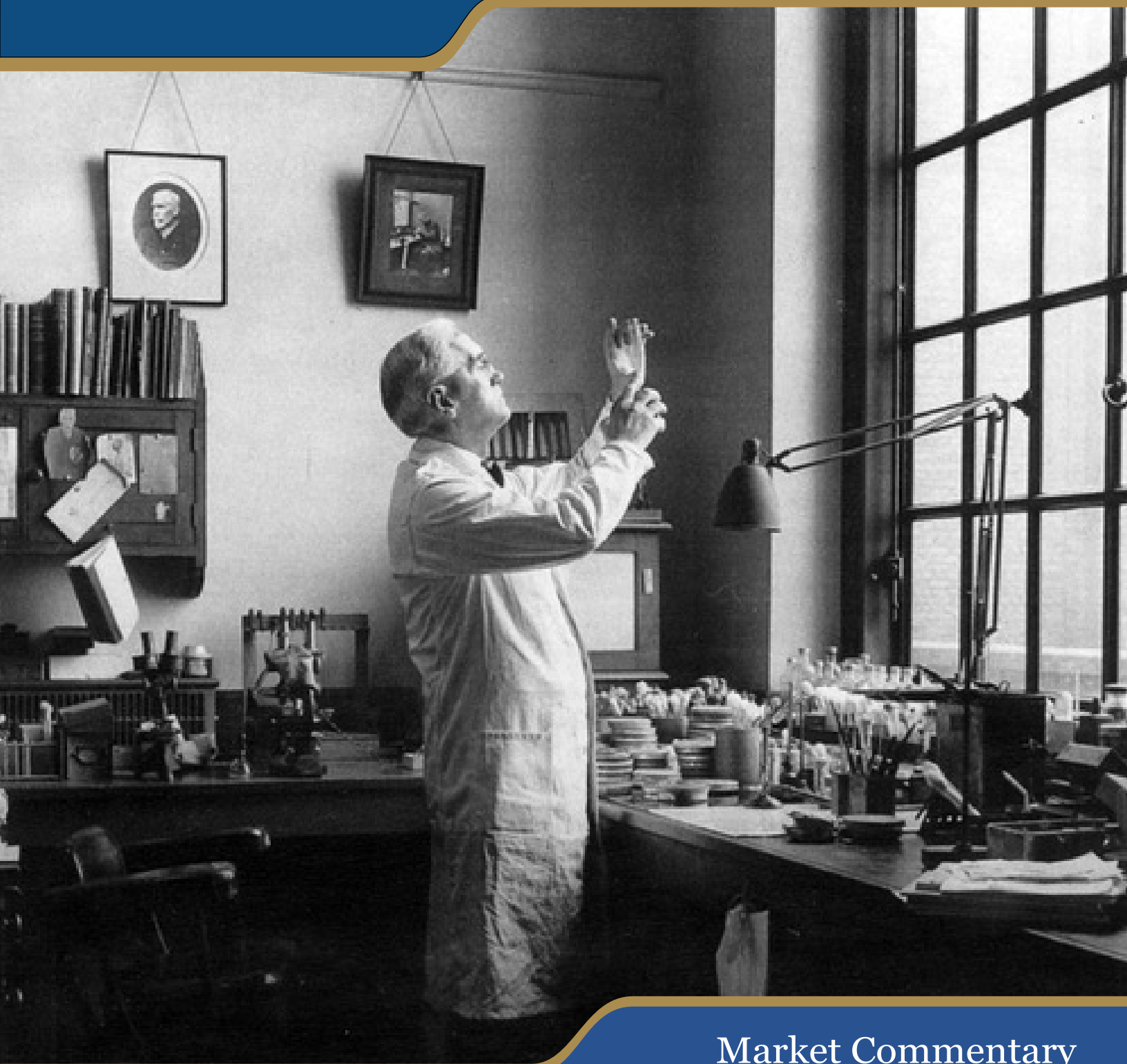




LLOYD TEVIS
INVESTMENTS, LLC

Securing your future through Precision Investing™



Market Commentary
April 2024



Russia-Ukraine War

Russia is maintaining pressure on the Ukrainians. The Ukrainian position is holding but their stocks of munitions are eroding. The beginning of the spring mud season may give them a temporary respite from Russian pressure. An increased Russian assault is expected in the summer.

