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By Richard Cluver **31 July 2019**

If you could guarantee that your grandchildren would be as beautiful as movie stars, free from all inheritable diseases and as bright as Nobel prize winners, would you be prepared to invest a few thousand Rands to make it happen?

More to the point, if you or someone close to you is suffering from a life-threatening disease such as cystic fibrosis or if you are suffering from the early onset of Altsheimers disease, would you reject the possibility that a single injection could set in process the change of you own genetic structure to effectively cure you?

It is, I am sure a no brainer. Most of us would leap at the chance of disease-free old age and of ensuring that our offspring had the best possible chance of being assured winners of life's challenging race.

So why are scientists and governments dead set against allowing this to happen? If you are a believer in conspiracy theories you might easily be led to believe that some people out there are keeping this away from you so that they alone might benefit. And you could be right. But a fairer assessment is that the full long-term implications of this remarkable new science are not yet understood and so science is proceeding with the utmost caution because the dangers of it going wrong are too devastating to contemplate. Though whether they are more life-threatening than global warming, human overpopulation or global debt management are open to question.

The good, or the bad news, depending upon how you view it, is that this option is now imminently possible...Indeed, with the development of CRISPR genome editing, it is probable that genetically enhanced children are already walking the earth. So the real question that you and I need to address right now is what will happen to our offspring if we DO NOT take advantage of the process.

If racism has been the massive evil of our time because of how it has set peoples of different racial origin apart from one another and fostered ideas of birth superiority, the development of cost effective genetic editing is going to take the process of discrimination to a whole new level.

It does not take much imagination to recognize that children of normal gestation could, within a very short time, see themselves ousted from institutions of higher learning because of their relative inability to compete academically with "test tube" babies.

And it does not require much imagination to recognize that so-called normal children, i.e. children that are born by the age old process which has provided so much pleasure to infinite generations of mankind, might find themselves locked into a

stunted career path because they will be simply outshone by the mental and physical abilities of the new super race which is now within our grasp.

So what is CRISPR and how costly is it? More importantly, how dangerous is it? In December Dr. Jiankui He at Southern University of Science and Technology in China revealed that the first CRISPR babies—a pair of twin girls named Nana and Lulu—had been born. Engineered to resist HIV infections, the girls were born perfectly normal and healthy, He said.

Dr He's statement was, however, dangerously ingenuous. While the CRISPR process has provided mankind with an effective means of knocking out targeted genes in DNA, science does not fully understand all the consequences. Nevertheless the great danger such mutations pose to humankind is that they are likely to be fully able to reproduce and thus introduce themselves into the human gene pool. This could be a good thing if only desirable traits are replicated, but nobody is really sure of what else could be the consequence which is why there is currently an international moratorium on such experimentation upon human tissue…until science is better informed.

But the reality is that the genie is now out of the bottle and rogue scientists like Dr He are likely to be tempted by offers of unlimited money to pursue the objective of creating a super race of human beings. Indeed, since the science already exists, the probability is that such experimentation is already under way.

Indeed it gets even scarier. Go on line and type in DIY CRISPR Kit and you can order your own set of instruments for just $159 along with a set of instructions to get you started on doing it yourself. So anyone can now try it out for themselves.

Part of the global outrage came from how the Chinese doctor performed his experiment. So let us start by noting that CRISPR can fundamentally delete disease-causing mutations in embryos, allowing parents to have healthy children. It's something scientists and ethicists have been carefully working towards—and something most people seem to support.

But with great power comes great responsibility: although the technology to fundamentally change DNA in future generations—called "germ line editing"—has been available for a few years, scientists have hesitated at growing any edited embryos to maturation.

According to Dr. Gregory Licholai, a biotech lecturer at Yale University it's very clunky name is an acronym for Clustered Regularly-Interspaced Short Palindromic Repeats which refers to the way it interacts with DNA. It's a way to manipulate DNA, to edit DNA, in a way that is much more powerful than previous methods, much simpler, much cheaper. And the important part is it's exceptionally precise.

"So as you probably know, our book of life is made of DNA. DNA itself is many millions of base-pairs, which is like a language. And within that language, there are

certain regions which code for genes, and those genes are incredibly important because they go on to make up everything about us. There are 40,000 proteins that become outputs of those genes and they are involved in our health, our wellbeing, and any defect in them becomes problematic and causes disease.

