Bi-weekly Random Bits from the Internet

2015-07-05

(NEED TO GET A UKULELE THIS WEEKEND BUT U-SPACE IS NOT OPEN)

A Partnership with China to Avoid World War

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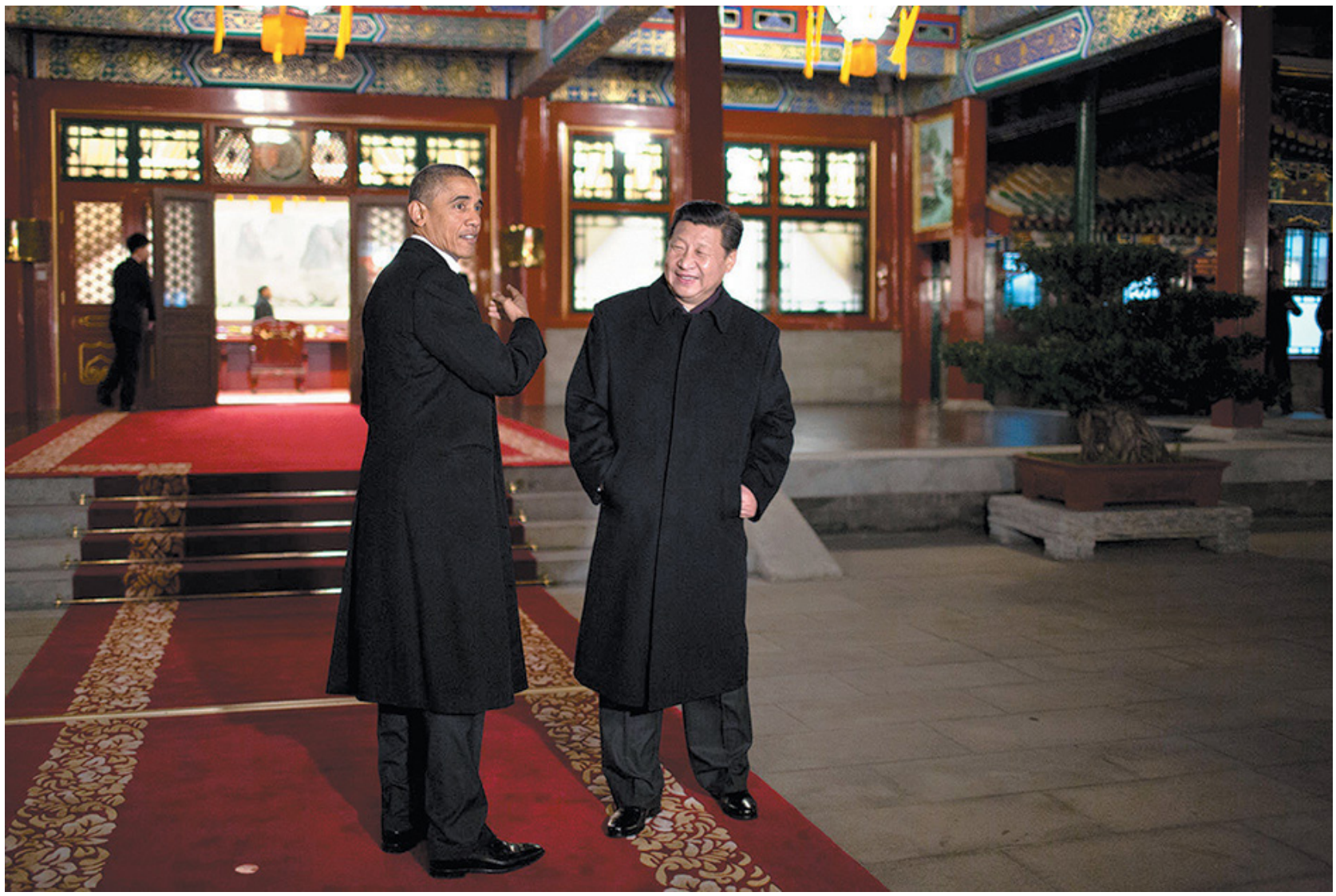
A Partnership with China to Avoid World War

George Soros, The New York Review of Books Jul 9, 2015 Issue



International cooperation is in decline both in the political and financial spheres. The UN has failed to address any of the major conflicts since the end of the cold war; the 2009 Copenhagen Climate Change Conference left a sour aftertaste; the World Trade Organization hasn't concluded a major trade round since 1994. The International Monetary Fund's legitimacy is increasingly questioned because of its outdated governance, and the G20, which emerged during the financial crisis of 2008 as a potentially powerful instrument of international cooperation, seems to have lost its way. In all areas, national, sectarian, business, and other special interests take precedence over the common interest. This trend has now reached a point where instead of a global order we have to speak of global disorder.

In the political sphere local conflicts fester and multiply. Taken individually these conflicts could possibly be solved but they tend to be interconnected and the losers in one conflict tend to become the spoilers in others. For instance, the Syrian crisis deteriorated when Putin's Russia and the Iranian government came to Bashar al-Assad's rescue, each for its own reasons. Saudi Arabia provided the seed money for ISIS and Iran instigated the Houthi rebellion in Yemen to retaliate against Saudi Arabia. Bibi Netanyahu tried to turn the US Congress against the nuclear treaty the

US was negotiating with Iran. There are just too many conflicts for international public opinion to exert a positive influence.

In the financial sphere the Bretton Woods institutions—the IMF and the World Bank—have lost their monopoly position. Under Chinese leadership, a parallel set of institutions is emerging. Will they be in conflict or will they find a way to cooperate? Since the financial and the political spheres are also interconnected, the future course of history will greatly depend on how China tackles its economic transition from investment and export-led growth to greater dependence on domestic demand, and how the US reacts to it. A strategic partnership between the US and China could prevent the evolution of two power blocks that may be drawn into military conflict.

How did we reach this point of global disorder? During the cold war the world was dominated by two superpowers. Each maintained some degree of control over its allies and satellites, and avoided direct military confrontation with the other because of the danger of Mutually Assured Destruction. It was a MAD system but it worked: it produced a number of local military conflicts but it avoided a world war.

When the Soviet empire fell apart the United States had an opportunity to become the sole superpower and the guarantor of peace in the world, but it did not rise to the occasion. The US was founded on the principle of individual freedom and it was not predisposed to become the policeman of the world. Indeed, it did not have a coherent view of the meaning of leadership in international affairs. During the cold war it had a bipartisan foreign policy, on which Democrats and Republicans largely agreed; but after the cold war ended the partnership broke up. Both parties continued to emphasize American sovereignty but they rarely agreed on subordinating it to international obligations.

Then in 1997, a group of neoconservatives argued that the US should use its military supremacy to impose its national interests, and established a think tank called the Project for the New American Century, "to promote American global leadership." But that was a false approach: military force cannot be used to rule the world. After the terrorist attack of September 11, the neocons persuaded President George W. Bush to attack Iraq on dubious grounds that turned out to be false, and the US lost its supremacy. The Project for the New American Century had approximately the same lifespan as Hitler's Thousand-Year Reich: around ten years.

On the financial side, by contrast, there was a clear consensus—the so-called Washington Consensus—on America's role in the world. It became dominant in the 1980s under the leadership of Ronald Reagan and Margaret Thatcher. It had strong ideo-

logical support from market fundamentalists; it had a supposedly scientific foundation in the Efficient Market Hypothesis and Rational Choice Theory; and it was efficiently administered by the International Monetary Fund (IMF). The consensus was a much more subtle compromise between international governance and national self-interest than the neocons' view that military power is supreme.

Indeed, the Washington Consensus had its roots in the original compromise on which the Bretton Woods institutions were founded. John Maynard Keynes proposed a truly international currency, the bancor, but the US insisted on the dollar as the world's reserve currency and it prevailed. In the memorable words of George Orwell's Animal Farm, "all animals are equal, but some animals are more equal than others." The Washington Consensus promoted free trade and the globalization of financial markets. In the late 1990s, market fundamentalists even tried to modify the articles of agreement of the IMF so as to impose capital account convertibility, the free exchange of currencies. That attempt failed, but by allowing financial capital to move around freely the Washington Consensus also allowed capital to escape taxation and regulation. That was a triumph for market fundamentalism.

Unfortunately, the scientific foundations of this approach proved to be ill conceived. Unregulated financial markets are inherently unstable: instead of a general equilibrium that assures the optimum allocation of resources, they produce financial crises. This was dramatically demonstrated by the crash of 2008. By coincidence, 2008 marked both the end of America's political supremacy and the demise of the Washington Consensus. It was also the beginning of a process of financial and political disintegration that first manifested itself in the microcosm of the European Union, but then spread to the world at large.

The crash of 2008 had a lasting negative effect on all the economies of the world, with the notable exception of China's. The Chinese banking system was relatively isolated from the rest of the world and largely government-owned. As a consequence, the Chinese banks could, at the government's behest, offset the collapse of external demand by flooding the economy with credit. The Chinese economy replaced the American consumer as the motor of the global economy, largely by selling to the American consumer on credit. It has been a rather weak motor, reflecting the relative size of the Chinese and American economies, so that the global economy has grown rather slowly since the emergence of China's international economic power.

The main reason why the world avoided a global depression is that economists have learned some lessons from the experience of the 1930s. The heavy load of debt and lingering political prejudices limited the scale of fiscal stimulus globally (again

with the exception of China); but the Federal Reserve under the leadership of its chairman, Ben Bernanke, embarked on unorthodox monetary policies including quantitative easing—large-scale injection of money into the economy through the purchase of bonds by the Federal Reserve. This prevented the reduction in effective demand from deteriorating into a global depression.

The crash of 2008 was also indirectly responsible for the euro crisis. The euro was an incomplete currency: it had a common central bank but it did not have a common treasury. The architects of the euro were aware of this defect but believed that when the deficiency became apparent the political will could be summoned to correct it. After all, that is how the European Union was brought into existence—taking one step at a time, knowing full well that it was insufficient but that when the need arose it would lead to further steps.