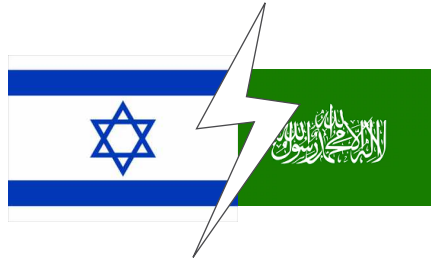
The US remains politically hamstrung. Under Trump's direction the Speaker of the US House of Representatives, Michael Johnson, is blocking a Ukrainian aid bill that otherwise would pass. US defense industry is also showing gaps. Apparently there is no domestic manufacturer of TNT or gun cotton (nitrocellulose) in the United States. Concerns about the adequacy of US artillery and missile production are substantial. France has taken the initiative as the US falters. President Macron is attempting to define a program for European direct participation in the war.

A collapse of the Ukrainian front seems just a matter of time. If it does, Trump and Mike Johnson will have delivered a victory for Putin.

Russia has displaced France from Mali as a provider of military equipment and services (i. e. mercenaries.) It is in the process of displacing the US from Niger. Immediately these initiatives are probably about making money. Longer term Russia is acquiring bases from which to apply pressure on NATO's southern flank – either by flooding the border with would be migrants or by threatening drone attacks against NATO facilities. Iran is believed to have secured supplies of uranium from Niger as well.

Catherine, the Princess of Wales, withdrew from public appearances for two months to recover from surgery. Her disappearance gave rise to a mounting wave of speculation on the internet which turned increasingly vicious and which ultimately sucked in mainstream media figures normally considered to be responsible persons. This furor is now thought to have been orchestrated by Russian intelligence operatives. As such it testifies both to ruthless nature of the assault on Western institutions by Russian influence operations and to the wide scope of those operations. Any “truth” about ourselves which we have taken in from the environment should be cross checked for reality. Particularly this is true for any negative information. As a case in point, many people believe the US is in the midst of a crime wave. Actually, FBI figures show violent crime at a 50 year low. While property crime has rebounded slightly from the pandemic low set in 2021 when even crooks were sheltering at home, the property crime rate in 2022 was only 68% of its rate in 2012. Between 2022 and 2023 murder decreased by 13%, all categories of violent crime decreased by 6% and property crime decreased by 4%.

The Russian Orthodox Church has long functioned as a department of state. Indeed the patriarch of Moscow is a former KGB officer. The Church appears to be taking over the position of Chief Ideologist – a state office unstaffed since the end of Communist rule. A recent Church policy document calls for Russia to expand its population from its current level of 144 million to 600 million by 2124. Such a step would certainly provide plenty of young men for wars of imperial conquest. Indeed the same church document refers to the Ukraine war as a “Holy War” against the Western secularism supposedly poisoning Ukraine. Naturally that war is presented as defensive and existential in nature. Russia seems to have decided that it is incapable of building a competent domestic economy and that its future is that of a predatory nation.



Israeli-Hamas War

The war is growing grimmer. The UN has accused Hamas of raping and abusing Israelis it holds as prisoners. The UN has also accused Israel of creating famine conditions among the 2 million population of Gaza. Famine is a particular condition – a sustained lack of nutrition in a population such that there is a general breakdown of people's immune system resulting in mass death from a combination of starvation and epidemic disease outbreaks. The Israeli government claims to be willing to supply needed foods and medicine to Gaza but asserts that local distribution is being foiled by Hamas. Only about 10% of normal supplies have been entering Gaza since October. Israeli vigilante groups have been acting to stop even this flow – their declared intent is to starve the Gazans until Hamas releases the Israelis it took as hostages. Diplomatic efforts to ease the conflict have been mediated by Qatar and Egypt. The Israelis offer a temporary ceasefire in return for release of the hostages. Hamas realizes that at the end of the temporary ceasefire Israel would resume its effort to liquidate Hamas and so it demands a permanent ceasefire.