“What was previously attempted with gene editing was to manipulate genetic information in blocks, basically in big pieces. It’s kind of like trying to edit a book by only being able to rip out a page at a time and transfer a page at a time, without really being able to control the actual words. The power of this technology: it literally comes down to the individual letters. So the precision is far better than anything that has happened before. The excitement in the scientific community is being able to go in and very precisely make changes in DNA of actual genes that you can actually turn off bad genes or you can potentially repair genes that have got mutations in them where the code is written incorrectly.

“There had been previous gene-editing technologies, such as viral gene editing, gene replacement, and those have developed over several decades. One of the most fascinating things about CRISPR is how quickly everything has developed, so in less than 10 years since the initial descriptions and initial papers were written, this technology has just exploded. It’s been less than five years since the initial patents were written, and since then at least a half-dozen companies have been formed, all of them are racing forward to try to get a leg up on each other to try to proceed with using CRISPR for various applications.

“There are three main applications for CRISPR. One is in manipulating genes to turn them on or off within people. Another is to create medications that can be infused, or in some cases, self-therapy—taking blood and certain cells out of a body, manipulating them with CRISPR, and then putting them back in. The third, which is sometimes overlooked, is actually in farming. Both farming with animals as well as farming with crops. And in fact, the application of CRISPR to foods has already been done. There are companies that have already been using CRISPR to create enhanced foods to resist bacteria or viruses and to create even better-tasting foods. And that’s already being done.

“Similarly, the application of CRISPR to animals has already been done. They actually call them CRISPR mice, and they are already being used in the research community. The ability to apply it to larger animals such as food animals is in the very near future.

In terms of human health, we can divide that into two different categories. One is taking cells out of the body, manipulating them in the laboratory—either removing a defective gene or adding and enhancing an ability to do something by turning on a gene or fixing a gene—and then putting those cells back in the body. That’s one category. The other category would be to actually inject something into the body which can edit people’s genes so that within their own tissues those genes can either be turned on or off. And all of these have got some pretty profound complications and risks.

“One of the biggest risks of CRISPR is what’s called gene drive, or genetic drive. What that means is that because you’re actually manipulating genes and those

genes get incorporated into the genome, into the encyclopaedia, basically, that sits within cells, potentially those genes can then be transferred on to other organisms. And once they're transferred on to other organisms, once they become part of the cycle, then those genes are in the environment.

"That's probably the biggest fear of CRISPR. Humans manipulating the genetic code, and those manipulations get passed on generation to generation to generation. We think we know what we're doing, we think we're measuring exactly what changes we're making to the genes, but there's always the possibility that either we miss something or our technology can't pick up on other changes that have been made that haven't been directed by us. And the fear then is that those changes lead to antibiotic resistance or other mutations that go out into the population and would be very difficult to control. Basically creating incurable diseases or other potential mutations that we wouldn't really have control over."

While there has been a self-imposed moratorium among scientists in the US and Europe working on the field of gene modification, this is not universally true and it is probably true that hundreds of such modified children are already living in the Far East!

According to Dr Licholai, in 2016 reports came out of China that researchers had begun working on human embryos. Initially in 2015 and '16, the reports were that the experiments were negative, and at least the Chinese researchers had claimed that they were working with nonviable human embryos anyway. In the short time since then, in the year and a half since then, those experiments have been repeated, apparently with scientific success, whatever that means, but without the kind of self-imposed regulation or even organizationally imposed regulation that we would have by the NIH or the scientific community in the United States and Europe.

Another example is that researchers in China have actually proceeded to human clinical trials using CRISPR much faster than has been possible in the West. Normally, the clinical trial process to test any new therapy requires several very well studied stages. The first stage is to test in animals to make sure that there's complete safety. Then it goes into very limited testing in human beings, just for safety, and then proceeds from there. Apparently in China, they took the animal data and they went right into therapeutic trials in human beings. And the most recent reports that are that somewhere between 80 and 100 people are already being tried, or already being tested using CRISPR.

"We know that in China, they're using CRISPR for cancer therapy. That's the example where cells are taken out of the body, their immune cells are manipulated with CRISPR and then they're re-infused. It's too early to tell if it's successful or not. But there is a lot of concern that the regulatory authorities in China have been extremely permissive with allowing these technologies to move forward. And that has a lot of profound implications."

The point is that where there is a will, or sufficient money to drive the process, there are clearly skilled people prepared to take the risk that we might unleash monsters or uncurable diseases into the human gene pool. But for many people, the potential

benefits are such that they would be prepared to cut corners and race ahead regardless of the risks.

