correspondence

total time in mental hospitals \times 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.

David Peter Birkett.
Robert Sheldon Gantz.
Fairfield Hills Hospital,
Newtown,
Connecticut.

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 hydralazine. 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
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,
al 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.

K. Davison.

Department of Psychological Medicine,
Newcastle University.

R. T. C. Pratt.

Institute of Neurology,
Queen Square,

D. A. Price Evans.

Department of Medicine,
Liverpool University.

Reference

1. Evans, D. A. P., Davison, K., and Pratt, R. T. C.
(1965). "The influence of acetylator phenotype
on the effects of treating depression with
phenelzine." Clin. Pharmacol. and Therap., 6,
430-435.