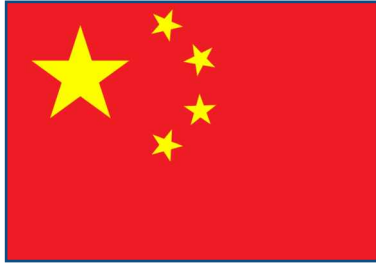
Approximately 25% of the Israeli public leans towards the view that the Gazans lost their claim to the land of Gaza due to the atrocities of October 7 and that Israel should take the land away from them. Where the Gazans should go is unspecified; presumably they are expected to die. Indeed on October 7, Hamas atrocities killed about 1,200 Israeli, but so far the Gaza war has resulted in about 32,000 Gazan deaths and of those about half are among noncombatants. By contrast, IDF losses are about 1% of that number. The expansionist view is still a radical one in Israel and the Netanyahu government has rejected it as impractical. However the government has not rejected it as illegal or immoral and elements of the governing coalition support limited annexation. The expansionist viewpoint has been supported by Candidate Trump's son-in-law and former

Mideast negotiator Jared Kushner. This is another extraordinary intervention against official US foreign policy by Trump.

The United State's official policy is 1. to insist on a two state solution 2. to regard Hamas as a terrorist organization which is not representative of the Gazan people and for whose acts the Gazan people cannot be held responsible 3. to support Israel's war against Hamas 4. to not support war crimes committed by Israel. In essence, the US sees the political elimination of Hamas as the prelude to implementation of the two state solution, while the Netanyahu government sees the physical elimination of Hamas as the prelude to establishing a permanent Israeli security state in Gaza. This divergence has led Senator Schumer, the most senior Jewish US official, to call for the mandate of the Netanyahu government to be tested by an election in Israel.

President Biden has ordered the US navy to construct a temporary port in Gaza at which food supplies will be landed. We think Biden is wise to create some independence of action for the US apart from Israel. The frustrations and conflict of war are leading Israel to create a humanitarian disaster and the world is ready to hold the US responsible for this disaster. The US cannot put its reputation so under the control of any US ally. At the same time, once the US starts landing supplies in a starving population it is easy to predict that the population will vote with its feet. The US could end up running a refuge camp holding a good fraction of the Gaza population. In essence Hamas, Israel and the UN have all failed to create order in Gaza. The US is getting pulled in by this vacuum of authority and it might end up in a situation resembling a new quasi-mandatory power. That possibility should give the other players considerable pause for thought.

The US led naval intervention against the Houthis continues. The Houthis managed to hit a Chinese owned and operated tanker. The crew quickly extinguished the fire that resulted and the ship continued its voyage.



China

China has muted direct conflict with the US – likely as a result of a deal between Biden and Xi to keep things calm over the US election season. But China continues pressure on Taiwan, the Philippines and Vietnam. This pressure takes the form of pin-prick encroachments by Chinese actors who give the government plausible deniability. Over time these pin-pricks add up to substantial erosion of the victim's sovereignty. So far the victims have not found an effective counter strategy.

China's economy remains a mix of hot and cold. We expect that state to continue for several years.

The US had delayed renewing its alliance with the central Pacific states of Micronesia, Palau and the Marshall islands. These small nations sit astride strategic central Pacific shipping lanes. China had hoped US negligence would allow it political penetration of the region, but the US House of Representatives ultimately awoke to the danger created by its neglect and passed the necessary bill.

The US water industry is extremely fragmented. The industry consists of 150,000 providers, almost all of whom are owned by municipalities. The industry has been a particular target of opportunity for Chinese hackers and there is a real concern that in case of international conflict the US water supply could be seriously disrupted. The EPA has regulatory oversight of the industry from a safety viewpoint and it attempted to impose cybersecurity audits on the industry. The Eighth Circuit Court of Appeals (responsible for North and South Dakota, Minnesota, Nebraska, Iowa, Missouri and Arkansas) staid the order as outside of the EPA's mandate. The industry representative organization advocates for self regulation under loose EPA supervision. Strategic cybersecurity is a concern across multiple industries, but

where this responsibility belongs in government remains unsettled. It would seem to be a natural responsibility of Homeland Security.