We had better be prepared!

Return on capital matters!

By Professor Brian Kantor

The best managers can do for their shareholders is to realise returns that exceed the opportunity cost of the capital entrusted to them. That is to generate returns that exceed the returns their shareholders could realistically expect from alternative, equivalently risky investments.

This difference between the returns a firm is able to earn on its projects and the charge it needs to make for that capital, is widely known as Economic Value Added (EVA).

This economic profit margin is sometimes described as a moat that protects a truly profitable firm from its competitors. But more than intellectual property or valuable brands that keep out the competition and preserve pricing power, a truly valuable firm will have a long runway of opportunities to invest more in cost of capital beating investments. It is the margin between the internal rate of return of the company and the required risk adjusted return, multiplied by the volume of investment undertaken that makes for EVA and potentially more wealthy owners- not margin alone.

The task for managers is to maximise neither margin nor scale – but their combination – EVA. For investments today in SA in rands an averagely risky project, given long term RSA interest rates of about 9% p.a. would have to promise a return of more than 14% p.a on average to hope to be EVA accretive.

The leading advisor on corporate governance in the US now agrees with the all importance of EVA when evaluating managers. Fortune Magazine of the 29th March reported that

“On Wednesday, ISS, the U.S.’s leading adviser on corporate governance, announced that it’s starting to measure corporate pay-for-performance plans using a metric that prevents CEOs from gaming the system by gunning short-term profits, piling on debt, or bloating up via pricey acquisitions to swell their long-term comp. ISS’s stance is a potential game-changer: No tool is better suited to holding management accountable for what really drives outsized returns to investors, generating hordes of new cash from dollops of fresh capital……”.

Positive EVA’s or improvements in EVA do not translate automatically into share market beating returns. The share market will always search for companies capable of realizing EVA. And who reward their managers accordingly in ways that align their

interest with those of their shareholders. Such remuneration practice provides investors with useful clues about prospective EVA. It will help them follow the money. Managers after all will do what they are incentivized to do.

When EVA is positive, realizing as much of it as may be possible, calls for raising cash rather than paying it out- negative rather than positive cash flow – after spending to sustain the established capital stock. Not only retaining cash – not paying dividends but raising fresh capital- equity or debt- can make every sense if EVA enhancing.

Paying up for prospective EVA will raise share prices and reduce realized market returns. And investment activity that is expected to waste capital will reduce share prices to improve prospective returns. Investors may change their minds about how sustainable EVA will be. Investors, by adding or reducing the period of time before margins inevitably fade away in the face of predictable competition, can make large differences to the market value of a company- and can do so overnight.

These expectations as well as changes in the climate for doing business, as in interest rates that help determine the cost of capital, are often well beyond the control of managers. Managers should be encouraged by shareholders and investors to maximise EVA – not their share prices or total shareholder returns over which they can have little immediate influence, given all the other value creating or destroying forces always at work. They should neither be indulged, when by luck more than their good judgment, the market takes all share prices higher. Nor should they be penalized when the market turns sour.

Shareholders and their managers with EVA linked rewards- should hope that positive EVA surprises – when sustained – will be appreciated by investors willing to pay up for their shares. It may take time to convince investors of the superior capabilities of a management team and their business models. But superiority can only be demonstrated by consistently adding economic value beating the cost of capital.

Better know your water!

By John Mauldin

There are these two young fish swimming along, and they happen to meet an older fish swimming the other way, who nods at them and says, "Morning, boys, how's the water?" And the two young fish swim on for a bit, and then eventually one of them looks over at the other and goes, "What the hell is water?"

—David Foster Wallace, ***This Is Water***

Most investors and fellow citizens have no idea what water we are swimming in. They swim in a pool of agreed-upon, commonly understood narratives. And that's all well and good until the water changes.

It is very important to know your water and what to do when it changes. Currently, the narrative says that central banks and governments "have our backs" and will do "whatever it takes" to make everything, including the water, go on as usual. Call it ***kicking the can down the road*** or whatever metaphor you like, but most investors extrapolate the recent past into the far future.

And that's usually the right move. The cautious optimist usually wins, which in our current social and political circumstances means that the one most important thing to know is: *What could change the narrative?*

I think most thinking investors, whether professional or managing their own portfolios, sense a shift in the zeitgeist as did William Butler Yeats in his poem "The Second Coming which presaged the 1920s and 1930s trauma that led to World War II.

