WHAT ARE TRICYCLIC ANTIDEPRESSANT DRUGS?

The term 'tricyclic' relating to antidepressant drugs was restricted for 12 to 15 years to those compounds containing two benzene rings fused to a central seven-membered ring, the prototypes being imipramine and amitriptyline. This usage has been recognized by pharmacologists and psychiatrists alike and it is generally accepted that this class of compounds has some specific effect in the treatment of endogenous or psychotic depressive illnesses.

The recent extension to include compounds such as iprindole (Prondol, Wyeth) and maprotiline or 34276-Ba (Ludiomil, Ciba-Geigy) involves a devaluation of a term which had previously been meaningful, since evidence that either of the compounds mentioned possess the specific efficacy of the earlier tricyclic drugs is so far inadequate.

Briant & George (1974) in a recent paper in this journal describe iprindole as a tricyclic compound which compares favourably with imipramine in antidepressant activity (but) has no significant effect on the peripheral uptake of amines. They refer to the data of Fann, Davis, Janowsky, Kaufmann, Griffith & Oates (1972) which led these authors to question the validity of the amine hypothesis of endogenous depression. We have confirmed their pharmacological finding that iprindole does not inhibit the uptake of 5-HT by human platelets at therapeutic plasma concentrations (Campbell & Todrick, 1973), but do not wholly accept the relevance of the clinical evidence which they cite.

Fann *et al.* (1972) quote nine clinical papers (repeated in Fann, Davis Janowsky, Kaufmann, Cavanaugh & Oates, 1974). Five of these appear to relate to out-patients: in at least four the patient population was not homogeneous but was a mixture of endogenous and 'reactive' depressions; the possibility has to be excluded that iprindole may have been more successful in the latter states (and imipramine in the former). The paper by Rickels, Gordon, Meckelnburg, Sablosky, Whalen & Dion (1968) specifically states that the diagnosis was neurotic depression.

Five papers compared iprindole with imipramine. McClatchey, Moffat & Irvine (1967) found both slightly superior to placebo but this was not statistically significant. Johnson & Maden (1970) found the drugs equal in out-patients. Sutherland, Sutherland & Phillip (1967) found imipramine slightly but not significantly better. Imlah, Murphy & Mellor (1968) found the drugs

equal as did El-Deiry, Forrest & Littmann (1967). One group (Sterlin, Lehmann, Oliveros, Ban & Saxena, 1968) found amitriptyline slightly more effective than iprindole.

In none of these trials does the comparison seem to have been made in a homogeneous sample of major endogenous depressions. Only such evidence can have relevance to the amine hypothesis of depression which, so far as we know, has never been seriously extended to neurotic reactions with (some) depressive affect.

In the light of the adequate evidence in favour of an amine hypothesis of depression, Briant & George's (1974) forecast, that effective anti-depressants without significant action on peripheral amine uptake might be developed, appears premature.

A.C.TAIT & A. TODRICK

Crichton Royal Hospital, Dumfries DG1 4TG

Received August 16, 1974

References

- BRIANT, R.H. & GEORGE, C.F. (1974). The assessment of potential drug interactions with a new tricyclic antidepressant drug. *Br. J. clin. Pharmac.*, **1**, 113-118.
- CAMPBELL, I.C. & TODRICK, A. (1973). On the pharmacology and biochemistry of the amine-uptake mechanism in human blood platelets. *Br. J. Pharmac.*, **49**, 279-287.
- EL-DEIRY, N.K., FORREST, A.D. & LITTMANN, S.K. (1967). Clinical trial of a new antidepressant (WY 3263). *Br. J. Psychiat.*, **113**, 999-1004.
- FANN, W.E., DAVIS, J.M., JANOWSKY, D.S., KAUFMANN, J.S., GRIFFITH, J.D. & OATES, J.A. (1972). Effect of iprindole on amine uptake in man. *Arch. gen. Psychiat.*, **26**, 158-162.
- FANN, W.E., DAVIS, J.M., JANOWSKY, D.S., KAUFMANN, J.S., CAVANAUGH, J.H. & OATES, J.A. (1974). Effect of antidepressant and antimanic drugs on amine uptake in man. *J. nerv. ment. Dis.*, **158**, 361-368.
- IMLAH, N.W., MURPHY, K.P. & MELLOR, C.S. (1968). The treatment of depression. A controlled comparison between iprindole (Prondol) and imipramine. *Clin. Trials J.*, **5**, 927-931.
- JOHNSON, J. & MADEN, J.G. (1970). The treatment of depression: Further evaluation of iprindole (Prondol). *Clin. Trials J.*, **7**, 341-344.
- MCCLATCHEY, W.T., MOFFAT, J. & IRVINE, G.M. (1967). A double-blind study of WY-3263, imipramine and placebo. *J. ther. clin. Res.*, **1**, 13-15.

