

THOUGHTS FRONTLINE

Things Are Getting Better

By John Mauldin | March 26, 2022



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In these letters, I look at the economy and tell you what I think, for better or worse. Recent missives were mostly negative. I regret being the bearer of bad news but sometimes that's just reality.

I often say that I am the most optimistic man in the room, and it's true. That's because I look over the horizon and see where we are going. I can also look at "boring" statistics and find out how far we have come. The trends are our friends.

Today I want to focus just on good news and sometimes great news. The world is getting better, but it doesn't make the headlines like the problems and catastrophes do. The byword in newspapers when I was growing up was "If it bleeds, it leads." Today's online headlines are even more so. Crisis and gloom sell. Good news, not so much.

Letting yourself wallow in negative thoughts won't solve whatever problems you face and may even make them worse. Humanity got where it is not by complaining, but by finding solutions. So let's take a break from the bad and look forward to better times.





Abundant Energy

Since energy is a top issue right now, we'll start the good news there. The war-related disruptions, plus the inflation that preceded them, are breaking down some of the entrenched positions that delay progress.

I'm especially pleased to see more flexibility on nuclear power. Germany is reconsidering its plan to shut down nuclear plants and France plans to build more. That's major progress. Modern nuclear technology greatly reduces the risks of older designs that caused incidents like Chernobyl and Fukushima. They can provide "base load" electricity when weather conditions don't favor wind and solar. There are numerous projects focused on small, clean nuclear plants that would provide cheap power.

And it's getting even better. A staggering amount of research funding is going into nuclear fusion (as opposed to the current fission) reactors. These would produce more energy while reducing radiation and radioactive waste. A fusion reactor essentially replicates the sun on a tiny scale. So in a sense, it will be 24-hour "solar" energy.

I have been following this industry for some time. They are getting money from very serious investors who understand that cracking the fusion code is a 1,000X investment multiplier.



Source: Nat Bullard

Fusion is no longer 30–40 years out. We could see it working by the end of this decade, which would be a worldwide game changer.





Geothermal power, tapping into the Earth's natural heat, also has tremendous potential. Right now it is only feasible in volcanically active places like Iceland. Quaise Energy, a startup spun out of MIT, is developing microwave drill technology that could punch 12-mile holes anywhere on the planet. The vision is to sink shafts near existing coal and natural gas generators, refitting them to use the geothermal heat instead. That could be a quick and relatively easy transition.

I have been looking at Hover Energy, a small company with a completely new technology for wind power. They have created a small wind turbine that is far more efficient than the typical windmills we associate with wind power. Basically it's a 10-foot cube sitting on top of a platform which contains a large cylinder. The cylindrical turbine is surrounded by airfoils which direct the wind and multiply wind force. (Physics nerds will love figuring out why in an array of seven of these turbines the middle turbine will be 50% more productive than the outer turbines.) In places like Puerto Rico and the Caribbean islands where energy is incredibly expensive, they are far and away the competitive choice.

There's also a lot of progress happening with air transportation. That's a particular challenge because you have to carry your power aloft with you. Petroleum delivers a lot of energy for its weight, but there are other ways being developed. Last year United Airlines actually flew a 737 with 100 passengers from Chicago to Washington using a sugar/corn fuel mix. Separately, ZeroAvia, a startup backed by British Airways, thinks it can have a 50-seat hydrogen-powered plane in the air by 2026.

And speaking of hydrogen, a project is underway using nuclear fission to manufacturer hydrogen cheaply. Think about the progress being made by fuel cell companies which would be an environmentally cleaner and potentially less expensive competitor for electric vehicles. This race is not over.

Abundant energy will make the world more peaceful and prosperous. Removing the need to fight for this precious resource and then laboriously move it around the globe will free attention for better things. I think that's something we will all welcome.

I've Got to Admit It's Getting Better

With a nod to The Beatles, it's getting better all the time, but we just don't notice it. <u>Stewart Brand</u>, founder of *The Whole Earth Catalog* (you qualify as young if you don't know what that is) and the Long Now Foundation. He is serious about ecology, but advocates nuclear power. (Kind of like me.) He is also a long-term optimist who recognizes short-term problems. A recent *New York Times* <u>article</u> about him with this quote from one of his recent tweets:

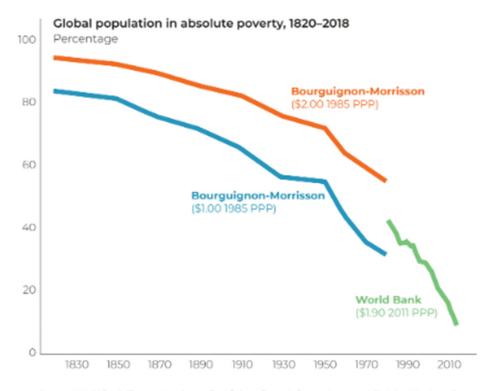
"Interesting: how much bad news is anecdotal and good news is statistical. (And how invisible the statistical is.) Still, if only one of the two can be good news, I would rather it be the statistical. It accumulates toward qualitative change that lasts."



