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a second patient, the genome of the RPE cell line was sequenced, and a mutation was discovered in a known oncogene. The trial was halted and a decision made to discontinue the effort for customized cell therapy in favor of using RPE cells derived from the national repository of banked iPSC lines which undergo extensive gene sequencing and quality controls. This outcome serves as a caution for the challenges involved in bringing a customized cell therapy to the clinic.

■ ■MESENCHYMAL STEM CELLS By far the largest number of human trials have been performed using MSCs sourced from a variety of sites including bone marrow, periph eral blood, adipose tissue, umbilical cord, and other sites. Interest in the potential utility of MSCs for regenerative therapy began with the optimistic report that bone marrow stem cells were pluripotent and capable of generating nerve and heart muscle as well as blood cells. The possibility that easily obtainable MSCs could be used to regenerate injured or diseased cells or organs to treat diseases ranging from stroke, neurodegenerative disease, myocardial infarct, and even diabetes, generated enormous enthusiasm. The enthusiasm proved irresistible to many, and even after the initial reports were discredited—MSCs turned out not to be pluripotent stem cells as initially thought—a veritable flood of papers began to appear claiming disease-modifying activity of MSCs in mouse models of a wide range of degenerative disease and injury models. But when it became clear that the MSCs were not transforming into or generating new neurons or cardiac myo cytes, alternative mechanisms of action were invoked, including the release of trophic factors, cytokines, or inflammatory modulators that were credited with producing their remarkable restorative effects. The relative ease with which blood or adipose tissue can be harvested from patients or donors and MSCs extracted has led to a rapidly expanding number of clinical trials for conditions ranging from stroke and MS to AD, ALS, and PD. Furthermore, a loophole in the regulatory frame work of the FDA allows autologous cell therapy to escape regulation provided that the cells have not been significantly processed. This lax regulation has spawned a veritable industry of stem cell clinics making unsubstantiated claims of success in treating nervous system diseases. Patients have died from treatments in unregulated clinics operating in countries around the world, and three patients became blind in a well-publicized incident following stem cell treatments delivered by a Florida clinic. The “stem cells” were derived from the patients’ own fat tissue and blood. These activities

represent the dark side of the stem cell revolution perpetrated by practitioners who exploit the desperation of patients and their families. Legitimate and effective stem cell thera pies will emerge over time, but given the prevalence and abundance of misleading information available on the Internet and elsewhere, a trusted and well-informed physician can play a key role in helping patients navigate the current cell therapy minefield. PART 13 Neurologic Disorders ■ ■MSCS FOR TRAUMATIC BRAIN INJURY An allogeneic bone marrow–derived MSC line received conditional marketing approval in Japan in 2024 for the indication of improving chronic motor paralysis resulting from traumatic brain injury. The MSCs were transiently transfecting with the human Notch-1 intracel lular domain gene to promote FDF-2 secretion in order to “enhance their ability to regenerate nerve cells” according to the pharmaceutical company that developed the cell-based therapy. The approval fol lowed results of a phase 2 clinical trial conducted in Japan and the United States. Forty-six patients with moderate to severe traumatic brain injury and chronic motor deficits had MSCs stereotactically infused into an area of encephalomalacia identified on MRI scan while a sham group of 15 patients had burr holes only. The trial met the primary endpoint showing significant improvement in motor function at 24 weeks on the Fugle-Meyer Motor Scale (FMMS) ($p = .04$). Inter estingly, a small improvement was noted in the sham-treated group as well, indicating the presence of a placebo effect. A larger, double-blind, randomized, sham-controlled study is now planned. ■ ■PERSPECTIVE The premise that stem cell biology would herald an era of regenerative medicine has fueled exaggerated claims, false starts, and a proliferation

of bogus clinics. But now we may be on the threshold of a new era of stem cell-based therapies for neurologic diseases and disorders includ ing PD, spinal cord injury, ALS, and epilepsy. Whether this promise becomes reality will depend on the outcome of the first wave of piv otal double-blind controlled trials that are now being conducted or planned. ■ ■FURTHER READING Ayers JI et al: Different α-synuclein prion strains cause dementia with Lewy bodies and multiple system atrophy. Proc Natl Acad Sci USA 119:e2113489119, 2022. Batista AF et al: The importance of complement-mediated immune signaling in Alzheimer’s disease pathogenesis. Int J Mol Sci 25:817, 2024. Carlson GA, Prusiner SB: How an infection of sheep revealed prion mechanisms in Alzheimer’s disease and other neurodegenerative disorders. Int J Mol Sci 22:4861, 2021. Condello C et al: Expanding the prion paradigm to include Parkinson and Alzheimer diseases. JAMA Neurol 81:1023, 2024. Eichmüller OL, Knoblich JA: Human cerebral organoids: A new tool for clinical neurology research. Nat Rev Neurol 18:661, 2022. Garton T et al: Neurodegeneration and demyelination in multiple sclerosis. Neuron 112:3231, 2024. Kandel ER et al (eds): Principles of Neural Science, 6th ed. McGraw Hill, New York, 2021. Kim TW et al: Pluripotent stem cell therapies for Parkinson disease: Present challenges and future opportunities. Front Cell Dev Biol 8:729, 2020. Lee HG et al: Neuroinflammation: An astrocyte perspective. Sci Transl Med 15:eadi7828, 2023. Li Q, Barres BA: Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol 18:225, 2018. Liu L et al: Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS. EBioMedicine 77:103908, 2022. Pallarés-Moratalla C, Bergers G: The ins and outs of microglial cells in brain health and disease. Front Immunol 15:1305087, 2024. Pease-Raissi SE, Chan JR: Building a (w)rapport between neurons and oligodendroglia: Reciprocal interactions underlying adaptive myelination. Neuron 109:1258, 2021. Section 2 Diseases of the Central Nervous System Patricia Dugan, Vikram R. Rao

Seizures and Epilepsy A seizure (from the Latin sacire, “to take possession of”) is a transient occurrence of signs or symptoms due to abnormal excessive or syn chronous neuronal activity in the brain. Depending on the distribution of discharges, this abnormal brain activity can have

various manifesta tions, ranging from dramatic convulsive activity to experiential phe nomena not readily discernible by an observer. Although a variety of factors influence the incidence and prevalence of seizures, ~5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood. The meaning of the term seizure needs to be carefully distinguished from that of epilepsy. Epilepsy describes a condition in which a person has a risk of recurrent seizures due to a chronic, underlying process. This definition implies that a person with a single seizure, or recurrent

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Revision #1
Created 2026-01-06 16:35:41 UTC by Omar Ayman
Updated 2026-01-06 16:35:41 UTC by Omar Ayman