Unfortunately, political conditions changed between 1999, when the euro was adopted, and 2008, when the need arose. Germany under the leadership of Helmut Kohl led the process of European integration in order to facilitate the reunification of Germany. But reunification proved expensive and the German public became unwilling to take on any additional expenses. When, after the bankruptcy of Lehman Brothers in 2008, the European finance ministers declared that no systemically important financial institution would be allowed to fail, Chancellor Angela Merkel, as a politician in touch with the prevailing public opinion, insisted that the responsibility should fall on each country separately, not on the European Union collectively. That ruled out the possibility of a common treasury just when it was needed. That was the beginning of the euro crisis. Crises in individual countries like Greece, Italy, or Ireland are essentially variants of the euro crisis.

Subsequently, the financial crisis has morphed into a series of political crises. The differences between creditor countries and debtor countries have transformed the European Union from a voluntary association of equals into a relationship between creditors, such as Germany, and debtors, such as Greece, that is neither voluntary nor equal and arouses increasing political tensions.

The European Union started out as a valiant attempt at international governance on a regional scale. In the aftermath of 2008, the EU became preoccupied with its internal problems and failed to pull its weight in the international economy. The United States also became inward-looking but by a somewhat different route. The inward turn of the EU and US led to a decline in international cooperation on a global scale.

Since the Western powers are the mainstay of the prevailing world order, their declining influence has created a power vacuum in international governance. Aspiring

regional powers and nonstate actors, which are willing to use military force, have rushed to fill the vacuum. Armed conflicts have proliferated and spread from the Middle East to other parts of Asia, Africa, and even Europe.

By annexing Crimea and establishing separatist enclaves in Ukraine, Putin's Russia has challenged both the prevailing world order, which depends on the Western powers for support, and the values and principles on which the EU was founded. Neither the European nor the American public is fully aware of the severity of the challenge. President Vladimir Putin wants to destabilize all of Ukraine by precipitating a financial and political collapse for which he can disclaim responsibility, while avoiding occupation of a part of eastern Ukraine, which would then depend on Russia for economic support. He has demonstrated his preference by twice converting an assured military victory into a cease-fire that threatened to destabilize all of Ukraine. Unfortunately, Putin is succeeding, as can be seen by comparing the "Minsk Two" cease-fire with "Minsk One," even if his success is purely temporary. Putin now seeks to use Ukraine to sow dissension and gain political influence within the European Union.

The severity of the Russian threat is directly correlated with the weakness of the European Union. The EU has excelled at muddling through financial and political crises but now it is confronted with not one but five crises: Russia, Ukraine, Greece, immigration, and the coming British referendum on EU membership—and that may be too much. The very survival of the EU is at risk.

International governance on a global scale is equally fragile. The world may break up into rival camps both financially and politically. China has begun to build a parallel set of financial institutions, including the Asian Infrastructure Investment Bank (AIIB); the Asian Bond Fund Initiative; the New Development Bank (formerly the BRICS Bank); and the Chiang Mai Initiative, which is an Asian regional multilateral arrangement to swap currencies. Whether the two camps will be able to keep their rivalry within bounds will depend on how China manages its economic transition and on how the US reacts to it.

The International Monetary Fund could play a positive part in this. It has abandoned its commitment to the Washington Consensus but the controlling shareholders of the Bretton Woods institutions—the US, the UK, France, and Germany among them—are unwilling to relinquish their voting control by increasing the representation of the developing world. This is very shortsighted on their part because it does not recognize changes in the relative weight of various economies and particularly the rise of China.

The controlling shareholders are unlikely to abandon their control, however tenuous; but the IMF has an opportunity to build a binding connection between the two camps. The opportunity arises from the fact that the composition of the IMF's Special Drawing Rights (SDR) basket will be up for its five-yearly review at the end of 2015.

The SDR is an international reserve asset, created by the IMF in 1969 to supplement the existing official reserves of member countries. The Chinese renminbi is not fully qualified to be included in the SDR basket, but the qualifications to be included are not as rigorously defined as is generally believed. The Japanese yen was introduced when it was not yet widely traded; the franc entered the basket when the French capital account was heavily controlled; and the Saudi riyal was introduced when it was completely pegged to the US currency. The criteria for inclusion have changed over the years but now call for (1) a large exporter country and (2) a "freely usable" currency. This term is often misconstrued as imposing complete convertibility of capital accounts and flexibility of exchange rates; but that is not the case. Indeed, the basket of Special Drawing Rights formerly included currencies with no or little capital account convertibility.

The Chinese leadership has now embarked on a major effort to have the renminbi included in the SDR basket, and the IMF staff is sympathetic. For instance, it has announced that the renminbi is "no longer undervalued," and it doesn't seek full and precipitous capital account liberalization, but rather a cautious and gradual pace of reform in order to ensure the smooth functioning of the SDR and the preservation of financial stability in China.

Much now depends on the attitude of the US government, which holds veto rights in the IMF—even if the decision regarding the SDR basket requires only a 70 percent majority of the IMF's board. The US would be making a major concession if it opened the door to allowing the renminbi to become a potential rival to the dollar. It could demand similar concessions from China in return, but that would be the wrong approach. The relationship between two great powers is not a zero-sum game: one party's gain is not necessarily a loss for the other.

China is seeking SDR status for the renminbi not to please or hurt the US but for reasons of its own that are only indirectly connected with China's ultimate ambition of replacing the US dollar as the dominant currency in the world. China seeks to use financial liberalization as an engine of growth for the Chinese economy. China wants to deepen the government bond market and open it up to international investors in order to enable the central government to clean up the bad debts of insolvent local authorities; it also wants to reduce the excessive leverage in the economy by

promoting conversions of debt to equity. Inclusion of the renminbi in the IMF basket would facilitate the process, and success would automatically advance the renminbi's weight and influence in the world.

The US government has little to gain and much to lose by treating the relationship with China as a zero-sum game. In other words it has little bargaining power. It could, of course, obstruct China's progress, but that would be very dangerous. President Xi Jinping has taken personal responsibility for the economy and national security. If his market-oriented reforms fail, he may foster some external conflicts to keep the country united and maintain himself in power. This could lead China to align itself with Russia not only financially but also politically and militarily. In that case, should the external conflict escalate into a military confrontation with an ally of the United States such as Japan, it is not an exaggeration to say that we would be on the threshold of a third world war.

Indeed, military budgets are rapidly increasing both in Russia and in China, and they remain at a very high level in the United States. For China, rearmament would be a surefire way to boost domestic demand. China is already flexing its military muscle in the South China Sea, operating in a unilateral and often quite belligerent manner, which is causing justifiable concern in Washington. Nevertheless, it may take a decade or more until a Russian–Chinese military alliance would be ready to confront the US directly. Until then, we may expect a continuation of hybrid warfare and the proliferation of proxy wars.

Both the US and China have a vital interest in reaching an understanding because the alternative is so unpalatable. The benefits of an eventual agreement between China and the US could be equally far-reaching. Recently there has been a real breakthrough on climate policy on a bilateral basis. By taking the nonbinding representations and promises made by the two countries at face value, the agreement has made more credible some recent efforts to bring climate change under control. If this approach could be extended to other aspects of energy policy and to the financial and economic spheres, the threat of a military alignment between China and Russia would be removed and the prospect of a global conflict would be greatly diminished. That is worth trying.

On his last state visit to the US in 2013, President Xi spoke of a "new type of great power relationship." The subject has been widely discussed in China since then. President Obama should outline his own vision by drawing a distinction between Putin's Russia, which has replaced the rule of law with the rule of force, and today's China, which does not always abide by the rule of law but respects its treaty obligations. Russian aggression needs to be firmly resisted; by contrast China needs to be

encouraged—by offering a more constructive alternative—to avoid the route of military aggression. This kind of offer may elicit a favorable response. Rivalry between the US and China is inevitable but it needs to be kept within bounds that would preclude the use of military force.

It does not follow that a far-reaching agreement amounting to a strategic partnership between the US and China would be easy to accomplish. The two countries have fundamentally different political systems. While the US is founded on the principle of individual freedom, China has no significant tradition of such freedom. It has had a hierarchical structure since time immemorial and it has been an empire throughout most of its history. In recent years the US has led the world in the innovative development of social media, while China has led the world in finding means to control it. Since the end of the cold war, China has been much more successful than Russia in creating a successful hierarchical system.

This is best seen by looking at the way information is distributed. Since the rise of social media, information increasingly travels along horizontal lines, but China is different: information is distributed vertically. Within the party–state apparatus, the closer one is to the top, the better one is informed and the more latitude one enjoys in expressing an opinion. This means that the party–state apparatus offers not only an opportunity for personal enrichment but also a semblance of individual freedom. No wonder that the apparatus has been able to attract much of China's best talent. The degree of latitude it allows is, however, strictly circumscribed by red lines. People have to walk within a grid; those who transgress the red lines may fall into the hands of the security apparatus and disappear without a trace.

The stranglehold of the security apparatus was gradually diminishing but recently there has been an ominous reversal: under the leadership of President Xi the informal rules defining the rights and status of NGOs, for instance, are now in the process of being significantly tightened.*

Comparing President Xi's "Chinese dream" with the American dream highlights the difference between the two political and social systems. Xi extols China's success in "rejuvenating the nation" by harnessing the talents and energies of its people in service of the state. By contrast, the American dream extols the success of the rugged individual who achieves upward social mobility and material prosperity by overcoming obstacles posed by social conventions or prejudices or authorities abusing their power, or sheer bad luck. The US would like China to adopt its values but the Chinese leadership considers them subversive.

In this respect China has more in common with Russia than with the US. Both Rus-

sia and China consider themselves victims of America's aspiration to world domination. From the US point of view, there is much to disapprove of in China's behavior. There is no independent judiciary and multinational companies are often mistreated and replaced by domestic favorites. And there are conflicts with the US and other nations in the South China Sea and over cyberwarfare and human rights. These are not matters on which cooperation will be easy to achieve.

Fully recognizing these difficulties, the US government should nevertheless make a bona fide attempt at forging a strategic partnership with China. This would involve identifying areas of common interest as well as areas of rivalry. The former would invite cooperation, the latter tit-for-tat bargaining. The US needs to develop a two-pronged strategy that offers incentives for cooperation and deterrents that render tit-for-tat bargaining less attractive.

