Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A previously healthy 42-year-old man presented with a 20-day history of an expanding, asymptomatic rash on his trunk. The initial lesion had been a red spot on the patient's left side. Ten days after that spot had first appeared, smaller lesions had developed elsewhere. The patient reported no viral prodrome. The skin examination — including the initial lesion that had appeared — is shown. What is the diagnosis? You are offered: Nummular eczema, Pityriasis rosea, Secondary syphilis, Tinea corporis, and Tinea versicolor. Hint: what you see here is called a "herald" patch. Maridebart cafraglutide (known as MariTide) is a long-acting peptide–antibody conjugate (Amgen) that combines glucagon-like peptide-1 receptor agonism and glucose-dependent insulinotropic polypeptide receptor antagonism and that is intended for the treatment of obesity. This material is injected monthly. We inspect a huge study involving obese non-diabetic and type-2 diabetics. MariTide caused remarkable (like other Glp-1 agonists) weight loss, lowered HbA1C, and blood pressure in all groups. Zimislecel (VX-880) is an investigational, allogeneic, stem cell-derived islet cell therapy developed by Vertex Pharmaceuticals for Type-1 Diabetes. In a Phase 1/2 study, a single infusion of zimislecel restored endogenous insulin production, with 10 of 12 participants achieving insulin independence at one year, offering hope for a functional cure for Type-1 diabetes by addressing the underlying cause of the disease. We inspect this 1–2 study of zimislecel in persons with type 1 diabetes. In part A, participants received a half dose of zimislecel (0.4×109 cells) as a single infusion into the portal vein, with an option for a second half dose within 2 years. In parts B and C, participants received a full dose of zimislecel (0.8×109 cells) as a single infusion. All the participants also received glucocorticoid-free immunosuppressive therapy. The primary end point in part A was safety. The primary end point in part C was freedom from severe hypoglycemic events during days 90 through 365, with a glycated hemoglobin level of less than 7% or a decrease of at least 1 percentage point from baseline in the glycated hemoglobin level at one or more time points between days 180 and 365. The results of this small, short-term study involving persons with type 1

diabetes support the hypothesis that zimislecel can restore physiologic islet function. Controversy persists regarding the appropriate duration of therapy with benzathine penicillin G in persons with early (i.e., primary, secondary, or early latent) syphilis (Treponema pallidum infection). Investigators assigned persons who had early syphilis, with or without human immunodeficiency virus (HIV) infection, to receive intramuscular injections of benzathine penicillin G in a one-time dose of 2.4 million units or in doses of 2.4 million units administered at three successive weekly intervals. The primary end point was sero-reversion to nonreactive status or a decrease in the rapid plasma reagin titer by two or more dilutions at 6 months, referred to here as a serologic response (noninferiority margin, 10 percentage points). A key secondary end point was a serologic response within subgroups defined according to HIV status, also assessed in a noninferiority analysis. One-time dose achieved “non-inferiority”. Heparin-induced thrombocytopenia (HIT) is an immune-mediated platelet disorder caused by antibodies that target complexes of platelet factor 4 (PF4) and heparin. HIT has been characterized as a polyclonal immune response; however, studies of other rare anti-PF4 disorders have identified clonally restricted antibodies. Investigators studied the clonality of pathogenic HIT antibodies. Antibodies against PF4–heparin were affinity-purified with the use of PF4–heparin beads from serum samples obtained from nine patients with clinically and serologically confirmed HIT. The pathogenic antibodies in all nine patients with HIT were found to be monoclonal. These findings provide insight into the pathogenesis of HIT and have implications for improved diagnostics and targeted therapeutics. Allogenic transplantation of pancreatic islets (zimislecel) was impressive in patients with Type-1 diabetes. But are there other novel approaches? Investigators report the outcomes of transplantation of genetically modified allogeneic donor islet cells into a man with long-standing type 1 diabetes. They used clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 12b (Cas12b) editing and lentiviral transduction to genetically edit the cells to avoid rejection; the cells were then transplanted into the participant’s forearm muscle. He did not receive any immunosuppressive drugs and, at 12 weeks after transplantation, showed no immune response against the gene-edited cells. C-peptide measurements showed stable and glucose-responsive insulin secretion. A total of four adverse events occurred, none of which were serious or

related to the study drug. The N Engl J Med reviews aortic dissections, particularly type B (distal to the left subclavian artery) dissections. The N Engl J Med patient develops leg pain and a hematoma after using a “massage gun”. She also has gingival bleeding and small perifollicular hemorrhages. But the clinicians did not figure that out until much later. In the Lancet, we learn that guidelines have reduced the goal for blood-pressure lowering to a systolic pressure of 120 mm Hg. Could this intensive treatment cause more harm than good? A meta-analysis of >80,000 patients suggests much good but some harm. Next, a large Chinese trial of influenza vaccine in heart failure again indicates that “flu” vaccine is helpful because hospital admissions are reduced and life is prolonged. Then, the results of the Option-Stemi trial are shown. Should MI patients have solely culprit lesions fixed and a second procedure to deal with everything else later? Or should everything be fixed at one sitting? Immediate complete revascularization was not shown to be non-inferior to staged complete revascularization. The Lancet review is on health and plastics; mostly dreary news is given here. In Science Magazine we learn about the resistance-like molecule Y (RELMy) and its role in myocardial infarction and stroke. In the Washington Post, we are informed that “Gray rocking” is a reasonable psychological strategy to confront “Gas lighting”. Join me on Wednesday, September 10 for the above and more in another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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