- RICKELS, K., GORDON, P.E., MECKELNBURG, R., SABLOSKY, L., WHALEN, E. & DION, H. (1968). Iprindole in neurotic depressed general practice patients, a controlled study. *Dis. nerv. Syst.*, 9, 208-214.
- STERLIN, C., LEHMANN, H.E., OLIVEROS, R.F., BAN, T.A. & SAXENA, B.M. (1968). A preliminary investigation of WY-3263 vs amitriptyline in depressions. *Curr. ther. Res.*, 10, 576-582.
- SUTHERLAND, M.S., SUTHERLAND, S.S. & PHILLIP, A.E. (1967). Depressive illness: Comparison of effects of pramindol (WY-3263) and imipramine. *Clin. Trials J.*, 7, 857-860.

Drs Briant and George reply as follows:

Our critics, Drs Tait and Todrick, are concerned that in describing Ciba 34276-Ba as a tricyclic antidepressant, we are devaluing the term (Briant & George, 1974). In reply, we would point out that the definition given by the International Union of Pure and Applied Chemists (IUPAC) applies to any chemical structure which possesses three rings. There is nothing specific about the term chemically (or therapeutically) and the compound which we have studied satisfies the definition given above.

Early studies on the use of tricyclic antidepressants (Kiloh, Ball & Garside, 1962) suggested that patients with endogenous depression responded more favourably than those with 'reactive' depression. However, many psychiatrists now feel that there is little difference in the response of the two forms of depression. Furthermore, it should be remembered that there are inconsistencies in psychiatric diagnosis, the reliability of which is discouragingly low (Cooper, Kendell, Gurland, Sartorius, & Farkas, 1969). Thus, to collect a homogeneous sample of patients with major endogenous depression may be neither possible nor relevant. Our tentative conclusion that drugs such as Ciba 34276-Ba could allow the possibility of effective antidepressant therapy

without undesirable interactions at adrenoceptor sites remains.

R.H. BRIANT

Department of Medicine, The University of Auckland School of Medicine, New Zealand

C.F. GEORGE

Faculty of Medicine, University of Southampton, Southampton SO9 3TU

Received October 3, 1974

References

- BRIANT, R.H. & GEORGE, C.F. (1974). The assessment of potential drug interactions with a new tricyclic antidepressant drug. *Br. J. clin. Pharmac.*, 1, 113-118.
- COOPER, J.E., KENDELL, R.E., GURLAND, B.J., SARTORIUS, N. & FARKAS, T. (1969). Cross-national study of diagnosis of the mental disorders: some results from the first comparative investigation. *Am. J. Psychiat.*, 125 (Suppl. 10), 21-29.
- KILOH, L.G., BALL, J.R.B. & GARSIDE, R.F. (1962). Prognostic factors in treatment of depressive state with imipramine. *Br. med. J.*, 1, 1225-1227.

INHIBITION OF IRON ABSORPTION BY TETRACYCLINE

Ferrous sulphate and other iron salts interfere with the gastro-intestinal absorption of tetracyclines in man (Neuvonen, Gothoni, Hackman & af Björkstén, 1970; Neuvonen & Turakka, 1974). This effect is obviously based on the well known ability of Fe^{++} and Fe^{+++} to form stable chelates

with tetracyclines (Albert, 1953). Moreover, it has been shown that tetracycline inhibits the absorption of ferrous sulphate in rats (Greenberger, Rubbert & Cuppage, 1967). On the basis of the supposed physicochemical mechanism of interaction it was surprising that the inhibition of iron