

This Week's Citation Classic®

Guth P S & Spirtes M A. The phenothiazine tranquilizers: biochemical and biophysical actions. *Int. Rev. Neurobiol.* 7:231-78, 1964.

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This article attempted to unify the array of findings in the phenothiazine literature. The central theme was that phenothiazines produce alterations in membrane permeability as their mode of action. Any therapeutically useful activity would derive from the patterns of localization within the body, especially within the brain. [The SCI® indicates that this paper has been cited in over 160 publications.]

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The subject of my PhD dissertation was the phenothiazines (PTs), and Morris Albert Spirtes (1911-1981) was my mentor. In 1955 the PTs were brand new and Morris said, "Let's just see what they do." The literature was soon filled with papers reporting what one PT, chlorpromazine (CPZ), did to this or that biochemical system. Within just a few years, the volume of CPZ literature became overwhelming and, to these young eyes, seemed impossible to unify or make coherent. In fact, Morris thought that CPZ should be renamed *Duz* since according to a commercial then current "Duz does everything."

Somehow the notion grew between us (I suspect that it was mostly Morris's) that the PTs must be affecting some property common to all those biochemical systems. Examination of the literature revealed that most studies used enzyme systems within membranes—whole cells, mitochondria, or intact tissue—rather than isolated enzymes. The property common to these studies and affected by the PTs might be membrane permeability. After all, if one is studying enzymatic activity within an organelle, then the added substrate must diffuse into and the product diffuse out of that organelle.

The PTs might inhibit such diffusion and cause an *apparent* inhibition of enzymatic activity.

Morris and I demonstrated that PTs did affect the membrane permeability of mitochondria, erythrocytes, lysosomes, and synaptosomes, while other investigators showed similar effects on other membranes. (I was so certain of the membrane-stabilizing effect of CPZ that I had my son, as a science fair project, use the drug to prevent the anoxic sickling of sickle-trait erythrocytes. It worked!)

If the PTs were acting on membranes generally, from whence came their specificity (i.e., why are some antipsychotic and others antihistaminic)? The answer might lie in the different patterns of distribution within the brain. I reported in this article that two antipsychotic PTs had very similar patterns of distribution while a nonantipsychotic PT of similar structure (thiethylperazine) had quite a different pattern. (The accepted orthodoxy now is that the phenothiazines act as antipsychotic agents by antagonizing the neurotransmitter dopamine; this notion was put forward by Matthyse by 1973 and there has been nothing new since.¹)

Some years after the *Classic* article was written, Philip Seeman published a review dealing with PT-membrane interactions.² The baton then clearly passed to him, and he since has done much more and with greater sophistication than we ever did.

In the late 1960s, I made the decision to quit PT research. That decision was made partly because I became interested in other fields and partly because I realized that when the causes of psychotic derangements were understood, specific therapy would replace the symptomatic treatment offered by the PTs. The antipsychotic PTs would then vanish from use. On the other hand, a study of *physiological* processes would yield results and, perhaps, concepts for the ages. I am now studying auditory and vestibular neurotransmission. Of course, the PTs and symptomatic treatment of psychiatric disorders are still with us.

1. Matthyse S. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? *Fed. Proc.* 32:200-5, 1973. (Cited 250 times.)

2. Seeman P. The membrane actions of anesthetics and tranquilizers. *Pharmacol. Rev.* 24:583-655, 1972. (Cited 1,885 times.) [See also commentary in: *Contemporary classics in the life sciences. Volume 1: cell biology.* Philadelphia: ISI Press, 1986. p. 307.]

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