THOUGHTS FRONTLINE

Let's look at a few of those statistical trends that are breaking in humanity's favor. Marian Tupy is the editor of HumanProgress.org and a member of other forward-thinking groups. He has written a book called *Ten Global Trends*, from which I will borrow heavily for the next few pages. His forthcoming *Superabundance* will help demolish the Malthusian myth that we are running out of everything. (It is a neck-and-neck race between Malthus and Marx as to whose thinking was the most destructive to humankind.) Here are some of Tupy's charts.

It's not a straight line but the trend is clear. Poverty is slowly diminishing:



Sources: World Bank, "Poverty Headcount Ratio" chart; François Bourguignon and Christian Morrisson, "Inequality among World Citizens: 1820–1992," American Economic Review 92, no. 4 (2002): 727–744.

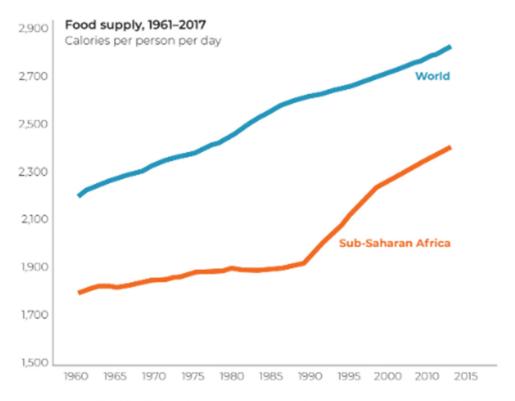
Note: PPP = purchasing power parity

Source: Marian Tupy





Over the last 60 years, the amount of calories per person available per day has risen dramatically. The Ukraine war is going to affect food supply and developed nations need to carry a bigger load to help those less fortunate. But new technologies and free markets will cause this trend to resume in a few years:



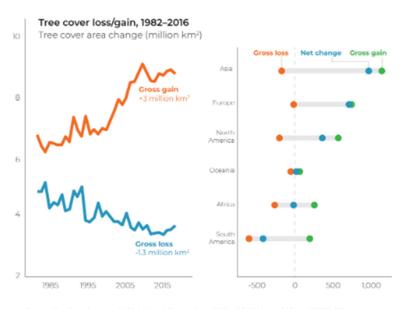
Source: FAOSTAT, Food Balance Sheets website, UN Food and Agriculture Organization, January 27, 2020.

Source: Marian Tupy

We've all seen pictures of burning forests. I have actually ridden through miles and miles of burnt Amazon jungle. It is a depressing sight. But what if I told you that over the last 50, 75, and 100 years the amount of forest on the globe was increasing? It's true on every continent except South America and even there has improved recently. I should note the increase in forest is an area roughly the size of France. Amazing.



THOUGHTS FROM FRONTLINE

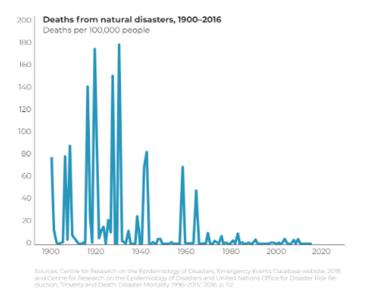


Source: Xiao-Peng Song et al., "Global Land Change from 1982 to 2016," Nature 560, no. 1 (2018): 639. Note: km² = square kilometers

Source: Marian Tupy

Quoting from my friend David Bahnsen yesterday:

"Did you know that the chance of dying in a natural disaster (earthquake, flood, drought, wildfire, landslide) has declined 99% in the last one hundred years? 99% – no typo. Why? Free enterprise has meant better building construction, better weather monitoring, better medical capacity post-disaster, etc. 90% of natural disaster deaths in the last twenty years were in poor countries that lack the infrastructure and capacity for such mitigation. More wealth and prosperity in a country = more protection from a natural disaster."



Source: David Bahnsen

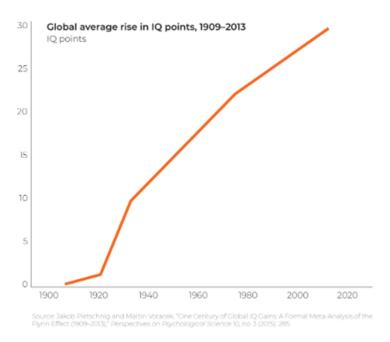






I could go on and on, citing statistic after statistic. Global income inequality is down over the last 70 years. There are differences but on a global basis things are improving. Global and per capita GDP are up dramatically. The percentage of people living in slums is decreasing significantly (though not as fast as any of us would like).

