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 47-year-old woman presented to the neurology clinic with a 1-month history of worsening headaches associated with blurry vision, galactorrhea, and irregular menstrual cycles. Physical examination was notable for reduced visual acuity of 20/50 in both eyes, with normal visual fields and extraocular movements. Magnetic resonance imaging (MRI) of the head showed a mass protruding from the sella turcica into the suprasellar cistern. Which of the following is the most likely diagnosis? You are offered: Craniopharyngioma, Meningioma, Pituitary macroadenoma, Pituitary metastasis, Optic chiasmic astrocytoma. We review the options. Limited evidence exists to support the simultaneous initiation of sodium–glucose cotransporter-2 inhibitors and finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in persons with chronic kidney disease and type 2 diabetes, albuminuria, and type 2 diabetes, who were already taking a renin–angiotensin system inhibitor, to receive finerenone (with empagliflozin-matching placebo) at a dose of 10 or 20 mg per day, empagliflozin at a dose of 10 mg per day (with finerenone-matching placebo), or a combination of finerenone and empagliflozin. The primary outcome was the relative change in the log-transformed mean urinary albumin-to-creatinine ratio from baseline to 180 days. The combination beat empagliflozin and finerenone alone in lowering both proteinuria and blood pressure. The aminoglycoside antibiotic, streptomycin, was the first antibiotic used against plague. Bubonic plague is a high-consequence infectious disease with epidemic potential. Current treatment guidelines are based on historical weak evidence. Investigators enrolled persons in Madagascar who had clinically suspected bubonic plague during 2020–2024. Using an open-label noninferiority design, they compared two treatments included in the national plague guidelines: oral ciprofloxacin for 10 days (ciprofloxacin monotherapy) or injectable aminoglycoside for 3 days followed by oral ciprofloxacin for 7 days (aminoglycoside–ciprofloxacin). The primary end point was treatment failure defined as death, fever, secondary pneumonic plague, or alternative or prolonged plague treatment. Oral ciprofloxacin was “non-inferior” to ciprofloxacin plus an injected aminoglycoside and far easier to administer.

Estrogen-receptor (ER) positive breast cancer comprises 70% of cases. Response to estrogen deprivation has been known for 60 years, first with oophorectomy, then with selective estrogen-receptor modifiers (SERM), aromatase inhibitor treatment (AIT), and selective estrogen-receptor degraders (SERD). Vepdegestrant is an oral proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader that directly harnesses the ubiquitin–proteasome system. In a phase 3, open-label, randomized trial, investigators enrolled patients with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer who had received one previous line of cyclin-dependent kinase 4 and 6 inhibitor therapy plus one line of endocrine therapy. Patients were randomly to receive vepdegestrant or fulvestrant (SERD), with randomization stratified according to ESR1-mutation status and presence or absence of visceral disease. The primary end point was progression-free survival as assessed by blinded independent central review among the patients with estrogen receptor mutations (ESR1) and among all the patients who underwent randomization. Progression-free survival was estimated with Kaplan–Meier methods and hazard ratios with a stratified Cox proportional-hazards model. Vepdegestrant beat fulvestrant but only in the patients with ESR1 mutations, with a similar side-effect profile. Mutations in ESR1 are the most common mechanism of acquired resistance to treatment with an aromatase inhibitor plus a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor for advanced breast cancer. Camizestrant, a next-generation selective (SERD) degrader and complete ER antagonist, has shown antitumor activity in ER-positive advanced breast cancer. Other investigators now tested patients with advanced breast cancer with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative tumors for ESR1 mutations in circulating tumor DNA (ctDNA) once every 2 to 3 months. Patients who were found to have an ESR1 mutation and did not have radiologic progression were assigned in a 1:1 ratio to switch to camizestrant (75 mg once daily) with a continued CDK4/6 inhibitor plus placebo in place of an aromatase inhibitor or to continue to receive an aromatase inhibitor plus a CDK4/6 inhibitor plus placebo in place of camizestrant. The primary outcome was investigator-assessed progression-free survival. Camizestrant beat the ATI-receiving control group in these ESR1-harboring patients. The N Engl J Med review is on testosterone therapy in “older” men, a condition called “low T” in direct-to-consumer US advertisement. The

N Engl J Med patient is a 76-year-old smoking woman, who recently had severe hyponatremia. She then develops a rather generalized muscular-weakness syndrome. In the Lancet, we confront more estrogen-receptor positive breast cancer. Treatment with the SERM, tamoxifen for about 5 years is routine; duration of treatment is debated. In a meta-analysis of >20,000 ER-receptor positive breast-cancer patients, we learn that AIT should “probably” be continued for another 5 years to minimize recurrence. KRAS is a monomeric G protein, commonly mutated in numerous solid tumors. Adagrasib inhibits the $KRAS^{G12C}$ mutation. In a randomized trial of non-small-cell lung-cancer (NSCLC) patients, adagrasib improved progression-free survival. Rabies is invariably fatal and is endemic in India. Pasteur discovered that drying the spinal cords of rabbits that had died from rabies weakened the virus and introduced this treatment >100 years ago. But passive immunization with an antibody is probably better. Clinicians compared post-exposure prophylaxis regimens. A monoclonal anti-rabies-virus antibody was effective, but a horse-based antibody was also acceptable. Lancet next reviews the general topic if epilepsy. Next, the Lancet reviews vesicular monoamine transport inhibitors, their current uses, and future directions. Alzheimer’s disease (AD) is the most common neurodegenerative disease leading to dementia. A key pathological hallmark of AD is the formation of neuritic plaques composed of aggregated amyloid-β protein (Aβ). The US Food and Drug Administration (FDA)–approved antibody drugs aducanumab, lecanemab, and donanemab have demonstrated modest efficacy in reducing Aβ plaque burden and slowing cognitive decline but do not halt disease progression. How are these antibodies supposed to cross the central-nervous-system’s blood-brain barrier? Earlier, in Science Magazine, we learned that the transferrin receptor could perhaps enable other molecules in crossing the blood-brain barrier. We now learn that a modified antibody against Aβ that uses the transferrin receptor to cross the blood-brain-barrier, substantially improving antibody delivery to the brain in a mouse model of AD. The modified antibody was also associated with markedly reduced incidence of cerebral edema and vascular pathology. The Washington Post reports that ultra-processed foods (previously called junk food) now comprise more than half of consumed calories in the US and almost two-thirds in teenagers. Join me on Wednesday, August 13 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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