The areas for cooperation may prove to be wider than is obvious at first sight. Cooperating with China in making President Xi's financial reforms successful is definitely in the common interest. Success would fulfill the aspirations of the ever-increasing Chinese middle class. It may also allow Xi to relax some of the restrictions he has recently introduced and that would, in turn, increase the probability that his reforms will succeed and improve global financial stability. The weak point of his current approach is that both implementing and monitoring the reform process are in the same hands. Opening up the process to criticism by the media and civil society would greatly improve the efficacy of his reforms. This is particularly true of Xi's anticorruption campaign. And if China followed this path, it would become increasingly attractive to the US as a strategic partner.

Negotiations between the US and China could not possibly be completed by October 2015, when the board of the IMF is scheduled to consider the composition of the SDR basket. Realistically it would take until President Xi's state visit to Washington in September to complete the preparations. But there is much to be gained by extending the SDR deadline to 2016. China will then host the meeting of the G20, and 2016 will also be the last year of the Obama administration. The prospect of a strategic partnership between the US and China would mobilize all political forces in favor of international cooperation on both sides.

If a bona fide attempt fails, the US would then be fully justified in developing a strong enough partnership with China's neighbors that a Chinese–Russian alliance would not dare to challenge it by military force. That would be clearly inferior to a strategic partnership between the US and China. A partnership with China's neighbors would return us to a cold war, but that would still be preferable to a third world war.

The Trans-Pacific and Trans-Atlantic Partnerships, which are currently being negotiated, could offer an excellent opportunity for a two-pronged strategy but the current approach is all wrong. At present China is excluded; indeed the partnerships are conceived as an anti-Chinese alliance under US leadership. The president has asked Congress to give him and his successor authority for up to six years to negotiate trade agreements under fast-track rules that would deprive Congress of its right to introduce amendments. The bill has passed the Senate and at this writing is before the House. If the House approves, President Xi may be presented with an apparent threat on his visit in September. This is an appropriate response to China's aggressive behavior in the South China Sea and elsewhere, but it leaves little room for an alternative approach. It would, as a result, be difficult for President Obama to make a bona fide offer of strategic partnership.

It is to be hoped that the House will not authorize putting the bill on a fast track. Instead of railroading the bill through Congress, it ought to be taken off the fast track. In that case, Congress would have plenty of time to correct the fundamental flaws in the proposed treaties that make them unacceptable as they are currently written. And that would also allow President Obama to make President Xi a genuine offer of a strategic partnership with China when he visits Washington in September.

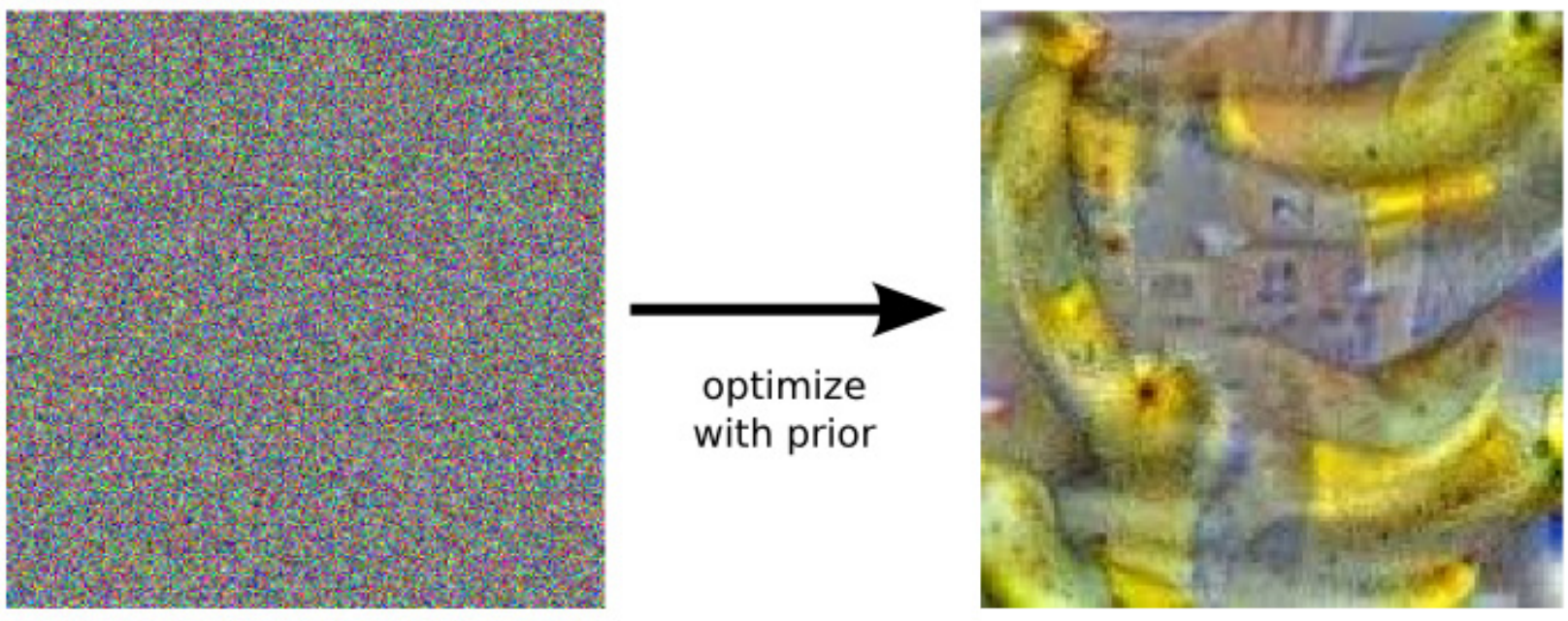
Inceptionism: Going Deeper into Neural Networks

Alexander Mordvintsev, Christopher Olah and Mike Tyka,
Google Research Blog Jun 17, 2015

Artificial Neural Networks have spurred remarkable recent progress in image classification and speech recognition. But even though these are very useful tools based on well-known mathematical methods, we actually understand surprisingly little of why certain models work and others don't. So let's take a look at some simple techniques for peeking inside these networks.

We train an artificial neural network by showing it millions of training examples and gradually adjusting the network parameters until it gives the classifications we want. The network typically consists of 10-30 stacked layers of artificial neurons. Each image is fed into the input layer, which then talks to the next layer, until eventually the "output" layer is reached. The network's "answer" comes from this final output layer.

One of the challenges of neural networks is understanding what exactly goes on at each layer. We know that after training, each layer progressively extracts higher and higher-level features of the image, until the final layer essentially makes a decision on what the image shows. For example, the first layer maybe looks for edges or corners. Intermediate layers interpret the basic features to look for overall shapes or components, like a door or a leaf. The final few layers assemble those into complete interpretations—these neurons activate in response to very complex things such as entire buildings or trees.



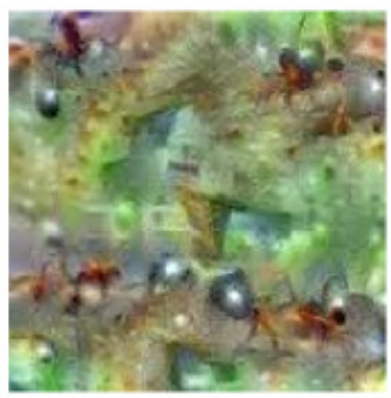
One way to visualize what goes on is to turn the network upside down and ask it to enhance an input image in such a way as to elicit a particular interpretation. Say you want to know what sort of image would result in "Banana." Start with an image

full of random noise, then gradually tweak the image towards what the neural net considers a banana. By itself, that doesn't work very well, but it does if we impose a prior constraint that the image should have similar statistics to natural images, such as neighboring pixels needing to be correlated.

So here's one surprise: neural networks that were trained to discriminate between different kinds of images have quite a bit of the information needed to generate images too. Check out some more examples across different classes:

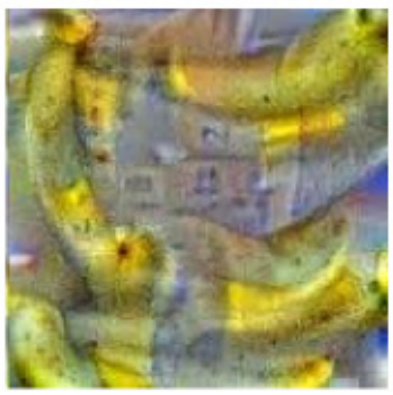

Hartebeest


Measuring Cup


Ant


Starfish


Anemone Fish

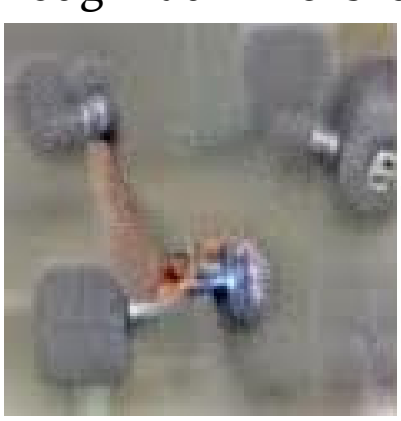

Banana

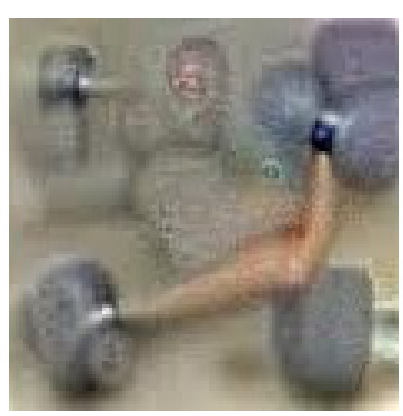
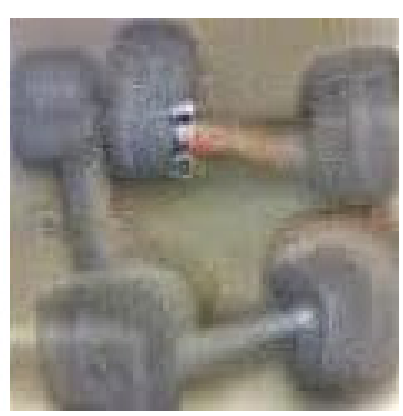

Parachute


Screw

Why is this important? Well, we train networks by simply showing them many examples of what we want them to learn, hoping they extract the essence of the matter at hand (e.g., a fork needs a handle and 2-4 tines), and learn to ignore what doesn't matter (a fork can be any shape, size, color or orientation). But how do you check that the network has correctly learned the right features? It can help to visualize the network's representation of a fork.

