develop initially as gadolinium-enhancing lesions and have about a 50% chance of being either transient, that is, lasting 6–12 months, or being permanent (107).

i. Results From the Gold Study

Gold et al. (108) conducted a clinical trial on subjects with relapsing-remitting multiple sclerosis. The study drug was dimethyl fumarate (Tecfidera®). The control arm received placebo. The drug had its origin in Germany during the 1950s, when it was thought (incorrectly) that psoriasis resulted from disruptions in the Krebs cycle (109) and because of the realization that the Krebs cycle includes fumarate as an intermediate (110). Psoriasis and multiple sclerosis are both autoimmune diseases.

The mechanism of action of dimethyl fumarate involves its influence on shifting lymphocytes in the body from expressing Th1-type cytokines to Th2-type cytokines. Also, dimethyl fumarate appears to stimulate a pathway that reduces the concentration of toxic oxygen, such as nitric oxide, hydrogen peroxide, and peroxynitrate. By stimulating the Nrf2 antioxidant response pathway, dimethyl fumarate reduces toxic oxygen, and thus reduces toxic oxygen's destruction of nerve tissue.

The Gold study enrolled 1237 subjects, and 952 subjects completed the trial. The researchers were careful to note that the rate of discontinuation was similar in the study drug arm (31%) and in the placebo arm (35%). The primary endpoint was:

- Percent of subjects having a relapse by 2 years into the study.

The secondary endpoints were:

- Number of new or enlarging lesions (mean number of lesions per subject). The Supplementary Appendix broke down the number of patients, in the study drug arm and the placebo arm, having zero lesions, one lesion, two lesions, three to four lesions, or five or more lesions.
- Total number of relapses divided by patient-years.
- The endpoint was the percent of patients that progressed to disability, according to the EDSS scale.

In greater detail, "relapse" was defined as new or recurrent neurological symptoms that lasted for at least 24 h, and that were accompanied by new objective neurological findings.

The Clinical Study Protocol (111) provided general information on the characteristics of a relapse, which is reproduced in the footnote (112). The Clinical Study Protocol is available on

[107]Neema M, Stankiewicz J, Arora A, Guss ZD, Bakshi R. MRI in multiple sclerosis: what's inside the toolbox? Neurotherapeutics 2007;4:602–17.

[108]Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. New Engl. J. Med. 2012;367:1098–107.

[109]Meissner M, et al. Dimethyl fumarate—only an anti-psoriatic medication? J. Dtsch. Dermatol. Ges. 2012;10:793–801.

[110]Krebs HA, Eggleston LV. The oxidation of pyruvate in pigeon breast muscle. Biochem. J. 1940;34:442–59.

[111]Clinical Study Protocol no. 109MS301 (ver. 6). Biogen IDEC (May 26, 2010).

[112]"Subjects with relapsing-remitting MS experience discrete episodes of neurologic dysfunction (referred to as relapses, exacerbations, or attacks), each lasting several days to several weeks, which occur intermittently over many years. Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Early in the course of this phase of the disease, these symptoms tend to subside completely after each attack. Over time, recovery from attacks tends to be incomplete, leading to the accumulation of functional disability."