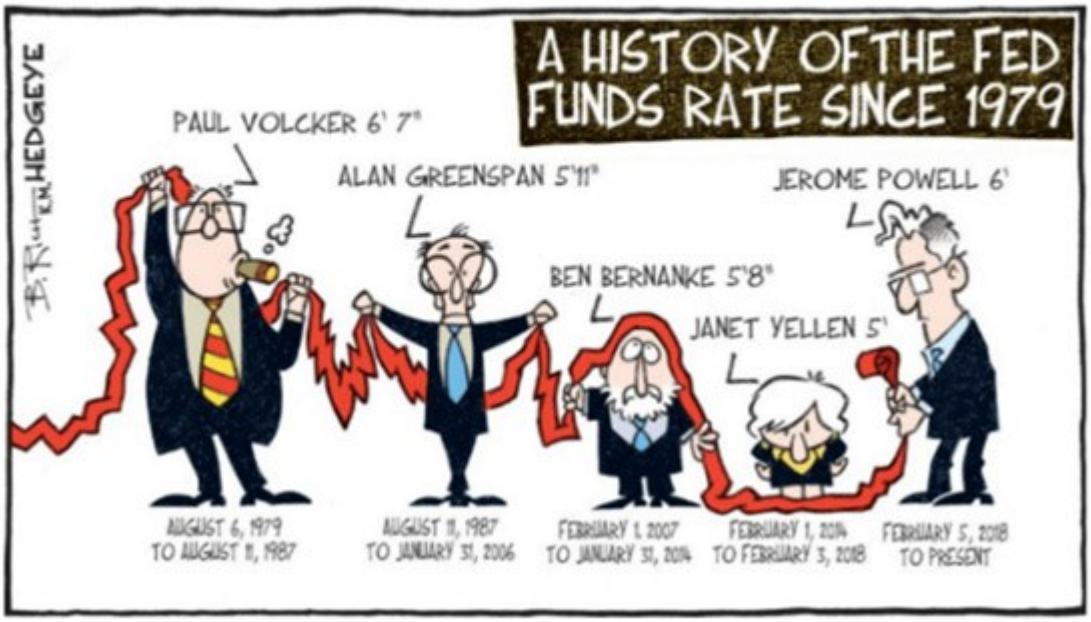
We understand that things are changing, but the question we should ask ourselves is, "Change to what?" We know that whatever happens won't be rainbows and unicorns. Yet if you are truly aware of what's going on in the world, you have to be optimistic about humanity, about the potential explosion of creativity in the midst of turmoil.

Opportunity and crisis both beckon, and I believe both will happen at the same time. This will require a particularly delicate balance in both our lives and our portfolios.

First, recognize that I am writing stream-of-consciousness late on Thursday night at the end of a conference. I am emotionally overwhelmed, intellectually sated, and trying to assimilate probably the most stimulating and overpowering of 16 annual events. Dear gods, I love it when a plan comes together.

