DATATOP AND ITS FOLLOW-ON PROTOCOLS

DATATOP (**D**eprenyl **A**nd **T**ocopherol **A**ntioxidative **T**herapy **O**f **P**arkinsonism), led by Ira Shoulson, MD, and Stanley Fahn, MD, and sponsored by NINDS, is the largest and longest prospective controlled study of therapeutic interventions in Parkinson's disease conducted in the world. It was the first of PSG's multi-center trials.

The original cohort of 800 subjects in DATATOP represents the largest group of early Parkinson's disease patients to be followed prospectively and systematically. In-person evaluations of this cohort began in 1987 and continued under several government and industry-sponsored protocols (described below) until 1995. Organized follow-up concluded in 1997 after two additional years of telephone ascertainment of vital status. Thus, the term "DATATOP" refers specifically to the initial NIH-sponsored trial and generically to the decade of follow-up of the initial cohort throughout the subsequent trials.

DATATOP. The NIH-sponsored DATATOP trial was carried out to determine whether long-term therapy with deprenyl (selegiline) and/or tocopherol would extend the time before advancing disability required the initiation of levodopa therapy in patients with early, untreated Parkinson's disease. Deprenyl, 10 mg/day, was found to significantly delay the initiation of levodopa. Tocopherol, 2000 IU/day, produced no benefits and there was no interaction of the two drugs.

PEP. The DATATOP study was designed to follow subjects for up to 24 months from the time of enrollment into the study. Subjects who reached endpoint (need for levodopa treatment) prior to completion of 24 months were given the opportunity to be re-started in blinded fashion on their previously assigned study drugs for the balance of their 24-month enrollment period. The purpose of this study, called PEP (Preliminary Endpoint Protocol), was to investigate the effectiveness of deprenyl and/or tocopherol, used in combination with levodopa (Sinemet), in delaying the onset and reducing the severity of levodopa-related adverse effects (wearing-off, on-off, toxicity). Of the original 800 DATATOP subjects, 191 subjects were followed in PEP beginning in May 1988.

DATX & PEPX. When a preliminary analysis indicated the significant benefit of deprenyl in postponing the need for levodopa in otherwise untreated patients with early PD, the DATATOP and PEP protocols were modified to allow all subjects to cross over in blinded fashion to active deprenyl while remaining on their blinded

assignment for tocopherol/placebo. Beginning in August 1989, 367 DATATOP subjects not requiring levodopa were enrolled in DATX and 240 subjects who had required levodopa were enrolled in PEPX. The results of DATX and PEPX were published in Annals of Neurology in 1996, indicating that the initial advantage of deprenyl in delaying the need for levodopa treatment was not sustained and that prior treatment with deprenyl or tocopherol did not reduce the occurrence of subsequent levodopa-associated adverse effects.

DATE. At the completion of the NIH-funded DATATOP/PEP/DATX/PEPX studies, an open-label observational study of the long-term effects of deprenyl in early Parkinson's disease continued under the leadership of Ira Shoulson and Stanley Fahn. DATE (DATATOP EXTENSION) was designed to evaluate the long-term effects of deprenyl prior to and following the need for levodopa or dopamine agonists. In 1991, consenting subjects who were still active in DATX (214) or PEPX (347) continued with open-label administration of deprenyl. Open-label tocopherol was prescribed at the investigator's discretion. Subjects who developed the need for an agonist during the study were randomly assigned to either bromocriptine (Parlodel) or pergolide (Permax). Additional financial support for DATE was provided by Somerset Pharmaceuticals.

BLIND-DATE. By 1993 the vast majority of the DATATOP subjects were being treated with levodopa. In order to examine in a controlled fashion the long-term effects of deprenyl on the course of levodopa-treated Parkinson's disease, DATE subjects, beginning in April 1993, consented to enroll in BLIND-DATE ("**BLIND**ed Withdrawal of Deprenyl in the **DAT**ATOP **E**xtension"). In this trial, supported primarily by Somerset Pharmaceuticals, 368 subjects were randomized to continue or withdraw from deprenyl (selegiline) treatment while remaining on levodopa. After two years of prospective follow up, sustained deprenyl therapy was found to accelerate the occurrence of dyskinesias but postpone on-off motor fluctuations and freezing of gait. A full report is in preparation.

Vital Status. At the conclusion of BLIND-DATE in 1995, active subjects and original DATATOP subjects who were no longer trial participants, were invited to return for a final in-person evaluation and consent to contribute a blood DNA sample. Four hundred sixty-eight of the original 800 subjects provided this valuable data. In both 1996 and 1997 investigators and coordinators mounted a telephone ascertainment of the status of the 800 DATATOP subjects. Neither deprenyl nor tocopheral significantly affected mortality; however, the DATATOP cohort as a whole had a remarkably low mortality

rate, about the same as age-matched persons without Parkinson's disease (March 1998 issue of Annals of Neurology).

A summary of the collective findings of the DATATOP protocols was published in 1998 in Annals of Neurology. PSG Investigators are continuing to explore the wealth of clinical, biological, and genetic data collected over the years of DATATOP and its follow-on protocols.

DATE-MATE

DATE-MATE, led by Julie Carter, RN, ANP, Barbara Stewart, RN, PhD, and Pat Archbold, RN, DNSc, FAAN, and sponsored by the Parkinson Study Group, Medical Research Foundation of Oregon, American Parkinson's Disease Association, and the Oregon Chapter of American Parkinson's Disease Association, was a longitudinal study of spouse caregivers of patients participating in the DATATOP trial. The purpose of this study of 321 spouses was to examine how the consequences and outcomes of caregiving in the healthy spouse are affected by the progression of PD. The PSG report (Carter JH, primary author), "Living with a Person with Parkinson's Disease: The Spouse's Perspective by Stage of Disease", was published in the January 1998 issue of Movement Disorders. Data analysis is continuing and a second report is being prepared for publication.