Literacy grew dramatically over the last 100 years. The number of children in school and especially young girls is also increasing. OK, one last chart which I found astonishing:



Source: Marian Tupy

Who knew? (Nutrition is a huge factor.) Perhaps that is a reason we are seeing more scientific breakthroughs. More geniuses = more breakthroughs!

Now let's turn to my favorite calls for optimism: health care and anti-aging and actual age reversal breakthroughs.

Healthcare Breakthroughs

Showing again how problems lead to solutions, the COVID-19 pandemic sparked all kinds of innovations. There will be hundreds of new innovations and therapies as a result of the research on COVID.

The vaccines, while not perfect, are making the virus much more manageable. I said early on we would probably end up having annual COVID boosters, much like the yearly flu shots that are updated for new strains. Now several groups are working on a "pan coronavirus vaccine" that can recognize multiple variants. One candidate developed by US Army researchers just began human trials. If it works, this will be much simpler than trying to manufacture and deliver billions of new shots every year.





Other vaccine breakthroughs...

- We now have an effective <u>vaccine against malaria</u>. This mosquito-borne disease kills hundreds of thousands of children every year.
- Scientists at the Cleveland Clinic are participating in a trial for a vaccine for breast cancer. Other cancers will be targeted. CRISPR technologies are producing therapies for numerous genetic disorders.
- A new Ebola vaccine helped end an outbreak last year in Guinea. As recently as 2013–2016, Ebola killed 11,000 in West Africa. The latest outbreak claimed only 12 lives—still too many but a vast improvement.

We Are Going to Live Longer

I distinguish between research that I call the "Fountain of Middle Age" (which at 72 sounds pretty phenomenal) and the "Fountain of Youth." The former has had major developments and the latter is making significant progress. Much of this is gleaned from my doctor Mike Roizen of the Cleveland Clinic and my good friend Pat Cox who is doing research for a new soon-to-be-revealed startup from Mike focused on anti-aging.

Let's start with some very new research from a company called MyMD Pharmaceuticals. (Full disclosure: I am an investor but have no other financial relationship with the company.) This is clearly in the fountain of middle age category.

Their drug, MYMD-1 is a TNF-α inhibitor, like Humira and the other monoclonal antibodies (mAbs) that make up a \$25 billion market treating multiple serious diseases. Unlike mAbs, which are grown from human or animal cells, MYMD-1 is a synthesized version of a naturally occurring molecule found in plants. It's also safer than the mAbs that come with a black box warning indicating serious risk. Moreover, it doesn't have to be injected. It is a simple pill and, based on a phase 1 human trial, has virtually no side effects.

The most important thing about TNF- α is that it is a major driver of aging itself.

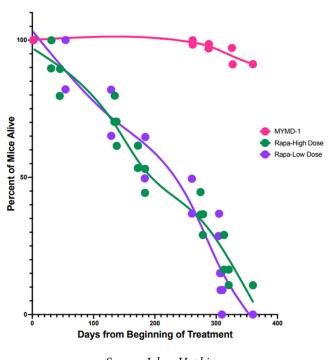
One of the primary and most obvious symptoms of aging caused by TNF- α is sarcopenia, or age-related frailty caused by the loss of muscle mass and strength. The scientists studying MYMD-1 believe it will dramatically slow the onset of aging and sarcopenia, so they tested it in old laboratory mice.







We won't get data regarding the results of that trial until June. As you can see in this chart prepared by scientists at the Johns Hopkins medical school, old mice given MYMD-1 were compared to old mice given two different dosages of rapamycin, the most promising anti-aging drug available for off-label use today.



Source: Johns Hopkins

Bottom line: As you can see, the MYMD-1 mice did far better than the rapamycin mice, who typically live longer than untreated mice.

I talked to neuropsychiatrist Dr. Adam Kaplin, Johns Hopkins Medicine adjunct professor in the departments of psychiatry and neurology. Adam told me MYMD-1 not only extended the lifespans of the mice, it also preserved muscle function. Male mice in the MYMD-1 group had no muscle strength loss whereas there was a significant loss of muscle strength in rapamycin mice. The female mice treated with MYMD-1 had a very small diminution in muscle strength, dramatically less than rapamycin-dosed females. We'll find out soon whether it does something similar in people.

From Mike Roizen (quoting):

"History: Life expectancy at birth has increased an average of 2.5 years every decade since 1890. But the headlines say Life expectancy fell 1.5 years in 2020–21.