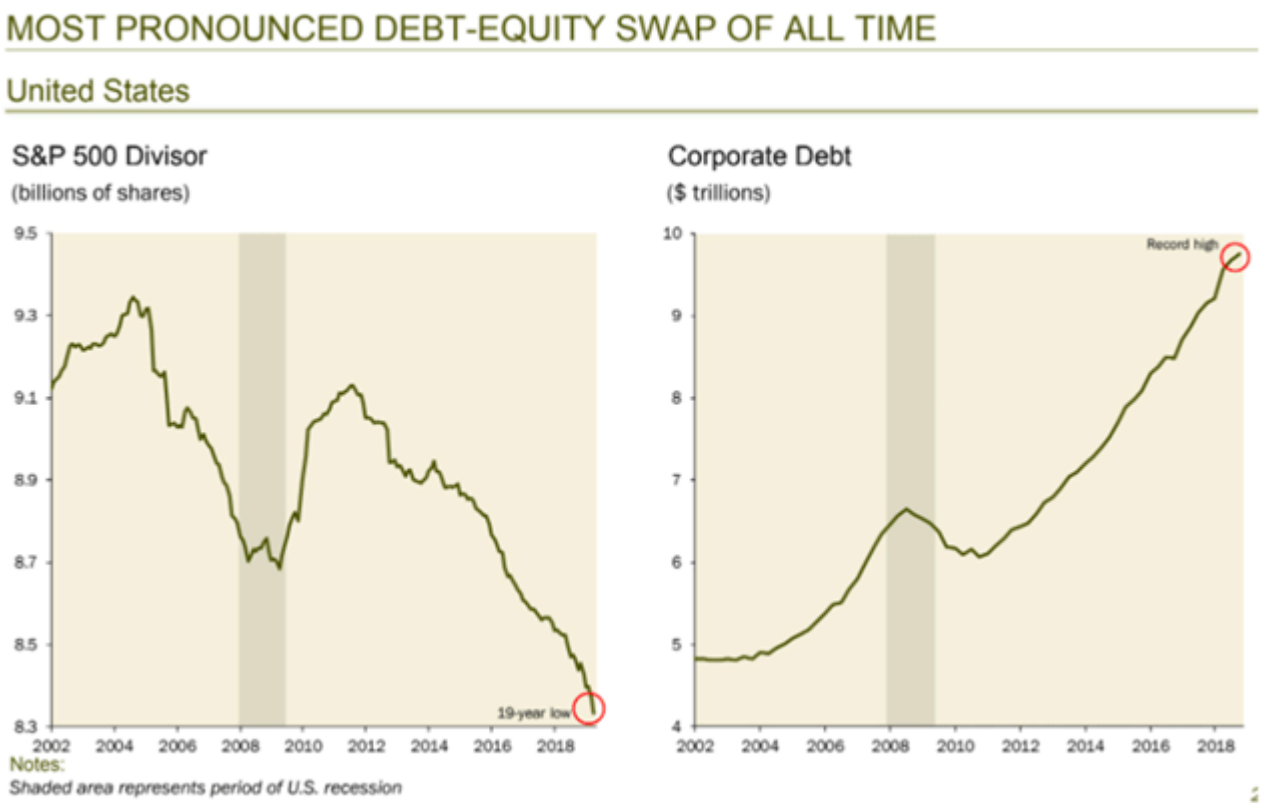
There were speakers that discussed the next 6–12 months and others who looked out over the horizon. Both were equally important. David Rosenberg was his usual brilliant self, with scores of slides making his case for recession and bear market. He has been my opening speaker for 10 years and I joked that I am going to keep inviting him back until he gets it right. His slide decks are simply brilliant.

RATES WILL BITE WITH EXTRA HEIGHT



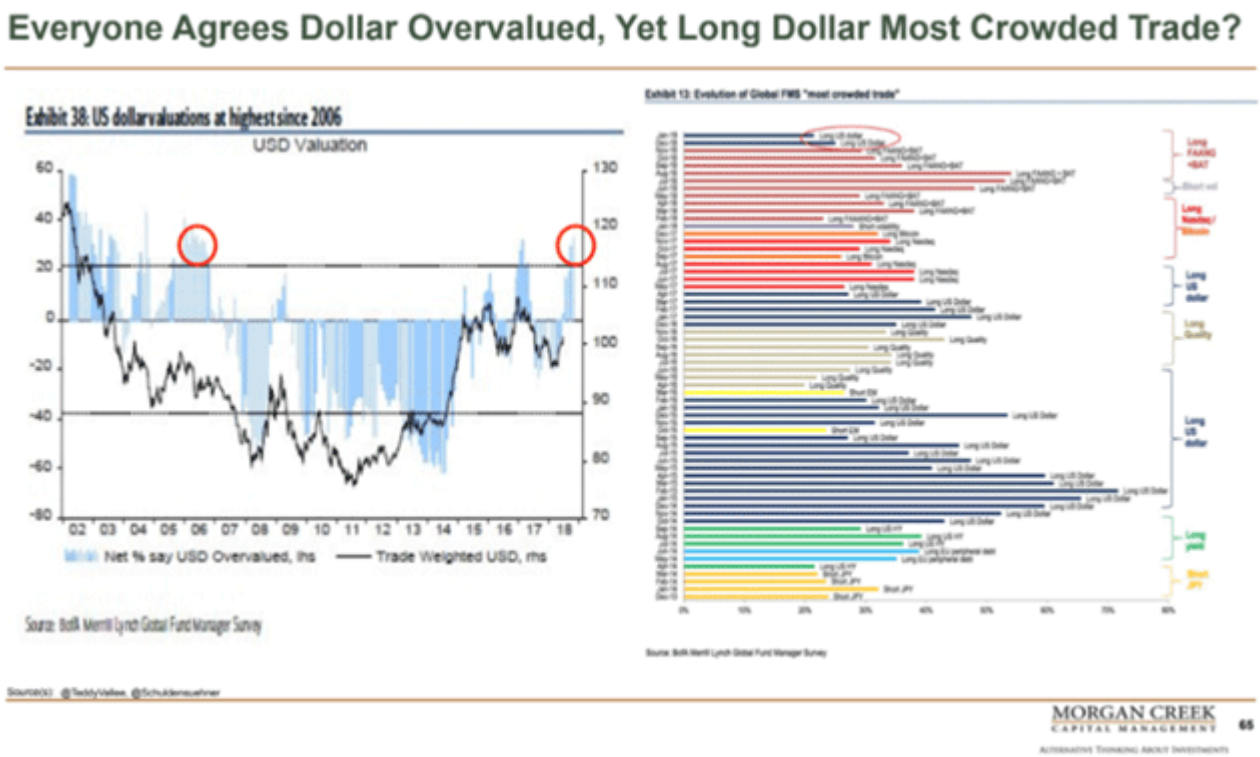
Rosie focused on the Fed overshooting the neutral rate, actually tightening as we go into recession with a combination of balance sheet reduction and interest rate increases (something I've also been ranting about). His deck was worth the price of admission.