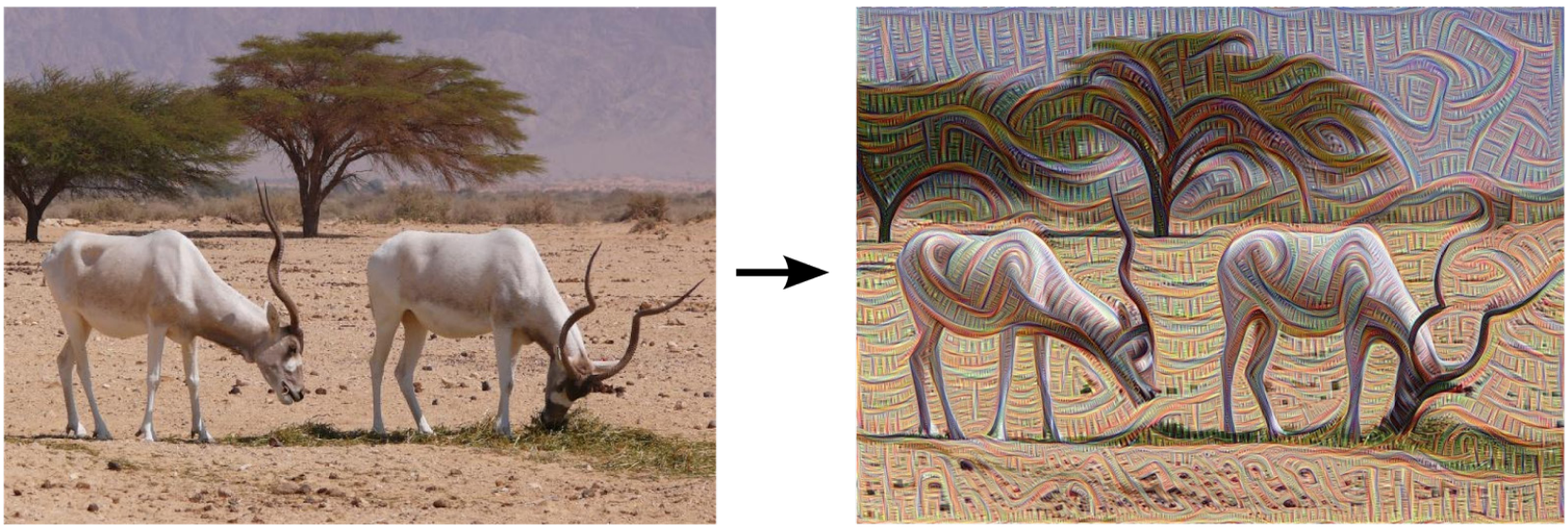
Indeed, in some cases, this reveals that the neural net isn't quite looking for the thing we thought it was. For example, here's what one neural net we designed thought dumbbells looked like:

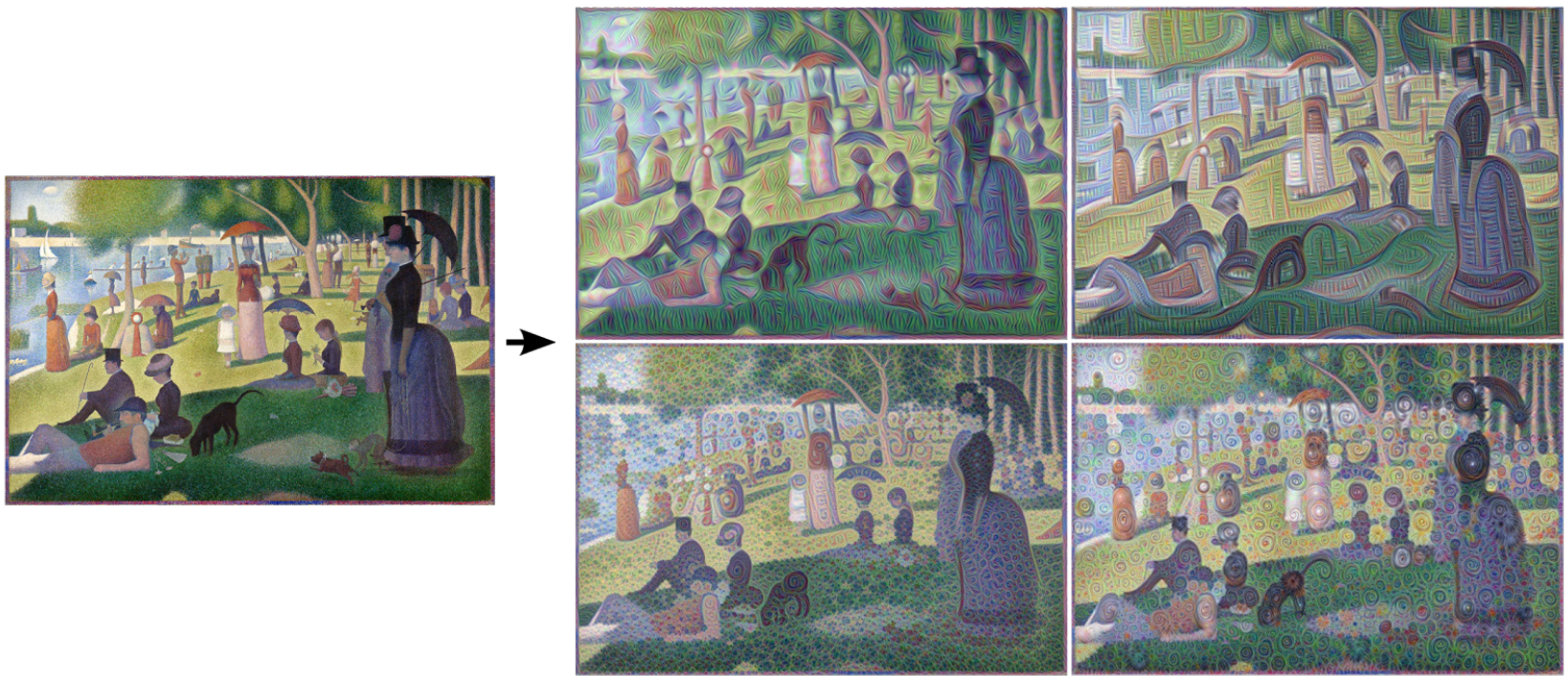


There are dumbbells in there alright, but it seems no picture of a dumbbell is complete without a muscular weightlifter there to lift them. In this case, the network failed to completely distill the essence of a dumbbell. Maybe it's never been shown a dumbbell without an arm holding it. Visualization can help us correct these kinds of training mishaps.

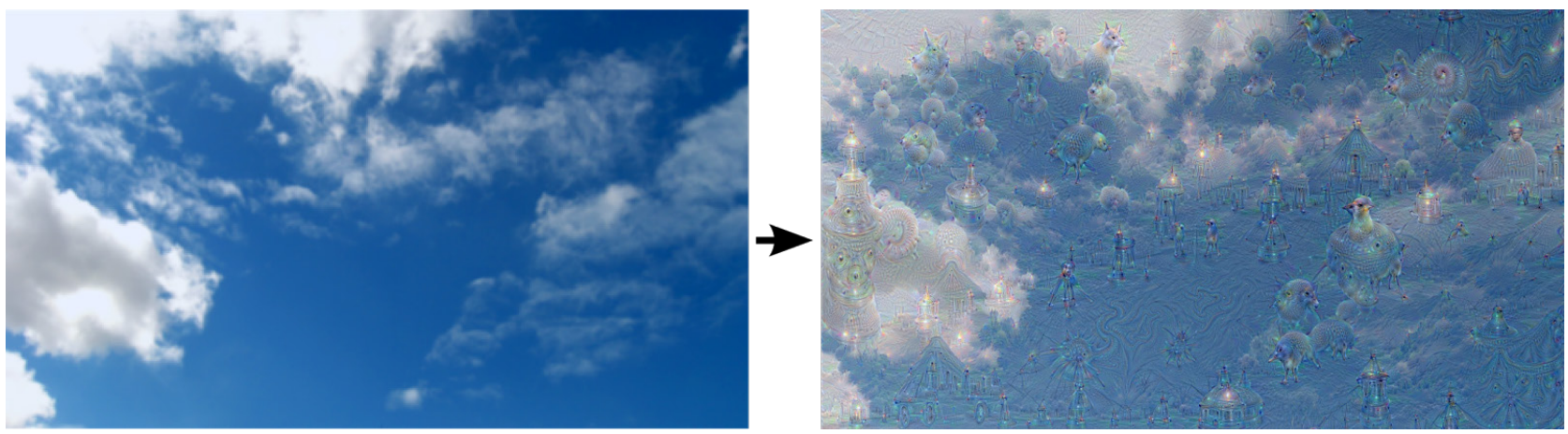
Instead of exactly prescribing which feature we want the network to amplify, we can also let the network make that decision. In this case we simply feed the network an arbitrary image or photo and let the network analyze the picture. We then pick a layer and ask the network to enhance whatever it detected. Each layer of the network deals with features at a different level of abstraction, so the complexity of features we generate depends on which layer we choose to enhance. For example, lower layers tend to produce strokes or simple ornament-like patterns, because those layers are sensitive to basic features such as edges and their orientations.