Trump

Several courts in civil proceedings have found clear and convincing evidence that Trump engaged in insurrection. But after forty months, those claims, along with claims of violation of the Espionage Act and Obstruction of Justice, remain untried in a criminal proceeding. The Supreme Court will hear arguments on April 25 as to whether Trump should be granted immunity from prosecution. The Appellate Court has already ruled unanimously that he should not be immunized. However, the Supreme Court feels it needs to review this decision. We think an important precedent is being set. If the civil Courts are unable to adjudicate a case such as Trump's the likelihood is that in the future such cases will be referred to military commissions. We would regard that development as unfortunate.

While campaigning for President and defending serious criminal indictments, Trump is also struggling to protect his real estate business from the half billion dollars of legal judgments against him. At 78 and visibly not fit, we wonder how long his health can hold up under this level of stress.

Immediately Trump's difficulty has been to raise a bond for approximately \$464 million to secure his properties from seizure while he appeals the civil fraud judgment against him. He has not been able to do so. Trump's difficulty is that his portfolio is highly concentrated in a single asset class and that asset class, commercial real estate, is currently depressed. His difficulties are a textbook example of the perils of not diversifying and of leveraging illiquid assets. Trump's difficulties are causing people to wonder if his alleged wealth was not just a put on. We would not draw that conclusion. As a hypothetical example (table 1) illustrates,

Trump could have started with a secure fortune but now be faced with the risk of it unzipping entirely. The real teachings from the story are the need to diversify and also that no one can be so secure that they can afford to be stupid about managing their assets.

Table 1: Trump's Financial Difficulties
 How to turn \$6 billion into \$200m
 All figures are notional

Item	Amount (\$m)
Trump's Plumped Up Valuation	10,000
<u>Mortgages at 40%</u>	<u>4,000</u>
Net Equity	6,000
Actual Valuation, Normal Economy	8,000
<u>Mortgages as before</u>	<u>4,000</u>
Net Equity	4,000
Current Valuation, Depressed CRE	6,000
<u>Mortgages as before</u>	<u>4,000</u>
Net Equity	2,000
Duress Valuation	5,000
<u>Mortgages as before</u>	<u>4,000</u>
Gross Proceeds	1,000
<u>Gain Tax</u>	<u>300</u>
Net Proceeds	700
<u>Judgment</u>	<u>500</u>
Residue	200

The Heritage Foundation is a conservative think tank. In contrast to the longer established American Enterprise Institute, the Heritage Foundation is less closely associated to the viewpoint of big business, more concerned with social policy issues and closer to the policy viewpoints of evangelicals. It has prepared a 900 page document "Project 2025" laying out its vision for a second Trump administration should it be elected at year end. It takes more patience than we possess to systematically extract its concrete policy proposals from the rich helpings of political blather it provides, but the following proposals represent essential elements of its vision:

1. Biden climate initiatives will be terminated. The fossil fuel industry will be actively promoted.

2. Senior ranks of the civilian bureaucracy are viewed as disloyal to a conservative agenda and they will be culled and replaced with party loyalists.

3. The military is accused of being overweight in general officers who allegedly operate at low levels of accountability. They will be culled and there will be limited promotion of field grade officers with war fighting experience to replace them. While it is not stated that a political filter should be applied to promotions, the proposal certainly opens the door to substantial filtering.

4. The Department of Homeland security will be dissolved and its constituent components returned to their prior homes. The Border Patrol and Naturalization service will be raised to cabinet rank.

5. The State Department is viewed as another disloyal section of the government to be purged. US foreign and military policy is to be organized around the idea of confronting China.

We read this document as largely an extension of what has been the conservative political thinking for a generation. Conservative politics has not revolved around passing laws or other policies to deal with national issues. Instead it has sought to embed conservative loyalists in positions of power and to count on them to advance the conservative agenda. The primary focus of this political initiative has been the Supreme Court and conservative efforts there have resulted in a number of conservative victories which had no hope of success in the legislative branch. The Heritage Foundation is advocating for the broad extension of this program to the other levers of power.

