731-631

April 19, 1973

Seymour Kety, M.D.,
Professor of Psychiatry,
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Fruit Street,
Boston, Mass. 02124.

Dear Seymour,

Since reading the summary of the ECT conference, I have had time to reflect on the conclusions. I am writing to raise some questions, not about the summary presentation, but the conclusion of the role of cholinergic mechanisms. As I understand the relevant paragraphs (pages 5-6), the data for the role for acetylcholine are unimpressive, and do not meet the criteria for relevance, set forth in your earlier paragraphs. The paragraph focuses on the report by Karczmar.

Some years ago I reviewed the data relevant for a cholinergic hypothesis. (1) I found the changes in cholinergic measures to have a time course similar to the behavioral (and electrographic) effects. (2) Specificity was hard to demonstrate, but cerebral trauma and neurological illnesses did not exhibit the same cholinergic effects of seizures. (3) Using anticholinergic drugs, I was able to reverse the electrographic and behavioral effects of ECT. The data are not overwhelming, but taken as a whole, the data impressed me that cholinergic mechanisms were relevant to the ECT process.

An objection to the hypothesis is that anticholinergic drugs, like Ditran, have clinical antidepressant activity; and the suggestion I made in 1958 that imipramine has anticholinergic activity also reflects on a cholinergic hypothesis.

In your summary in Dorado Beach, you viewed acetylcholine as relevant to the seizure threshold and as reflecting the widespread activation of neurons, without specificity. I thought then that your argument was cogent. Particularly, that acetylcholine, as an ubiquitous transmitter, may reflect the impact of the massive discharges occasioned by the seizure-inducing agent. But this hypothesis, of non-specificity, is

on no more substantial footing than the suggestions of specificity. Indeed, the more prudent course may be not to anticipate which neurohumor is the more important, but to reflect on all.

The evidence for the role of biogenic amines and changes in protein synthesis in ECT is well documented. In part, this may reflect the availability of adequate and technically simple methods of analysis. In considering the cholinergic hypothesis, we are faced by the technical problems and inaccuracy of bioassay methods. Such difficulty must have contributed to the paucity of studies in ECT. I know that this technical difficulty has severely impeded my studies, for when we did bioassays for ACh, we found them too unreliable. But, from this vantage point, descriptions of improved methods for assaying acetylcholine (gas chromatography - mass spectrometry as described by Jenden at the ACNP in 1972, is an example) encourage me that more adequate tests of cholinergic hypotheses in ECT are feasible.

Your summary will be read and as your opinion is highly valued, your conclusions may influence further studies of ECT. Alex did not present the cholinergic data well; and I cannot do better.

Presuming on our companionship, I am enclosing a copy of my 1966 summary. The data are meager, but may be sufficient to quicken your interest in presenting the cholinergic data with slightly more optimism. Should you wish to do so, fine; should you wish to ignore this point, I will not be offended.

The volume is almost complete, and once again I thank you for your advice and encouragement.

My best regards,

Sincerely yours,

Max Fink, M.D.

MF/ij
Enc.