I'll give you one more chart with staggering implications on a topic other speakers also mentioned. Corporations are using record profits to increasingly borrow cheap debt and buy back their own shares. This increases the P/E ratio and creates the appearance of strength and growth even when neither is actually happening. It is, as Dr. Woody Brock told us later, a bastardized form (his words) of capitalism that Adam Smith would not recognize.



If Rosie was a shotgun, Mark Yusko was a high-velocity machine gun with 100+ slides in his deck. It reminded me of The Joker who, on seeing one of Batman's miraculous escapes, asked the world, "Where does he get all those cool toys?" Where does Mark get all those cool charts?

More than one speaker pointed out how the US dollar could go higher, but not necessarily for good reasons and not for ones that we would like—at least those of us in the US. But it comes with the territory when yours is the world's reserve currency. Again, a common theme was that the dollar's reserve status is by default, as there is no other realistic option. It's the cleanest dirty shirt in the laundry.



Carmen Reinhart was a revelation. Arguably the world's leading expert on government debt, she co-authored (with Ken Rogoff) the definitive book on government debt and debt crises, ***This Time Is Different***. Now, with a different set of collaborators and what must be a battalion of grad students, she is studying every government debt issue since the Battle of Waterloo. It turns out there are similar characteristics between emerging market government debt, with all its write-downs and defaults, and high-yield corporate debt. There are ways to make a significant premium over the risk-free rate.

In the Q&A, I mischievously asked her, "How has the fact that you arrived in the United States in 1966 at 10 years old with your mother and father and three suitcases from Cuba affected your outlook and analysis?" Her answer (paraphrasing)…

> ***"I talk with my students and colleagues about crises. But there are various degrees of crises. There are times when the crises are cataclysmic. And we need to understand the difference. At 10 years old I watched them take truckloads of men to be executed by firing squad. That was a cataclysmic crisis."***

The audience reacted viscerally to Carmen's thoughts. The only question I had for myself was, "Why did it take 16 years for me to get her to my conference?"

Lacy Hunt gave his best presentation ever. That was not just my analysis but that of many long-term conference attendees. He presented two theorems. First, federal debt acceleration leads to lower, not higher interest rates. This is because the economic stimulus effectiveness ends quickly, but the debt overhang causes weaker business conditions that reduce loan demand.

Similarly, monetary easing eventually leads to lower, not higher interest rates. Debt productivity falls, making the velocity of money decline so monetary policy becomes asymmetric and inefficient.

These are not intuitive to most people, so Lacy walked through algebraic proof of both theorems. He also showed empirical evidence, comparing government debt to interest rates in the US, UK, Eurozone and Japan since 2007. All the graphs looked almost identical.

These theorems are ominous if true, because they show it is almost impossible for higher savings to both absorb the debt load and sustain consumer spending and business investment. The only solution is prolonged austerity. But the slightly good news is that in this scenario the US will likely stay the world's strongest economy, simply because it has the best combination of debt productivity and demographics. Somewhat analogous to the cleanest dirty shirt in the laundry.