"Nonsense: While this data may be accurate in a snapshot of time, the implication of a declining life expectancy is not. We have seen drops because of the pandemic (COVID-19) and an epidemic (deaths by opioids), but this is "period life expectancy." That is, how long would someone born in 2020 live if death rates and causes of deaths that occurred in 2020–21 continued at that rate forever."





This will not be the case. We are on the cusp of a monumental change in the way our health and medical fields work due to advances that will change longevity and wellness exponentially. The typical child born in 2020 will almost certainly live 10, and perhaps even 30, years longer than the CDC/CBO 2022 predictions indicate.

One example of scores (from both Mike and Pat):

Therapeutic plasma exchange (TPE), is a relatively simple procedure that involves replacing a percentage of a person's blood plasma, mostly with saline solution or salt water. TPE is an FDA-approved procedure long used to treat a variety of conditions, including multiple sclerosis, autoimmune encephalitis, renal diseases, neuromyelitis optica spectrum disorders, refractory Kawasaki disease, severe refractory hypertriglyceridemia, autoimmune hemolytic anemia, severe hyperthyroidism, and burns.

Ironically, TPE's effect on the biological age of the genome came out of a discredited field called young blood therapy. It was noticed that old animals that had a substantial part of their blood replaced with a transfusion from a young animal exhibited real improvements in health. Further research showed that the benefits came solely from plasma, the clear liquid that makes up 55% of blood.

Further research, led by professors Irina and Michael Conboy of UC Berkeley, surprisingly found that significant age reversal shown by plasma transfusion in animals could be duplicated if not exceeded using saline solution. The impact of these saline replacements is profound, with noticeable improvements in numerous tissue types, including brain neurons, muscle tissues, liver, and the hippocampus, the learning and memory organ.

This happens because the procedure removes old, senescent cells. These cells stop multiplying but don't die when they should. So they hang around in bodies, increasing in numbers and effects as we age, and cause a whole lot of destruction. (They actually are formed even when we are infants but are recycled by our bodies and don't start accumulating until near age 30.) They contribute to inflammation, and, even more destructively, they secrete substances that turn neighboring healthy cells senescent. The science of senolytics which gets rid of these zombie cells has been studied with increasing intensity and dollars since the 1960s.

The rational skeptic will react by pointing out that lab mice are not humans but, fortunately, TPE has been thoroughly investigated in the most stubborn and expensive of all diseases of aging— Alzheimer's disease (AD). After decades of research, a strictly randomized, controlled, and blinded human trial involving multiple prestigious medical organizations (the AMBAR trial) found that TPE reverses early to moderate AD.

The reversal of AD is a huge deal, but it isn't the point. The point is that AD is considered one of the ultimate markers of aging and decline, but TPE turns back the epigenetic clock. One result is reversing AD.

Is it safe? We know it is because it is carried out tens of thousands of times daily in the multibillion-dollar plasma donation business, performed mostly on young donors. The process for those of us who are older is slightly different, but it promises substantial rejuvenation of our genomic control systems, the epigenome, and extension of our health spans.





There is lots of research to be done. How often do you do it? How are results verified? Some of us are toying with the idea of starting a large-scale human trial that would eventually be self-funding.

Other breakthroughs are working their way through the complex processes of regulatory approval and acceptance by a skeptical public and gun-shy medical establishment.

But the Holy Grail is true age reversal. Dr. Mike West pioneered the field which he calls induced tissue regeneration (ITR). There are another half dozen firms, mostly led by billionaires or large organizations pursuing what they call "reprograming," but it is the same thing. Jeff Bezos recently launched a firm focused on age reversal which you should take seriously because of the depth of the scientific team he hired. Google has Calico. David Sinclair of Harvard has significant backing. Lineage Cell Therapeutics is backed by BlackRock, Raffles Capital Management, Wells Fargo, and others.

I believe that before the end of this decade we will see a breakthrough in this field. Frankly, there is room for another serious startup if you are rich and interested.

Ray Kurzweil is right—the objective is to live long enough to live forever. Stay active, eat healthy, you know the drill.

I Feel the Need to Travel

I feel better already. It's fun to write a positive letter, but I am not tone deaf. Next week back to the real world of the present.

I have no travel scheduled but I know I need to get to New York and Shane and I need to get to Cleveland Clinic for our annual checkups which we have missed for the last two years.

In an effort to keep this letter a reasonable length, I will wish you a great week and hit the send button. And don't forget to <u>follow me on Twitter</u>. You can get me at my most outrageous and follow what I think is interesting.

Your needing to get into the gym more often analyst,

John Mauldin

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