Politics is of course the struggle for power. But we are particularly disturbed by the proposals for the senior military ranks. We find the Heritage Foundation's level of ambition troubling. We feel an anti-elitist political stance is being used to justify an attack on senior civilian and military officials, but this is just a political cloak for an ambitious power grab. The conservative unwillingness to listen to senior experts was much on display in the Trump administration's conflict with the CDC and the result was a death rate in the US 3x

higher than Canada's. We are not eager for a replay of such maladministration. Yet even ignoring expert advice is comparatively risk free compared to allowing an insurrectionist to purge the senior levels of government in furtherance of a political program.



ESG

For the most part this publication ignores the nation's cultural wars, colorful as they sometimes are, because they have little bearing on our chief interest – the direction of the capital market. However, one cultural war issue does directly bear on investing and so we will briefly review it. ESG is the idea that investing activities should either be in harmony with or even express the investor's values in other areas of life. The letters ESG stand for Environmental, Social and Governance. As a very general idea of linking investments to values, ESG does not stand for specific expressions of values. Many different ideas swim under the banner of ESG.

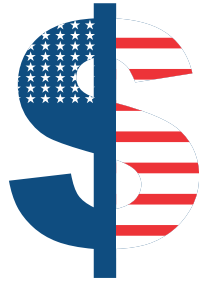
The idea that investing should be linked to values is hardly new. No one thinks it remarkable that the Episcopal Church's endowment avoids investment in publishers of pornography or that the Baptists avoid investment in brewers and distillers. Whether or not one shares these concerns oneself, one can understand why those investors would feel that maintaining their integrity requires their investment policies to be reflective of these core values.

About four years ago, some asset managers spied a business opportunity in crafting investment portfolios supposed to be compatible with various ESG viewpoints. We are not especially impressed with the accuracy of the filters being applied and so we are not advocates for these tools. But we see nothing wrong with the owners of the capital wanting to apply even imperfect tools and so directing their investment managers.

Certain conservatives see the matter differently. In their minds ESG is just another effort to embed a “woke political agenda” into the fabric of American life. Ron De Santis was an early advocate of confronting ESG and his example has garnered followers. Interventions take the form of passing laws forbidding investment managers of certain funds from considering ESG issues in their investment process. Pension funds of public employees and endowments of public cultural and educational institutions are particular targets of these laws. In general, we disagree with this legislative program. We feel investment managers should be taking direction from the boards representing the beneficiaries of these investments and not from legislatures.

Two specific legislative targets give us particular concern: environmental and governance. The E of ESG generally stands for considering climate change and conservative politicians who advocate for climate warming industry are naturally opposed. But the green energy transition is a global event of obvious material investment consequence. Ordering investment managers to ignore it is simply to order them to not do their job.

The G of ESG stands for a wider less focused set of ideas, but the core concern is that corporations should not be run by very narrow boards beholden to inside owners and managers. We agree that public investors have different economic interests than founding families, managers or employees. We think it important that the public investor interest is securely represented on boards. We are concerned that hostility to woke governance can be used to empower insiders at the expense of outside investors. We note that political action committees of a number of billionaires with large inside interests in specific public corporations have been funding attacks on “woke” governance. We think governance proposals only weakly connected to the welfare of the governed entity should be rejected (e. g. mandates for boards to have specific gender or racial profiles.) But governance is already pretty heavily tilted towards insiders and we think external investors need protection. We doubt insider owners can be genuine advocates for that.



The US Economy

Inflation appears to have stabilized at about the 2.5% level. The Federal Reserve's rate policy is in “wait and see” mode. The Street has postponed expectations of rate easing from the spring to the summer. Real GDP increased by 3.3% in the final quarter of 2023. Real personal disposable income increased by 3.8%. All sectors contributed to growth, except for finance, insurance and wholesale trade which exhibited modest weakness. The workforce continues to expand, but not quickly enough to absorb all additions to the workforce. As a result the unemployment rate increased to 3.9% from 3.7%. More than 80% of the unemployed will find jobs in the near term. The rate of long term unemployed is about 0.7%. Thus, there is currently little evidence of secular job shifts causing significant unemployment.