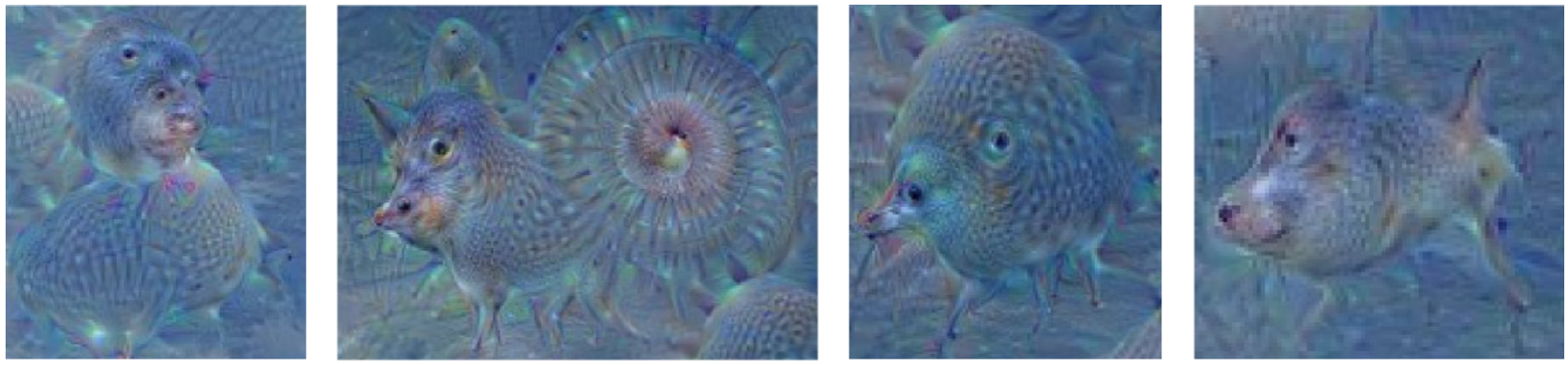




If we choose higher-level layers, which identify more sophisticated features in images, complex features or even whole objects tend to emerge. Again, we just start with an existing image and give it to our neural net. We ask the network: "Whatever

you see there, I want more of it!" This creates a feedback loop: if a cloud looks a little bit like a bird, the network will make it look more like a bird. This in turn will make the network recognize the bird even more strongly on the next pass and so forth, until a highly detailed bird appears, seemingly out of nowhere.

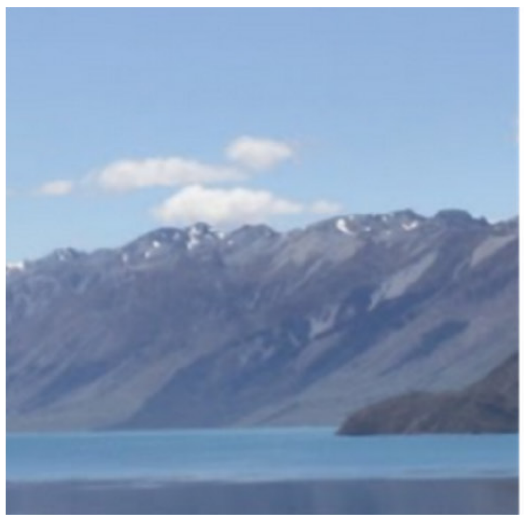




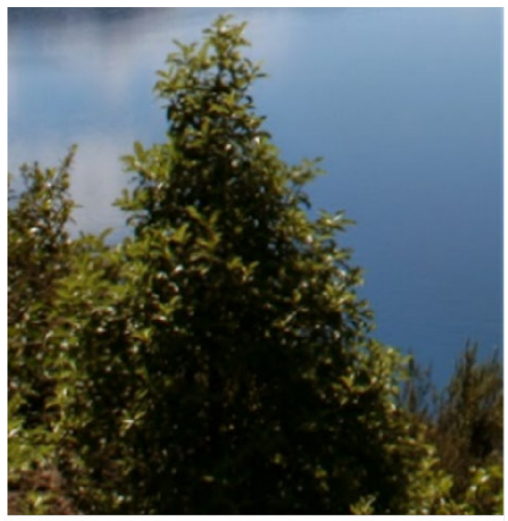
"Admiral Dog!" "The Pig-Snail" "The Camel-Bird" "The Dog-Fish"

Of course, we can do more than cloud watching with this technique. We can apply it to any kind of image. The results vary quite a bit with the kind of image, because the features that are entered bias the network towards certain interpretations. For example, horizon lines tend to get filled with towers and pagodas. Rocks and trees turn into buildings. Birds and insects appear in images of leaves.

This technique gives us a qualitative sense of the level of abstraction that a particular layer has achieved in its understanding of images. We call this technique "Inceptionism" in reference to the neural net architecture used. See our Inceptionism gallery for more pairs of images and their processed results, plus some cool video animations.



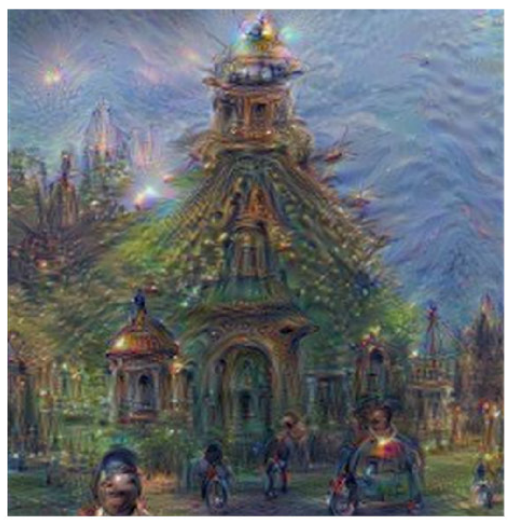
Horizon



Trees

Leaves

Towers & Pagodas



Buildings

Birds & Insects

We must go deeper: Iterations

If we apply the algorithm iteratively on its own outputs and apply some zooming after each iteration, we get an endless stream of new impressions, exploring the set of things the network knows about. We can even start this process from a random-noise image, so that the result becomes purely the result of the neural network, as seen in the following images:

The techniques presented here help us understand and visualize how neural networks are able to carry out difficult classification tasks, improve network architecture, and check what the network has learned during training. It also makes us wonder whether neural networks could become a tool for artists—a new way to remix visual concepts—or perhaps even shed a little light on the roots of the creative process in general.

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, Arne Astrup, Ken Fujioka, Frank Greenway, Alfredo Halpern, Michel Krempf, David C.W. Lau, Carel W. le Roux, Rafael Violante Ortiz, Christine Bjørn Jensen, and John P.H. Wilding, The New England Journal of Medicine Vol 373 No 1

The increase in the rate of obesity, a chronic disease with serious health consequences, largely explains the recent tripling in the prevalence of type 2 diabetes. Weight loss of 5 to 10% has been shown to reduce complications related to obesity and improve quality of life; however, weight loss is difficult to maintain with lifestyle intervention alone.

Liraglutide, a glucagon-like peptide-1 analogue with 97% homology to human glucagon-like peptide-1, is approved for the treatment of type 2 diabetes at doses up to 1.8 mg once daily. Weight loss with liraglutide is dose-dependent up to 3.0 mg once daily and is mediated by reduced appetite and energy intake rather than by increased energy expenditure.

This 56-week, randomized, placebo-controlled trial aimed to evaluate the efficacy and safety of 3.0 mg of liraglutide, injected subcutaneously once daily, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline.

METHODS

Study Overview

We conducted the study from June 1, 2011, through March 18, 2013, at 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. The trial protocol was approved by local ethics committees or institutional review boards and is available with the full text of this article at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. A 2-year extension of the trial involving patients with prediabetes that was designed to evaluate whether liraglutide is associated with delayed onset of type 2 diabetes was recently completed. All the authors were involved in the design or conduct of the study and the preparation of the manuscript, including the decision to submit it for publication, and all attest to the accu-

racy and completeness of data and the data analyses. The sponsor, Novo Nordisk, planned and performed the statistical analyses, provided editorial and writing assistance, and provided the trial drugs.

Patients

The trial enrolled patients 18 years of age or older who had stable body weight and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher if the patient had treated or untreated dyslipidemia or hypertension (Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients provided written informed consent before participation. Key exclusion criteria were type 1 or 2 diabetes, the use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of pancreatitis, a history of major depressive or other severe psychiatric disorders, and a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. Details of the eligibility and exclusion criteria are provided in the Supplementary Appendix.

Study Design and Treatments

Randomization was performed with the use of a telephone or Web-based system provided by the sponsor. Eligible patients were randomly assigned, in a 2:1 ratio, to receive once-daily subcutaneous injections of liraglutide, starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg, or placebo; both groups received counseling on lifestyle modification (Fig. S1 in the Supplementary Appendix). Patients were stratified according to prediabetes status at screening and according to BMI (≥30 vs. <30). Patients, investigators, and the sponsor were unaware of the study-group assignments. Liraglutide and placebo were provided in FlexPen devices (Novo Nordisk). After 56 weeks, patients in the liraglutide group who did not have prediabetes at screening were randomly assigned in a 1:1 ratio to continue receiving liraglutide or to switch to placebo for 12 weeks to assess whether efficacy was maintained after discontinuation of liraglutide treatment and whether there were safety issues related to discontinuation. Patients in the placebo group continued to receive placebo.

Study Procedures and End Points

Patients were evaluated every 2 weeks until week 8; thereafter, patients were evaluated every 4 weeks until week 44 and were evaluated again at weeks 50, 56, 58, 60, 64, 68, and 70. All patients received standardized counseling on lifestyle modification approximately monthly (see the Supplementary Appendix). Patients who with-

drew early were asked to return at week 56 for measurement of their weight and recording of adverse events.

The three prespecified coprimary end points, assessed at week 56, were weight change from baseline, the proportion of patients who lost at least 5% of their baseline body weight, and the proportion of patients who lost more than 10% of their baseline body weight. Secondary end points included changes from baseline in BMI, waist circumference, glycemic control variables, cardiometabolic biomarkers, and health-related quality of life. The timing of assessments is described in the Methods section in the Supplementary Appendix. Health-related quality of life was assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; in which higher scores indicate better quality of life) and the Impact of Weight on Quality of Life–Lite17 (in which higher scores indicate better quality of life) and Treatment Related Impact Measure–Weight18 (in which higher scores indicate better quality of life) questionnaires. The proportion of patients who modified their use of lipid-lowering or antihypertensive medications was also assessed. Additional methods are described in the Supplementary Appendix.

Specific attention was given to types of adverse events that have an increased prevalence among obese persons or that were relevant to the drug class of liraglutide: of 17 types of adverse events, 9 were prospectively assessed by independent medical experts who were unaware of the study-group assignments (Table S2 in the Supplementary Appendix). We report adverse events that occurred during the main 56-week trial period, with onset on or after the first day of treatment and no later than 14 days after the last day of treatment, unless otherwise stated.

