total time in mental hospitals × 100
(age on 30 January, 1965) minus (age at first psychiatric consultation)

This correlation coefficient came to −0·11.

We concluded from this that the patients who first received phenothiazines at early ages did not do significantly better or worse than those who first received them at later ages.

Since our basic assumptions may have been incorrect, we cannot regard these negative findings as disproving the hypothesis stated.

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GENETIC POLYMORPHISM IN METABOLISM OF PHENELZINE

DEAR SIR,

A current problem in clinical psychiatry is to account for the variability in the response of patients to individual antidepressant drugs. One factor which has so far not received much attention is the possibility of individual or group variations in the rate of metabolism of the drug within the body. We should therefore be grateful for the hospitality of your columns to bring briefly to the attention of your readers our recently published observations on the influence of a genetic enzyme polymorphism on the treatment of depression with phenelzine (Nardil) (1).

Our hypothesis derives from the observation that the anti-tuberculous drug, isoniazid, is metabolized at two different rates, so that human beings are clearly divisible into either slow or rapid inactivators, slow inactivation being a Mendelian recessive factor. This polymorphism depends on the activity of liver acetyl transferase and is also shown by sulphamethazine and hydrallazine. As phenelzine possesses a mono-substituted hydrazine chain similar to isoniazid (Fig. 1) we suggest that it may be subject to the same acetylator polymorphism. Technical considerations made direct testing of this hypothesis impossible, but instead observations were made on depressed patients receiving phenelzine therapy who were previously phenotyped as slow or rapid acetylators using isoniazid.

Forty-seven previously untreated out-patients with a diagnosis of neurotic (24) or endogenous (23) depression were rated on the Hamilton and Hildreth scales before and after 4 weeks' treatment with

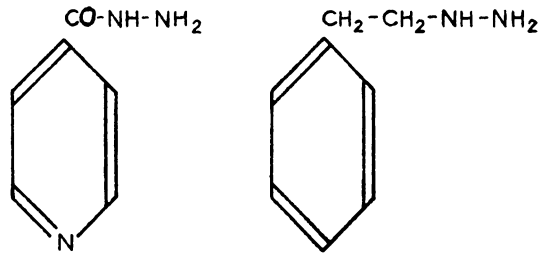

FIG. 1.—The structural formulae of isoniazid and phenelzine.

phenelzine 15 mg. t.i.d. In addition, the day on which subjective improvement was first noticed and the occurrence of side-effects, rated as mild or severe, were noted. The phenotyping procedure was carried out before the commencement of treatment, but the results were concealed from the clinicians until the end of the experiment. There were 30 slow (15 neurotic, 15 endogenous) and 17 rapid (9 neurotic, 8 endogenous) acetylators.

The only statistically significant finding was the occurrence of "severe" side effects in nine patients, all of whom were slow acetylators ($p < 0.05$). Other trends which did not reach the 5 per cent. level of statistical significance were a tendency for slow acetylators to respond to phenelzine better, and, for endogenous depression, more quickly, than rapid acetylators.

The results observed, although not conclusive, are in keeping with the hypothesis that phenelzine is subject to polymorphic acetylation in human populations and this has therapeutic relevance.

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REFERENCE

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