Currently the US economy is 40% larger than China's. Assuming the US grows at an average rate of 3.3% and China grows at 5%, it would take China about 22 years to catch up to the US. The US economy is about 30% larger than the EU and is growing faster, so the EU is unlikely to narrow that differential. Russia's economy incidentally is about the same size as the economy of Texas. In the most recent quarter Texas's GDP grew by 5.0%, which was ahead of Russia's reported figure of 4%.

In short, the US is doing well and Texas – despite the complaining - is doing even better.



Opportunities in Medical Technology

As part of our continuing attention to technology based investment opportunities, we take a look at the current opportunity for medical technology. Development of new pharmaceuticals, treatments and diagnostic technologies has been a growth industry for more than a century. But people keep dying sooner than they wish and so the opportunity to earn a return by improving care is as wide open as ever.

In this brief note we describe the opportunity space in terms of therapeutic areas. There are two different measures of the opportunity space. The first measure is the percentage of the population killed by the disease. The second is the number of years of life lost to the disease. Here we take 100 as the natural human lifespan. A disease which kills a small number of children each year will rank low on the first measure but higher on the second. The economic value of a curative therapy is better estimated by the first measure, while the value of a management therapy is better estimated by the second.

Table 1 on the next page provides a breakdown. Birth problems result in the greatest number of years lost per case but happily cases are rare. Only 1.4% of years of life lost prematurely are due to problems present at birth. A variety of problems appear in the late teens to early thirties which are conventionally labeled as Social. Examples include suicide, homicide and substance abuse. In many cases there is actually an underlying mental illness and 7.5% of years lost are taken by these causes. Although significant publicity has been given to drug overdoses, drinking oneself to death is nearly 5x more common. Accidental death is important in childhood (poisoning and drowning) and continues on into middle age (road traffic accidents and other injuries.) Falls are a menace in old age. Altogether 14.5% of premature death is due to accidents. In the Social and Accidental categories of

mortality the opportunity for medical interventions is greatest with mental illness and trauma care. However, non-medical interventions are also important. A significant wave of mortality appears in the 70s. In terms of years of life lost the key groupings are major organ failure (5%), infectious diseases (3.5%), metabolic disease (6.2%) and cancer (18.1%.) Diseases of the circulatory system are the greatest single source of years lost (21.5%.) They appear somewhat latter in the 70s. All of these are diseases of late middle age. Many can be considered as consequences of less healthy lifestyles maintained in midlife. Disease which appear in old age typically cause fewer years of life to be lost prematurely per case. Here we note lung disease (4.2%) and neurological disease (3.5%.) Overall cancer therapy currently represents the best combination of substantial opportunity and promising new technologies.

Advances in computer technology are directly beneficial to technology development in this area. Increases in modeling power support drug discovery. Increases in analytic power improve diagnostics.

AI is expected to improve diagnostics and certain treatments (prosthetic limbs, heart pacemakers, feedback adjusted drug dosing.) AI should also play an important role in containing the cost of service delivery as it improves the ability to discover wasteful practices and fraudulent billing.

Personalized medicine refers to tuning treatments to a particular individual. Doing so holds the promise of more effective therapies with fewer side effects. Cancer treatment is currently the most promising area of endeavor. Here targeted drug therapies and immunotherapies both tune the delivered agent to killing the patient's specific cancer.

Medical technology remains an opportunity rich area.

Table 1: US Causes of Death
Figures are from 2022 except for Covid-19 which is 2023