Statistical Analysis

We estimated that with a sample size of 2400 patients assigned to receive liraglutide and 1200 assigned to receive placebo, the study would have more than 99% power to detect a between-group difference in the three coprimary efficacy end points of the main 56-week trial and in the primary end point of the 2-year extension. The power for the first coprimary end point, weight change, was calculated with the use of a two-sided Student's t-test at a 5% significance level. The power for the two categorical coprimary end points was calculated with the use of a two-sided chi-square test, also at a 5% significance level (see the Supplementary Appendix).

The prespecified efficacy analyses used data from the full-analysis set, which included all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. The safety-analysis set included all patients who were randomly assigned to a study group and had expo-

sure to a study drug. Missing values were imputed with the use of the last-observation-carried-forward method for measurements made after baseline. For weight, only fasting measurements were used. The three coprimary end points were analyzed in hierarchical order. An analysis of covariance model was used to analyze mean changes in continuous end points. The model included treatment, country, sex, BMI stratification, status with respect to prediabetes at screening, and interaction between BMI strata and prediabetes status as fixed effects, with the baseline value of the relevant variable as a covariate. Categorical changes for dichotomous end points were analyzed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of covariance. Sensitivity analyses, performed to assess the robustness of the primary analyses, included repeated-measures and multiple-imputation analyses, which used a model-based approach for missing data (see the Supplementary Appendix). A total of 63 prespecified subgroup analyses were performed to investigate whether prediabetes status had any effect on the primary and secondary end points and whether baseline BMI (in four categories) had any effect on weight or glycated hemoglobin level (see the Methods in the Supplementary Appendix). Results are presented only if an effect was shown.

RESULTS

Trial Population

A total of 3731 patients underwent randomization: 2487 to lifestyle intervention plus liraglutide, at a dose of 3.0 mg once daily, and 1244 to lifestyle intervention plus placebo. The baseline characteristics were similar in the two groups (Table 1., and Tables S3 and S4 in the Supplementary Appendix). A total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the placebo group, completed 56 weeks of treatment (Fig. S2 in the Supplementary Appendix). A larger percentage of patients in the liraglutide group than in the placebo group withdrew from the trial owing to adverse events (9.9% [246 of 2487 patients] vs. 3.8% [47 of 1244]); a smaller percentage of patients in the liraglutide group withdrew from the trial owing to ineffective therapy (0.9% [23 of 2487] vs. 2.9% [36 of 1244]) or withdrew their consent (10.6% [264 of 2487] vs. 20.0% [249 of 1244]).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N=2487)	Placebo (N=1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
Race or ethnic group — no. (%)†		
White	2107 (84.7)	1061 (85.3)
Black	242 (9.7)	114 (9.2)
Asian	90 (3.6)	46 (3.7)
American Indian or Alaska Native	5 (0.2)	4 (0.3)
Native Hawaiian or other Pacific Islander	2 (<0.1)	2 (0.2)
Other	41 (1.6)	17 (1.4)
Hispanic or Latino ethnic group†	259 (10.4)	134 (10.8)
Weight — kg	106.2±21.2	106.2±21.7
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)
Waist circumference — cm	115.0±14.4	114.5±14.3
Glycated hemoglobin — %	5.6±0.4	5.6±0.4
Fasting glucose — mg/dl	95.9±10.6	95.5±9.8
Fasting insulin — μIU/ml§	16.3±79.8	16.1±89.3
Blood pressure — mm Hg		
Systolic	123.0±12.9	123.2±12.8
Diastolic	78.7±8.6	78.9±8.5
Cholesterol — mg/dl		
Total	193.7±19.1	194.3±18.8
LDL	111.6±27.9	112.2±27.6
HDL	51.4±26.2	51.0±26.4
VLDL	25.1±49.6	25.7±49.4
Free fatty acids — mmol/liter	0.45±40.5	0.46±39.7
Triglycerides — mg/dl	126.2±56.9	128.9±61.0
Prediabetes — no. (%)¶	1528 (61.4)	757 (60.9)
Dyslipidemia — no. (%)‖	737 (29.6)	359 (28.9)
Hypertension — no. (%)‖	850 (34.2)	446 (35.9)

* Plus–minus values are observed means ±SD. For fasting insulin and lipid levels, plus–minus values are geometric means and coefficients of variation. There were no statistically significant differences between the two groups for any characteristic. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.
† Race and ethnic group were self-reported. Patients from France did not report race or ethnic group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The reference range is 3.0 to 25.0 μIU/mL for both sexes and all ages.
¶ Prediabetes was defined according to American Diabetes Association 2010 criteria.[15]
‖ The diagnoses of dyslipidemia and hypertension were based on self-reported medical history.

Table 2. Changes in Coprimary End Points and Cardiometabolic Risk Factors between Baseline and Week 56.*

End Point	Liraglutide (N=2437)	Placebo (N=1225)	Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)†	P Value
Coprimary end points				
Change in body weight				
% of body weight	−8.0±6.7	−2.6±5.7	−5.4 (−5.8 to −5.0)	<0.001
Kilograms of body weight	−8.4±7.3	−2.8±6.5	−5.6 (−6.0 to −5.1)	<0.001
Loss of ≥5% body weight (%)‡	63.2	27.1	4.8 (4.1 to 5.6)	<0.001
Loss of >10% body weight (%)‡	33.1	10.6	4.3 (3.5 to 5.3)	<0.001
Body weight-related end points				
Body-mass index	−3.0±2.6	−1.0±2.3	−2.0 (−2.2 to −1.9)	<0.001
Waist circumference (cm)	−8.2±7.3	−3.9±6.6	−4.2 (−4.7 to −3.7)	<0.001
Glycemic control variables				
Glycated hemoglobin (%)	−0.30±0.28	−0.06±0.30	−0.23 (−0.25 to −0.21)	<0.001
Fasting glucose (mg/dl)	−7.1±10.8	0.1±10.4	−6.9 (−7.5 to −6.3)	<0.001
Fasting insulin (%)	−12.6	−4.4	−8 (−12 to −5)	<0.001
Fasting C-peptide (%)	−8.9	−7.9	−1 (−3 to 2)	0.51
Vital signs				
Systolic blood pressure (mm Hg)	−4.2±12.2	−1.5±12.4	−2.8 (−3.56 to −2.09)	<0.001
Diastolic blood pressure (mm Hg)	−2.6±8.7	−1.9±8.7	−0.9 (−1.41 to −0.37)	<0.001
Pulse (beats/min)	2.5±9.8	0.1±9.5	2.4 (1.9 to 3.0)	<0.001
Fasting lipid profile				
Cholesterol (%)				
Total	−3.1	−1.0	−2.3 (−3.3 to −1.3)	<0.001
LDL	−3.0	−1.0	−2.4 (−4.0 to −0.9)	0.002
HDL	2.3	0.7	1.9 (0.7 to 3.0)	0.001
VLDL	−13.1	−5.5	−9.1 (−11.4 to −6.8)	<0.001
Non-HDL	−5.1	−1.8	−3.9 (−5.2 to −2.5)	<0.001
Triglycerides	−13.3	−5.5	−9.3 (−11.5 to −7.0)	<0.001
Free fatty acids	1.7	3.5	−4.2 (−7.3 to −0.9)	0.01

* Plus–minus values are observed means ±SD. For fasting insulin, fasting C-peptide, and fasting lipids, the relative change from baseline is presented. Post hoc analysis was performed for non-HDL cholesterol.

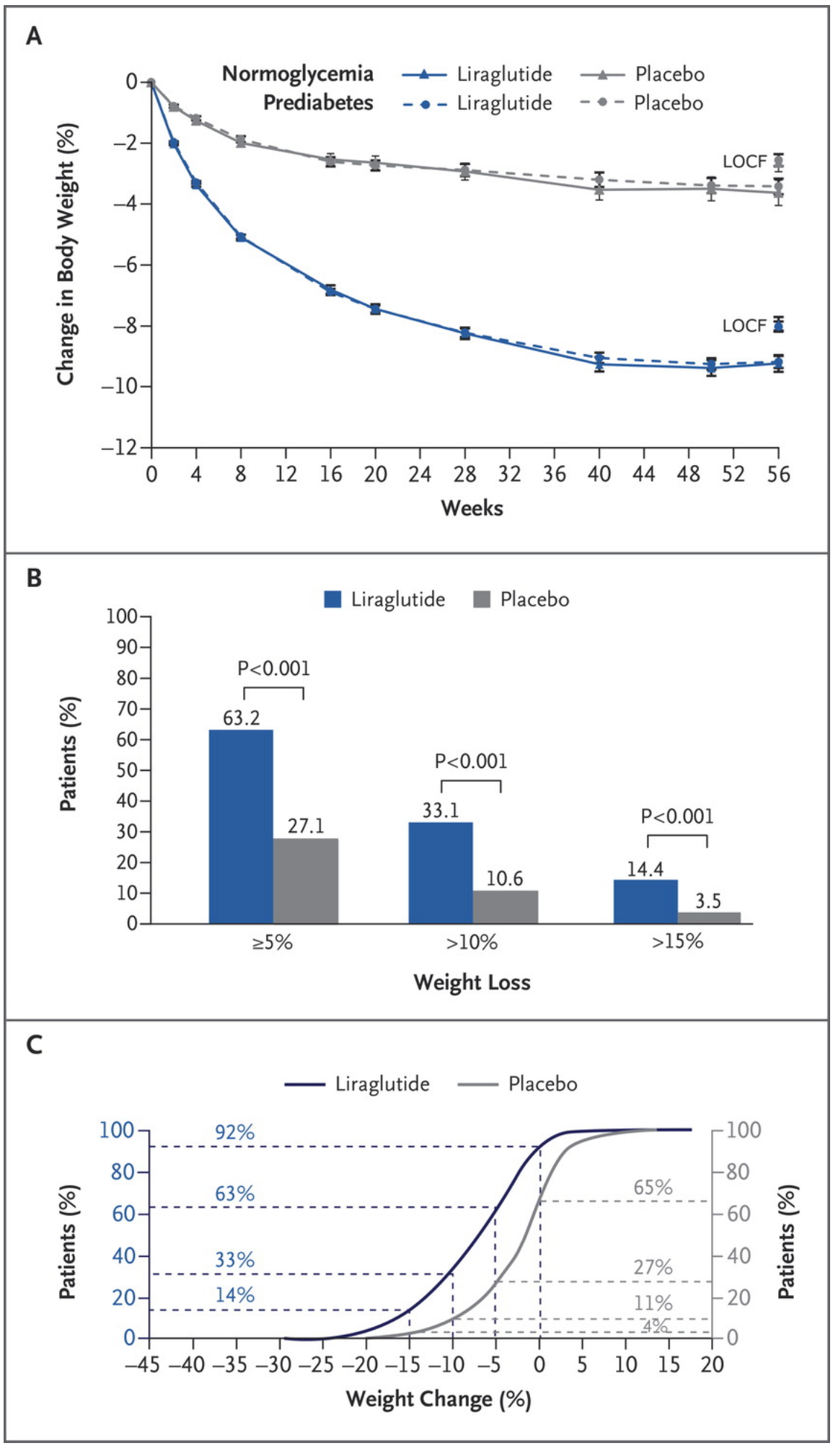
† Estimated treatment differences are from an analysis of covariance with data from the full-analysis set, with last-observation-carried-forward (LOCF) imputation. The full-analysis set comprised patients who underwent randomization, were exposed to at least one treatment dose, and had at least one assessment after baseline (69 patients were excluded from the full-analysis set: 61 owing to lack of an assessment and 8 owing to no exposure). Data on pulse are based on the safety-analysis set, which included all patients who were randomly assigned to a study group and had exposure to a study drug. Data for fasting insulin, fasting C-peptide, and fasting lipids were log-transformed for analysis and are presented as relative treatment differences.

