

THE COUNCIL FOR TOBACCO RESEARCH--U.S.A., INC.

July 12, 1979

MEMORANDUM

TO: Drs. Bing, Ford, Hockett, Jacobson and Stone

FROM: W. U. Gardner

SUBJECT: Application 1279.
Walter B. Essman, M.D., Ph.D., Queens College, City University of
New York, Flushing.
"Smoke Effects on Fetal Brain."

During the past year Dr. Essman has been permitted to retain the unexpended balance of his last grant to finish some of the work that he had started. He has published or submitted for publication 5 different chapters or sections to monographs on a range of subjects including early development and drug actions and thyroid medullary tumors. It is difficult to determine in most of these just how much is review and how much is the presentation of new data. (See item 13, publications, in his application for the titles.)

Proposal. This is a proposal to study the effects of cigarette smoke/nicotine exposure (cs/n) during pregnancy on the subsequent development of the young, both behavioral and physiological aspects. The former will be delivered by a Walton vertical(?) smoking machine, and the latter by i.p. injections several times daily. The test animals to be used are the CF-Is mice maintained in their vivarium since 1967 (derived from Swiss mice at Carworth Farms). I cannot be sure of the schedule of the treatments but it seems that different amounts of either cigarette smoke or air or nicotine and saline will be given during each of the trimesters of pregnancy and for each of the 3 weeks following pregnancy and hence during nursing. Mice will be killed at birth, 21 days of age and then at 2 week intervals until 77 days old. Weights of the mice and some of the brain components -- cerebral cortex, diencephalon and a number of its components, hippocampus, septal area, fornix and cerebellar cortex.

Additional end-points will be the levels of norepinephrine (NE), dopamine (DA), serotonin (5HT) in the different brain components, the amount of protein synthesis as estimated by ³H-leucine uptake. All will be expressed as percent differences from control. Three different behavioral tests will be done: passive avoidance, barbiturate sleeping time, and seizure susceptibility.

The chemical changes or differences will be determined on enriched fractions of glial and synaptosomal and mitochondrial components expressed in relation to controls. These techniques, with modifications to determine turnover rates have been used in the applicant's laboratory for a number of years. He also shows some data for smoke-exposed mice, reporting levels of GABA and histamine and effects on levels of serum prolactin.

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A large number of papers have been published on the effects of maternal smoking on fetal development; some have implied a nicotine effect, some a CO effect, some a pituitary-hypothalamic effect. Passive smoking effects have been referred to. The most consistent observation in man has been the small-for-age of the babies of smoking mothers and possibly a slightly higher neonatal mortality. Nutritional, socioeconomic, age, drug use, extra-marital pregnancy, etc., form many epidemiological studies.

Animal studies have been difficult to evaluate when convulsive or nearly convulsive doses of nicotine have been used in one or more injections per day. It is difficult to control for the stress factor in experimental animals have been exposed to cigarette smoke.

It is my impression that the work being done by Collins and by Peterson and Erwin at Colorado and by Fuxe at The Karolinska may be more enlightening. The placental ACh levels (Rama Sastry) and placental protease and protease inhibitor levels (Kullander) might also be followed up.

W. U. Gardner

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