Category	Disease	% deaths	% years lost age at death	
Birth	Congenital Anomalies	0.19%	0.91%	32
Birth	Low Birth Weight	0.08%	0.50%	7
Birth	All	0.26%	1.41%	25
Social	Suicide	0.94%	3.52%	47
Social	Homicide	0.51%	2.35%	35
Social	Alcohol	0.33%	1.01%	57
Social	Malnutrition	0.33%	0.40%	83
Social	Drug Use	0.07%	0.27%	50
Social	All	2.18%	7.54%	51
Accident	Poisonings	1.98%	7.91%	44
Accident	Road Traffic Accidents	0.91%	3.51%	46
Accident	Other Injuries	0.60%	1.54%	64
Accident	Falls	0.87%	1.20%	81
Accident	Drownings	0.08%	0.34%	43
Accident	All	4.44%	14.50%	54
Organ Failure	Liver Disease	1.10%	3.04%	61
Organ Failure	Kidney Disease	1.10%	1.76%	77
Organ Failure	Skin Disease	0.12%	0.22%	75
Organ Failure	All	2.32%	5.01%	70
Infection	COVID-19	1.53%	1.51%	72
Infection	Influenza & Pneumonia	0.82%	1.33%	77
Infection	HIV/AIDS	0.10%	0.31%	55
Infection	Diarrhoeal diseases	0.14%	0.23%	76
Infection	Peptic Ulcer Disease	0.08%	0.14%	74
Infection	All	2.66%	3.52%	73
Metabolic	Diabetes Mellitus	2.01%	3.87%	73
Metabolic	Endocrine Disorders	1.16%	2.30%	72
Metabolic	All	3.17%	6.18%	73
Cancer	Cancers of Digestive System	3.28%	6.33%	73
Cancer	Lung Cancers	2.62%	4.69%	75
Cancer	Cancers of Breast & Urogenital System	2.38%	4.24%	75
Cancer	Leukemia & Lymphoma	1.12%	1.88%	76
Cancer	Other Cancers	0.32%	0.49%	78
Cancer	Skin Cancers	0.21%	0.44%	75
Cancer	All	9.96%	18.07%	75
Circulatory	Coronary Heart Disease	7.31%	11.82%	77
Circulatory	Stroke	3.17%	4.52%	80
Circulatory	Hypertension	2.42%	3.95%	77
Circulatory	Inflammatory/Heart	0.55%	1.11%	71
Circulatory	Rheumatic/Heart	0.08%	0.12%	77
Circulatory	All	13.52%	21.52%	78
Lung	Lung Disease	2.68%	4.05%	79
Lung	Asthma	0.07%	0.20%	60
Lung	All	2.75%	4.24%	78
Neurological	Alzheimers	2.32%	2.26%	86
Neurological	Parkinson's Disease	0.75%	0.83%	84
Neurological	Epilepsy	0.07%	0.23%	56
Neurological	Multiple Sclerosis	0.09%	0.19%	69
Neurological	All	3.23%	3.52%	85



Capital Markets

It was another good month for equities. However, the growth equities which have been leading the advance show signs of a temporary plateau and their pause allowed the other equity sectors to partially catch up with them. Fixed income showed modest weakness as it became clear inflation will slow only gradually from its current levels and Fed easing will come later and more slowly in consequence. Relative strength was in TIPS and REITS, both of which are relative beneficiaries of inflation. Gold was the strongest sector this month – again reflecting the inflation outlook and mounting international conflict. Oil also pipped up as conflict in the Mideast continued.

Table 2: Recent Market Performance

Asset Group	Asset Class	6-month trend	3-month return	1-month return
Equity	US Large Cap	rising	11.83%	2.01%
	...Large Cap Growth	rising	15.70%	0.70%
	...Large Cap Value	rising	7.50%	4.13%
	...Growth – Value	rising	8.20%	-3.43%
	US Mid/Small Cap	rising	9.11%	2.96%
	Intl Developed	rising	7.67%	3.38%
	Intl Emerging	rising	4.34%	2.90%
Fixed Income	Treasury 3-7 year	flat	-0.76%	-0.08%
	Treasury 7-10 year	flat	-1.89%	-0.73%
	TIPS	flat	0.54%	0.21%
	Municipal	flat	-0.97%	-0.88%
	Investment Grade	flat	-0.14%	0.79%
	Medium Grade	flat	0.44%	-0.40%
	Preferred	flat	3.05%	-0.34%
	REIT	flat	-0.24%	0.82%
Commodity	Euro	flat	-1.46%	-0.07%
	Gold	rising	10.82%	8.46%
	Crude Oil	flat	13.10%	4.39%



Advice

The peace of the United States is currently disturbed mostly by internal bickering and secondarily by regional conflicts kicked up by ambitious foreign powers. Those foreign troubles could coalesce into a major war directly involving the US or they could wear themselves out and dissipate without important consequences. The situation bears monitoring. As to the internal conflict, bickering is productive mostly of audience fatigue. Unless the radicals of left and right are reanimated by an unforeseen disaster, we think politics will gradually move back towards the center.