‡ Loss of at least 5% and more than 10% of body weight were analyzed by logistic regression with data from the full-analysis set, with LOCF imputation, and are presented as the proportions of patients (%) and odds ratios.

Body Weight

After 56 weeks, patients in the liraglutide group had lost a mean (±SD) of 8.0±6.7% (8.4±7.3 kg) of their body weight, whereas patients in the placebo group had lost a mean of 2.6±5.7% (2.8±6.5 kg) of their body weight (Table 2). Weight loss with lira-

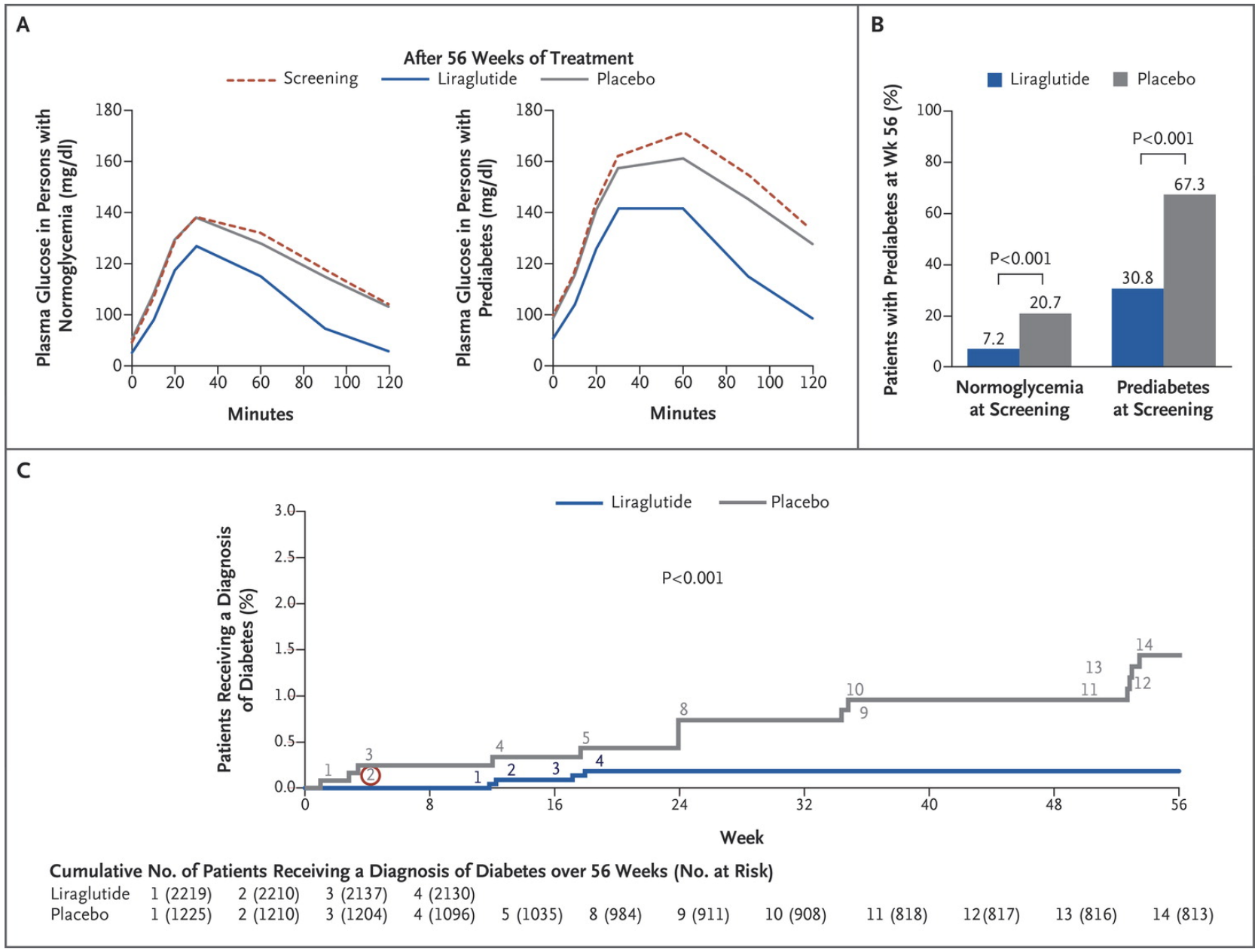
glutide was maintained over 56 weeks and was similar regardless of prediabetes status (Figure 1A). A greater proportion of patients in the liraglutide group than in the placebo group lost at least 5% of their body weight (63.2% vs. 27.1%), more than 10% of their body weight (33.1% vs. 10.6%), and more than 15% of their body weight (14.4% vs. 3.5%) (Figure 1B). Overall, approximately 92% of the patients in the liraglutide group and approximately 65% of the patients in the placebo group lost weight (Figure 1C). The liraglutide group also had a greater reduction than the placebo group in mean waist circumference and BMI (Table 2).



Several sensitivity analyses confirmed the superiority of liraglutide over placebo with respect to the coprimary end points (Table S6 in the Supplementary Appendix). Liraglutide appeared to be less effective in patients with a mean BMI of 40 or higher than in patients with a lower BMI (Fig. S4 in the Supplementary Appendix). Estimated mean changes in body weight and secondary end points are presented in Tables S6 and S8 in the Supplementary Appendix.

Glycemic Control

There was a greater reduction in glycated hemoglobin, fasting glucose, and fasting insulin levels in the liraglutide group than in the placebo group (Table 2). Liraglutide was also associated with a lowering of plasma glucose levels (Figure 2A) and higher insulin and C-peptide levels relative to placebo during an oral glucose-tolerance test (Fig. S3 in the Supplementary Appendix). The effects of liraglutide on glycated hemoglobin, fasting glucose, and glucose levels during the oral glucose-tolerance test were greater in patients with prediabetes than in those without (P<0.001) (Table S9 in the Supplementary Appendix). Measures of insulin resistance and beta-cell function also showed improvement with liraglutide as compared with placebo (Table S10 in the Supplementary Appendix).



The prevalence of prediabetes was significantly lower in the liraglutide group than in the placebo group at week 56 (Figure 2B), a finding that was consistent with the improvement in glycemic control with liraglutide. Type 2 diabetes developed in more patients in the placebo group than in the liraglutide group during the course of treatment.

Cardiometabolic Variables

Systolic and diastolic blood pressure decreased more in the liraglutide group than in the placebo group by week 56 (Table 2). All measures of fasting lipid levels (Table 2), as well as levels of high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin (Table S8 in the Supplementary Appendix), showed greater improvement in the liraglutide group than in the placebo group.

Health-Related Quality of Life

Liraglutide treatment was associated with higher scores on the SF-36 for overall physical and mental health, a higher total score (indicating better quality of life) on the Impact of Weight on Quality of Life–Lite questionnaire (Table S7 in the Supplementary Appendix), and more favorable individual domain scores on both instruments (Fig. S5 in the Supplementary Appendix) than was placebo. The total score and the scores for weight management and treatment burden on the Treatment Related Impact Measure–Weight questionnaire were also higher in the liraglutide group than in the placebo group, although the liraglutide group had a lower score for the experience of side effects.

Side Effects and Adverse Events

Among patients in the safety-analysis set, the most common side effects in the liraglutide group were related to the gastrointestinal system (Table 3); 94% or more were of mild or moderate severity. Gastrointestinal events were also the most common reason that patients in the liraglutide group withdrew from the trial (159 of 2481 patients [6.4%], as compared with 9 of 1242 patients [0.7%] in the placebo group) (Fig. S6 in the Supplementary Appendix). Nausea (Fig. S7 in the Supplementary Appendix) and vomiting occurred primarily within the first 4 to 8 weeks after initiation of liraglutide treatment. The incidence of serious adverse events was higher in the liraglutide group than in the placebo group (Table 3). Three patients died — 1 in the liraglutide group (with death due to cardiomegaly and hypertensive heart disease) and 2 in the placebo group (one death each from pulmonary fibrosis and cardiorespiratory arrest).

