great director or cast and crew won't be able to save it. On the other hand, even a great script won't matter with a terrible production. This is to say that genes are definitely important, but our environment and how genes express is more important in most cases.

This explains why identical twins are similar but not the same. Identical twins are matched for genes, age, sex, pre-gestational environment, and often post-gestational environment, but while it's true that they have a higher risk of having the same diseases, that risk is not 100 percent the same. In fact, we see discordance rates of up to 50 percent in identical twins, even in highly heritable conditions. Schizophrenia is a good example of this. It's a disease that's known to have a strong genetic component, yet if one identical twin has it, the other twin only has a 50 percent chance of having it, so this, of course, suggests that the exposome and epigenetics play an important role even in diseases with a strong genetic component.

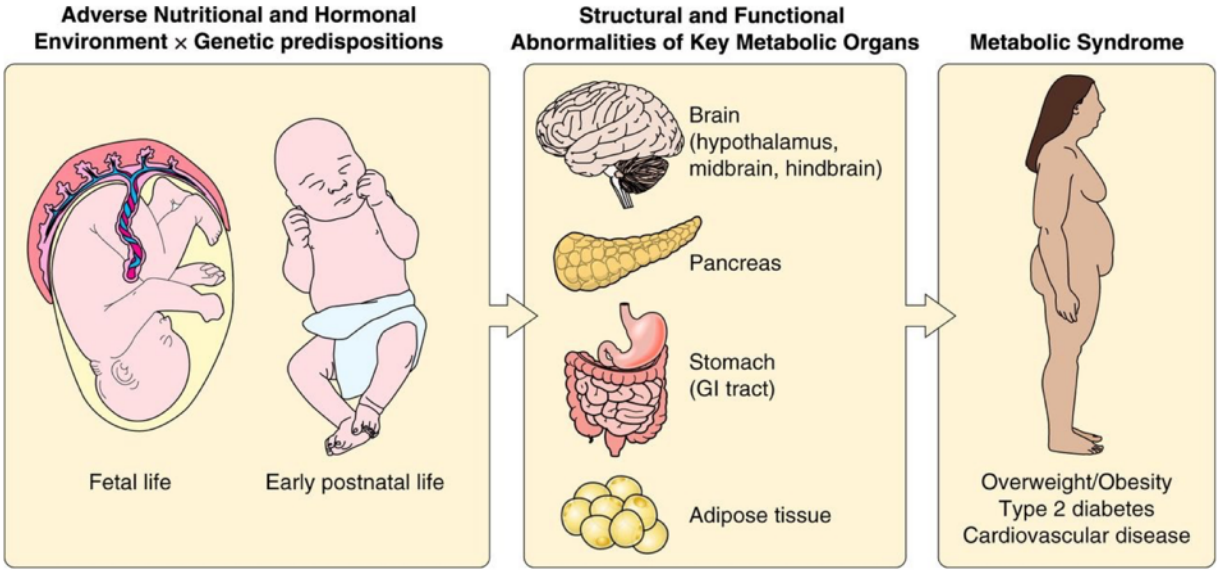
The Agouti gene in mice causes the production of a yellow coat instead of a black coat and also leads to a high risk of obesity and diabetes. But when methyl donors like B12 and folate are given to pregnant mice with the Agouti gene, that gene is silenced in their offspring. This means that Agouti gene doesn't express in their offspring, and their offspring will be lean with a dark coat. This is also, interestingly enough, true for the pregnant mice's offsprings' offspring, their grandchildren.

Another example in mice showed that behavior and cognitive function is even subject to epigenetic influences. In one study, researchers exposed mice with genetic memory problems to an environment that was rich in toys, exercise, and extra attention that would be expected to improve cognitive function, and these mice showed a big improvement, in fact, in memory formation and cognition. But what was remarkable is that their offspring also showed a similar improvement despite their genetic predisposition to having issues in this area and despite no extra attention or enrichment like their parents received.

We don't just see this in animal studies; we also see it in human studies. One of the best known examples is the Dutch winter hunger cohort. This is a group of people that lived through a period of extreme famine in Holland during World War II from November 1944 to May of 1945. Because of the German blockade at that point, food rations of people living there were less than 1,000 calories a day.

Babies that were in utero during this period experienced a wide range of adverse health effects later in life, including higher rates of obesity, diabetes, and cardiovascular disease. They were more likely to be infertile. They had higher rates of personality disorder, depression, and psychosis.

Another similar example is the Norrbotten cohort. This is a snow-swept, sparsely populated area of Northern Sweden, and at least in the early 20th century, it was so isolated that it was entirely dependent on the local harvest. A Swedish physician named Dr. Lars Bygren drew a random sample of 99 people born in 1905 and then used historical records to trace their parents and grandparents, and he analyzed agricultural records to determine food availability for that entire cohort.



What he found was that boys who enjoyed rare overabundant winters had higher risk of obesity, diabetes, and early death compared to other boys who didn't experience those overabundant winters. On average, they also had a lifespan that was six years shorter than the other boys, and this was true, once again, for their offspring as well, so all of these effects were passed on to at least one successive generation.

All of these examples that we've just talked about illustrate the role of the exposome and epigenome in health and disease and particularly the importance of early-life exposures.

So what does this all mean? There's bad news and good news. The bad news is that choices our parents and even our grandparents made affect our disease risk and our health and that choices that we've made—perhaps before we knew as much as we know now—affect our children's and even grandchildren's health. The good news is that genes are not our destiny. Genes certainly have an influence over our destiny, as we've discussed, but changes we make in real time can affect our gene expression and, of course, not only our own health, but if we're still procreating, our children's health and their children's health. And it makes the focus on the exposome—primarily a healthy diet and lifestyle and environment—even more important. In the previous examples I gave, not

everybody who was at higher risk of a disease actually went on to acquire that disease or die early, and the environment or the exposome was almost certainly the main factor that determined which of those people that were at higher risk got sick and which stayed well. So while we can't control what our parents or grandparents did or our genes, we can control these diet, lifestyle, and environmental influences.