Meanwhile the US economy is moving ahead strongly with multiple new technologies to exploit and the promise of a productivity driven increase in the standard of living. As we have remarked before – like the honey badger the US economy just doesn't care and it will keep on doing what it does. We think this economic expansion could continue for years and in the long run equity markets should perform well. However the road forward may well be punctuated by episodes of overvaluation, correction and sectorial slow down.

As always we urge investors to carefully consider their personal goals in detail and to hold the portfolio that best aligns to those goals rather than getting caught up in tactical moves, bursts of enthusiasm for specific opportunities or other transient plays.



About Lloyd Tevis Investments

Lloyd Tevis Investments LLC is a registered investment adviser offering its services over the internet to US individual investors and their families. Our Precision investing™ service provides clients with highly personalized investment solutions tuned to the client's specific circumstances and objectives. We believe the strategic asset allocation decision is the key decision faced by our investors. Accordingly, our monthly commentary focuses on matters which can shape the longer term performance of asset classes. We do not time market swings or pick individual stocks. Discussion at this level of detail is made for the light which it throws on relative valuations and such discussion should not be read as an investment recommendation. Indeed, our investment focus is on maximizing diversification, careful risk budgeting and maximizing implementation efficiency. These are the proven builders of long term investment success.

In evaluating political and social developments our perspective is that of long term investors. We believe the investor's interest is best served by a stable environment in which change occurs incrementally as broadly supported policies rather than by an environment of abrupt changes and frequent U-turns driven by transient partisan advantages. Finally, our assessments should always be read as what we consider likely to occur and not as expressions of what we would like to see come about. To learn more about our firm visit us at lloydtevis.com.

Cover Photo

Alexander Fleming at work in his lab captures both the excitement and years of meticulous laboratory work involved in drug discovery.

Modern research medicine is often thought to start with Louis Pasteur and Robert Koch. This first generation focused

on understanding the basic mechanism of contagion with the development of the germ theory. This understanding led to efforts to prevent contagious disease through hygienic procedures such as Pasteurization and through systematic vaccine development.

Important steps towards treatment of established infections were taken by Koch's follower Paul Erlich. He observed that organic dyes had high biological specificity and this led him to conceive of the “magic bullet” - a chemical which would bind selectively to the disease causing organism and poison it while not attaching to the patient's tissue. This concept led eventually to the sulfa drugs which were the first broadly effective antibiotics. Erlich's concept continues today under the name of rational drug design.

About the same time Fleming discovered the antibiotic properties of exudates produced by the penicillin mold. It was eventually realized that molds shared with humans an interest in creating antibiotics and that they had already put millions of years of evolution into developing effective compounds. This realization gave new energy and direction to the age old quest to discover medicinal compounds in the natural world.

While sulfa drugs were the primary antibiotic used in World War II, the war also stimulated manufacture of penicillin on an industrial scale. Most antibiotics today are derived from natural compounds rather than through rational drug design.

Just as molds have put millions of years into developing magic bullets, so too the human immune system has developed a complex and highly capable system for disease control. The newest class of therapeutic agents are immunotherapies. They aim to stimulate and support this natural system in its mission of controlling disease – and especially cancers for which other therapeutic modalities have been largely unable to achieve the highly specific targeting required of an effective agent.

Today the basic science of disease, immunology and pharmacology is worked out in considerable detail, but

applying this knowledge to drug discovery and design remains very challenging. Simulation of the complex in vivo interactions of disease and therapy is being pushed forward with application of high power computing. But it will be some time before this research can meet the high analytic challenge of simulating complex biological systems with high realism. Drug discovery rather than drug design is likely to remain the primary approach to developing medicines for some time.