Table 3. Adverse Events and Serious Adverse Events.*

Event	Liraglutide (N=2481)			Placebo (N=1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5
Serious adverse events in ≥0.2% of patients	154 (6.2)	194	8.7	62 (5.0)	75	7.0
Cholelithiasis	20 (0.8)	20	0.9	5 (0.4)	5	0.5
Cholecystitis acute	12 (0.5)	12	0.5	0	0	0.0
Osteoarthritis	6 (0.2)	7	0.3	0	0	0.0
Intervertebral disc protrusion	5 (0.2)	5	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	4 (0.2)	4	0.2	0	0	0.0
Cholecystitis	4 (0.2)	4	0.2	0	0	0.0
Breast cancer	4 (0.2)	4	0.2	1 (0.1)	1	0.1
Back pain	2 (0.1)	2	<0.1	2 (0.2)	2	0.2
Uterine leiomyoma	1 (<0.1)	1	<0.1	2 (0.2)	2	0.2
Cellulitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.3
Gastroesophageal reflux disease	0	0	0.0	2 (0.2)	2	0.2
Bronchitis	0	0	0.0	2 (0.2)	2	0.2
Bladder prolapse	0	0	0.0	2 (0.2)	2	0.2
Chest pain	0	0	0.0	3 (0.2)	3	0.3

* Adverse events and serious adverse events that occurred up to and including week 58 among patients in the safety-analysis set are included and are presented by their preferred terms from the Medical Dictionary for Regulatory Activities. Events are included if they had an onset date on or after the first day the study drug was administered and no later than 14 days after the last day the study drug was administered.
† "Pancreatitis acute" was reported as serious by the investigator but was classified as mild according to revised Atlanta classification of acute pancreatitis.[19]

Gallbladder-related events were more common in the liraglutide group than in the placebo group (occurring in 61 of 2481 patients [2.5%], 3.1 events per 100 patient-years of exposure; vs. 12 of 1242 patients [1.0%], 1.4 events per 100 patient-years of exposure), including more cases of cholelithiasis and cholecystitis in the liraglutide group. Most patients who reported cholelithiasis or cholecystitis underwent an elective cholecystectomy (40 of 51 patients [78%] in the liraglutide group and 6 of

8 patients [75%] in the placebo group), and most recovered and continued their assigned course of treatment or had treatment reintroduced after surgery (43 of 51 patients [84%] in the liraglutide group and 6 of 8 patients [75%] in the placebo group). The weight loss among patients with gallbladder-related adverse events was greater than the mean weight loss in the total population (Fig. S8 in the Supplementary Appendix).

The rates of adverse events of pancreatitis (Table S11 in the Supplementary Appendix) and neoplasms were calculated in terms of 100 patient-years at risk, covering the period from the start of treatment until the final contact with the patient (including events that occurred during the second randomized period after the end of the 56-week main study and those that occurred 15 days or more after the last day the study drug was received). Overall, 11 cases of pancreatitis were confirmed by adjudication; these cases occurred in 10 of 2481 patients in the liraglutide group (0.4%; 0.4 events per 100 patient-years at risk), of whom 9 had cases graded as mild,19 and in 1 of 1242 patients in the placebo group (<0.1%; <0.1 events per 100 patient-years at risk). Six patients (5 of whom were in the liraglutide group) had gallstone-related pancreatitis, which was indicated by the presence of gallstones on imaging, alanine aminotransferase levels that were 3 or more times the upper limit of the normal range, or both.20 Increases from baseline to week 56 in mean lipase and amylase activity (12.0 and 3.7 U per liter, respectively) were observed in the liraglutide group, but few patients had a lipase value that was 3 or more times the upper limit of the normal range (62 of 2447 patients [2.5%] in the liraglutide group and 13 of 1220 patients [1.1%] in the placebo group) or an amylase value that was 3 or more times the upper limit of the normal range (5 of 2447 patients [0.2%] in the liraglutide group and 1 of 1220 patients [<0.1%] in the placebo group) at any time during the trial. The positive predictive value of isolated enzyme elevations for diagnosing pancreatitis was low (<1% for a lipase value ≥3 times the upper limit of the normal range; there were no amylase values ≥3 times the upper limit of the normal range among patients who reported pancreatitis).

The mean resting pulse was increased in the liraglutide group by the end of the trial (Table 2). Additional data on vital signs are provided in the Safety Results section in the Supplementary Appendix. Prespecified cardiovascular events (Table S2 in the Supplementary Appendix) occurred in 217 of 2481 patients in the liraglutide group (8.7%; 11.9 events per 100 patient-years of exposure) and in 123 of 1242 patients in the placebo group (9.9%; 14.2 events per 100 patient-years of exposure). The rates of cardiac arrhythmia were similar in the two study groups, although the event rate for tachycardia was higher in the liraglutide group than in the placebo group (0.6 events per 100 patient-years of exposure vs. 0.1 events per 100 patient-years of exposure; all but 1 event in the liraglutide group were nonserious). Two nonfatal myo-

cardial infarctions and one death from cardiovascular causes occurred in the liraglutide group, as compared with one nonfatal myocardial infarction, one nonfatal stroke, and one death from cardiovascular causes in the placebo group.

The incidence of adjudicated and confirmed neoplasms was similar in the liraglutide group and the placebo group (1.9 per 100 patient-years at risk and 2.4 events per 100 patient-years at risk, respectively). A numerical imbalance was observed in the incidence of malignant and premalignant breast neoplasms: 10 events in nine women in the liraglutide group versus 3 events in three women in the placebo group. Most women with events had above-average weight loss (see the Safety Results section in the Supplementary Appendix). There were no cases of medullary thyroid carcinoma or C-cell hyperplasia, and liraglutide treatment did not increase serum calcitonin concentrations.

No clinically relevant between-group differences were observed with respect to mental health assessments, including adverse events related to psychiatric disorders and questionnaire-based depression or suicidal behavior scores (see the Safety Results section in the Supplementary Appendix).

Spontaneous hypoglycemia was reported by 32 of 2481 patients (1.3%) in the liraglutide group and by 13 of 1242 patients (1.0%) in the placebo group (see the Safety Results section in the Supplementary Appendix); no events were serious or required third-party assistance.21

Data on changes in the use of antihypertensive and lipid-lowering medications and additional safety information are provided in the Safety Results section in the Supplementary Appendix, and results from the second randomized period after the end of the 56-week main study are shown in Table S19 in the Supplementary Appendix. No adverse effects with respect to safety variables or cases of binge eating were observed in association with treatment cessation.

DISCUSSION

Liraglutide at a once-daily dose of 3.0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity, was associated with increased weight loss in overweight and obese adults who did not have diabetes, a finding that confirms the findings in previous trials. Liraglutide was shown to be superior to placebo with respect to all three coprimary end points. The treatment effect was similar in patients with prediabetes and those without prediabetes and was similar across baseline BMI categories. The mean change in body weight with liraglutide was −8.0±6.7% (−8.4±7.3 kg) and was generally maintained over the course of the 56-

week main study period, as long as the patients continued treatment.

Liraglutide treatment was associated with reductions in cardiometabolic risk factors, including waist circumference, blood pressure, and inflammatory markers. Modest improvements in fasting lipid levels were also observed, although the clinical relevance of these improvements is uncertain. Furthermore, patients in the liraglutide group had greater reductions in fasting and postprandial glycemic variables and more improvement with respect to beta-cell function and insulin sensitivity than did the placebo group. The combination of weight loss and improved glycemic control probably contributed to the observed reductions in the prevalence of prediabetes and the delayed onset of type 2 diabetes. There were improvements in health-related quality of life, notably physical function, with liraglutide, as compared with placebo.

The safety profile of liraglutide was consistent with findings in previous reports. Gastrointestinal disorders are common and mostly transient side effects of treatment. Gallbladder-related events were more common with liraglutide than with placebo; patients with such events had above-average weight loss, which is consistent with the known risk of gallstones in association with weight loss. Other mechanisms may be involved. In the current trial, half the pancreatitis cases in the liraglutide group were associated with gallstones, and elevations of pancreatic enzymes were not predictive. The lack of a treatment effect on calcitonin concentration and the absence of C-cell hyperplasia or medullary thyroid carcinoma events are consistent with the prior observation that liraglutide exposure is not associated with medullary thyroid carcinoma in humans. The reason for the numerical imbalance in breast neoplasms that we observed is unclear; whether there was enhanced ascertainment related to greater weight loss is unknown.

The clinical relevance of increased resting pulse with liraglutide is unknown but is probably related to the drug class. The presence of glucagon-like peptide-1 receptors on the sinoatrial node suggests a direct chronotropic effect. No increase in the number of serious cardiovascular events was observed in the liraglutide group, and beneficial effects of liraglutide were seen with respect to blood pressure and other cardiometabolic variables.

Limitations of the trial include the use of last-observation-carried-forward imputation in the prespecified primary analyses. However, the robustness of the primary analyses was confirmed in sensitivity analyses with the use of alternative imputation methods to account for patients who withdrew from the trial. Furthermore, no correction for multiple testing was performed for secondary end points. Strengths of the trial include the large sample size, the independent blinded adjudication of

specific adverse events, low attrition rates as compared with other weight-loss trials, and a lifestyle intervention with resultant weight loss.

In conclusion, 3.0 mg of once-daily subcutaneous liraglutide, as an adjunct to diet and exercise, was associated with clinically meaningful weight loss in overweight or obese patients, with concurrent reductions in glycemic variables and multiple cardiometabolic risk factors, as well as improvements in health-related quality of life.

Two Poems

Peter Cole, Xi Chuan, The Paris Review 213

THE UNSURE MORALIST — Peter Cole

after Zuhayr (and Creeley)

I'm tired of life and its troubles.
Whoever lives as long as I have or will
grows weary: it's inevitable.

I've seen the fates trample
the young in the dust, like a blinded camel.
When they strike they can maim and efectively kill;

when they miss — men live on, content if feeble.
A man's true nature in time is revealed,
no matter how hard he tries to conceal it.

I know what's happening now quite well,
and I clearly hear the past's babble.
As for what tomorrow will sell us —

my wisdom's already rubble.

MOURNING PROBLEMS — Xi Chuan

an ant dies, and no one mourns
a bird dies, and no one mourns if it isn't a crested ibis
a monkey dies, and monkeys mourn
a monkey dies, and people pry open its skull
a shark dies, and another shark keeps swimming
a tiger dies, and some people mourning are mourning themselves
a person dies, and some people mourn and some people don't
a person dies, and some people mourn and some even applaud
a generation dies, and the next generation doesn't really mourn
a country dies, most of the time just leaving apocrypha
a country that doesn't leave apocrypha wasn't a real country
if it wasn't a real country, when it dies no one mourns
no one mourns, and the wind blows in vain
rivers low in vain, washing over rocks in vain
glistening in vain, making vain ripples
the river dies, and it's not for man to mourn
the wind dies, and it's not for man to mourn
the river and wind make their way to the sea, the sea as vast as in Zhuangzi
the vast sea dies, and you will have to die
the dragon king dies, and you will have to die
the moon doesn't mourn, there's no one on the moon
the stars don't mourn, the stars aren't lesh and blood