THYROID-IMIPRAMINE INTERACTION:

CLINICAL RESULTS AND BASIC MECHANISM


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In recent years, our group has drawn attention to a new phenomenon that can be described quite simply. Patients with primary depression recover more quickly if, to a usual regimen of imipramine, one adds a small dose of thyroid hormone, L-triiodothyronine (T3) (Prange et al. 1968; Prange et al. 1969; Wilson et al. 1970; Prange et al. 1970). Since then we have worked in two directions in both our clinic and our laboratory. We have explored the clinical dimensions of our finding and have tried simultaneously to elucidate the mechanisms that underlie it. This paper will outline the phenomenon briefly and then discuss one of our attempts to understand it. In another paper (Prange, Wilson, and Lipton, in preparation) we shall publish data that verify the following qualifications:

1. When imipramine alone is given, men respond much faster than women.
2. When T3 is added to imipramine, women benefit enormously and men benefit little, if at all.
3. Whether patients are retarded or agitated has no influence on the T3 phenomenon, though it has some influence on basic response to imipramine.

We have learned other things about the tricyclic-T3 interaction. It is not limited to imipramine. In a double-blind study of

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outpatients, Wheatley (manuscript in preparation) showed that it pertains to amitriptyline, and Earle (1970) showed in an open trial that it pertains to other tricyclic drugs as well, including demethylated tricyclics. T3 potentiation even extends to some aspects of phenothiazine action in animals, as Park, Prange, and Happy (manuscript in preparation) have discovered in our laboratories.

Clearly, more than one drug may interact with T3. In addition, hormones other than T3 may interact with imipramine. McClure and Cleghorn (1968) believe that imipramine action in depression can be potentiated by the synthetic adrenal steroid, dexamethasone. Thyroid-stimulating hormone (TSH) will serve the purpose, as Figure 1 shows.

We have published a complete report of the clinical aspects of this study (Prange et al. 1970). Here it is necessary to note only that patients who received TSH improved very rapidly, and that the week of maximum improvement correlated well with the week of maximum thyroid stimulation.

Figure 2 shows that on Hamilton's retardation factor and his agitation factor (Hamilton 1960) patients are benefited equally by TSH.

Regarding possible mechanisms, we have an embarrassment of potential riches. In our view, the first question to be answered is whether depressed patients are truly euthyroid, that is, whether for each patient the balance between tissue need and tissue supply is ideal. We have a variety of evidence (Prange et al. 1969; Wilson et al. 1970; Prange et al. 1970), all of it unfortunately indirect, that in depressed women there is less thyroid hormone delivered than is required. But whatever the thyroid state of depressed patients, one must still ask what it is that a small dose of thyroid hormone does in the presence of imipramine that is antidepressant.

Thyroid hormone could have an effect on imipramine metabolism. The hormone could affect the uptake, distribution, or removal of the drug. We have some weak inferential evidence that this occurs in animals (Prange and Lipton 1962; Prange, Lipton, and Love 1963 and 1964), but somewhat stronger evidence in animals and in man that, in the dose range that interests us, a hormone effect on drug metabolism is unimportant.

There are a number of reasons to examine thyroid-amine interactions. Interactions between catecholamines and thyroid hormones are not only numerous but venerable. Goetsch showed in 1918 that an epinephrine infusion could be used to diagnose hyperthyroidism. The interactions of indoleamines with thyroid hormones are less well