# MC4703*
# A NEW PHENOTHIAZINE DERIVATIVE

By

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MC4703 is a new phenothiazine derivative which contains a trifluoromethyl group and which was made available in the form of 10 mg. and 50 mg. tablets by E. R. Squibb & Sons for clinical evaluation as an ataractic or "tranquillizing" agent. The interesting results obtained with the drug justify the presentation of this brief, preliminary report, but a more detailed account of the investigation will be supplied in due course.

## Selection of Cases

The drug was given to 153 patients of whom 118 were schizophrenic and 35 psychotic or psycho-neurotic non-schizophrenics. Within the schizophrenic group, the average age was 45 years and the average stay in hospital was 10 years. Eighteen typical paranoid and 15 simple schizophrenics were included, but the other patients in this group were mainly very restless, hallucinated schizophrenics of various diagnostic categories. Almost all the patients were selected from the refractory wards and were restless, deluded, hallucinated, troublesome, violent, unoccupiable, or difficult to manage.

The mixed group consisted of 2 alcoholic patients, one drug addict, 2 manics, 2 patients with Huntington's chorea, one case of congenital G.P.I., 10 depressives, 6 mental defectives, 4 epileptic patients with psychosis and a balance of patients with pre-senile and senile dementias. The control group was made up of 50 schizophrenics and 25 patients with mixed psychoses.

## Dosage and Method of Evaluation

The trial occupied 7 months and many of the patients were treated with MC4703 for 6 months. At the beginning of the investigation, doses of 50 mg. were given 3 times daily as routine, but as experience was gained the initial dose was lowered to 15 to 25 mg. twice or thrice daily with subsequent increase up to 100 mg. t.d.s. if required. The highest dose given was 150 mg. 3 times daily. Each case was scored on a scale of points before and after treatment with the drug, and evaluation was based on changes observed in the total score of each individual. This method will be described in greater detail in a subsequent communication.

## Results

Within the schizophrenic group the improvement of 36 patients (31 per cent.) was rated as "very good". Six of these had shown only limited improvement after insulin treatment, but responded well to MC4703, 5 being discharged and the other receiving continued treatment as an out-patient. Sixteen others made good social recoveries and 9 of them have been discharged, while the rest

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have been re-graded to voluntary status and are fit for discharge. The remainder are now fully occupied, are industrious and show few symptoms of psychiatric importance. Twenty patients (17 per cent.) are regarded as showing "good" improvement and they have become industrious, co-operative and friendly; in this group there is little evidence of delusions or hallucinations. The improvement of 25 (21 per cent.) is "fair". Their work, activity and co-operation is better and they are more manageable; some have retained their delusions but these are much less intense. The remaining 37 patients (31 per cent.) failed to respond.

In general, the non-schizophrenic patients showed little response apart from decreased restlessness and within this group was found the highest proportion of such side effects as occurred. However, the alcoholic patients and the barbiturate addict responded well, and the drug seemed to be a very effective form of replacement therapy in these cases.

Two patients who had chronic skin ulceration due to picking and scratching and who had not responded to other "tranquillizers" or local applications showed immediate improvement on MC4703. The scratching stopped and has not recurred. Four patients prone to epileptic fits as well as showing other psychotic symptoms were also given the drug. One who had had almost daily fits had none for a week after starting to take MC4703, but then had a succession of fits. Three others who had not had fits for a long time had a single seizure shortly after starting treatment; withdrawal of their previous barbiturate therapy might have been responsible.

In certain cases beneficial effects were observed when MC4703 was given with various barbiturates. Three of the treated patients were subjected to E.C.T. without ill effect. When the drug was discontinued, as it usually was after about 3 months, the relapse rate was negligible.

## Side Effects

Routine blood examination in all cases failed to reveal any fall in white cell count. No dryness of the mouth was noted. Two patients passed white stools and urine containing elevated bile pigments, but these phenomena disappeared when treatment was stopped and there was no case of frank jaundice. Three patients developed papular rashes which disappeared promptly on withdrawing the drug. Increased frequency of urination was seen during the first few days and increased sweating was sometimes noticed. Parkinson-like symptoms with drooling, tremor and rigidity occurred in 13 cases; these symptoms disappeared when the drug was stopped. Drowsiness was quite common during the first few days but it generally passed off quickly; a few patients became rather ataxic at the start but responded favourably to a reduction in dosage. Depressive symptoms were noted in 15 cases, usually in very excited, highly hallucinated and very detached patients, who were beginning to benefit. These effects disappeared within about a week, and were regarded, on the whole, as a good prognostic sign. Hypotensive effects, represented by falls of up to 40 mm. Hg, were troublesome at the beginning of the study when a high initial daily dose of 150 mg. was given routinely. Some hypertensives showed relative hypotension soon after taking the drug until the initial dose was lowered to the levels already mentioned, and from that time pronounced falls in blood pressure have been very infrequent.

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## Discussion

MC4703 is a powerful ataractic drug and appears to be much superior to other "tranquillizers" at present used in the treatment of schizophrenia. Improvement, when it occurred, was rapid, often being evident during the first week of treatment, but tended to continue slowly over many months. Paranoid schizophrenics responded best, but a large group of very deteriorated, hallucinated, over-active and violent patients reacted almost as well. Classification, methods of evaluating therapy and the human pharmacology of MC4703 will be discussed more fully in a later communication.

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