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ANTIDEPRESSANT DRUGS AND EXCESSIVE WEIGHT GAIN

DEAR SIR,

In their paper, 'Treatment of phobic reactions with antidepressants' (*Journal*, April 1970, **116**, 387), Kelly *et al.* note that 'A troublesome problem was excessive weight gain due to a craving for carbohydrates produced by the antidepressants'.

Excessive weight gain is a well-established side effect of tricyclic antidepressants (especially amitriptyline). When these drugs are combined with MAO inhibitors increase in weight can sometimes be extreme (Gander, 1965; Dally, 1967; Pare, 1968; Winston, 1971). Gander has graphically described the typical syndrome of intense hunger and a craving for sweet foods. This may result in uncontrollable increase in weight, often up to 25 kilos or more in a few months. However, the same phenomenon has been noted with the use of amitriptyline alone (Arenillas, 1964). Dally notes that amitriptyline causes the patient to feel excessively hungry and he suggests that this is due to disturbance of central weight regulating mechanisms. Although Gander has stressed the need for biochemical investigation into this phenomenon the cause remains obscure.

While this property of antidepressant drugs is no doubt of value in the treatment of patients who are underweight, obesity can be troublesome in some cases and may lead to the drugs being discontinued prematurely. Exhortations to diet are often of little avail, especially if there is an underlying metabolic cause for the increased appetite.

This symptom of excessive hunger combined with a craving for carbohydrates suggests a relative borderline fasting hypoglycaemia, and one may speculate whether it is caused by increased levels of circulating insulin.

One of the most important pharmacological properties of the tricyclic antidepressants is the inhibition of the uptake of norepinephrine into adrenergic cells (Sigg, 1959; Axelrod *et al.*, 1961). However, a secondary property is the blocking of alpha adrenergic receptors (Hurlimann *et al.*, 1967). Thus the total concentration of norepinephrine may be increased while at the same time alpha adrenergic blockage increases the relative beta adrenergic effects.

Presumably the addition of an MAO inhibitor, by further increasing the norepinephrine concentration, will again intensify the beta adrenergic effects.

In vitro studies on isolated rat pancreas have shown that simulation of the beta adrenergic receptor increases, and stimulation of the alpha adrenergic receptor inhibits insulin secretion (Turtle *et al.*, 1967; Malaisse *et al.*, 1967; Malaisse *et al.*, 1967). (Porte (1967) has shown that in man any drug that increases the alpha adrenergic effects of epinephrine or norepinephrine *inhibits* insulin release, and conversely any drug that increases the beta adrenergic effects of epinephrine or norepinephrine *stimulates* insulin release. Therefore we postulate a possible peripheral mechanism, by contrast to a central one. for obesity; specifically an increase in circulating insulin.

We chose two patients receiving combined antidepressants for an extended period who had gained over 24 kilos in weight and one patient whose weight gain was much less marked though on similar drugs. Assays for fasting serum insulin were performed to determine whether the results might be compatible with the above hypothesis.

Patients Nos. 1 and 2 fall between the 84th and 97th percentile and patient No. 3 below the 50th percentile for fasting serum insulin.

These results, while limited, suggest a corre ation between weight gain and level of fasting serum insulin. The raised levels of serum insulin do not in themselves imply primary augmented insulin release. They could possibly result from increased food intake consequent upon interference with the appetite centre in the brain (Dally, 1967).

However, it is more likely that they are the result of augmented insulin release by direct action on the pancreas by the tricyclic antidepressant via the mechanism outlined above. To test this hypothesis it would be necessary to demonstrate normal fasting insulin levels prior to therapy, and a more definitive test for augmented insulin release during therapy while the patient's caloric intake remained constant. The purpose of this report is to suggest that further study as outlined may prove this hypothesis to be true.

It has recently been suggested (Schuckit *et al.*,

TABLE I
Results

Patient	Maximum daily dose of antidepressants	Treatment in months	Original weight (kilos)	Maximum weight gain (kilos)	Fasting serum Insulin
1.	Tranylcypromine .. .. 30 mg. Amitriptyline .. .. 100 mg.	18	72	24	30 micro U/ml.
2.	Isocarboxazid .. .. 15 mg. Amitriptyline .. .. 100 mg.	12	50	32	37 micro U/ml.
3.	Isocarboxazid .. .. 15 mg. Amitriptyline .. .. 100 mg.	10	55	7	6 micro U/ml.

1971) that the combination of MAO inhibitors with tricyclic antidepressants may become a routine regime. Should this happen, the problem of weight will become of considerable import, since excessive weight gain, if not immediately dangerous, is undesirable and not without serious implications. Kline (1969) suggests that since much of the overwhelming compulsion to eat occurs at night a hypnotic might be given before the hunger sets in. This method has certain obvious disadvantages. Another possible method of minimizing excessive weight gain might be an alteration of the ratio of tricyclic antidepressant to MAO inhibitor. When patient No. 2 was changed to isocarboxazid 30 mg. and amitriptyline 25 mg. she lost 8 kilos in the next two months. In patient No. 3 reduction of amitriptyline to 50 mg. daily resulted in her weight returning to normal. Though she still experienced pangs of intense hunger from time to time she was able to keep her weight down by diet.

Since drugs which increase the relative alpha (insulin inhibitory) as contrasted to the beta (insulin stimulatory) adrenergic effects may prevent obesity and *vice versa*, it is theoretically possible that the giving of propranalol or other beta adrenergic blocker may prevent the excessive weight gain in certain selected cases. However, the safety of such a procedure has yet to be determined, and it must be pointed out that at present adrenergic augmenting psychotropic drugs (including MAO inhibitors) are listed as contraindications to propranalol.

[Serum insulin assays were performed through the courtesy of Dr. Richard Guthrie, University of Missouri School of Medicine.]

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