# TREATMENT OF CHRONIC PSYCHOTICS WITH B.A.S.

By

**R. L. JILLETT, M.B., B.S.(Lond.)**

*Junior Medical Officer*
*Herrison Hospital, Dorchester*

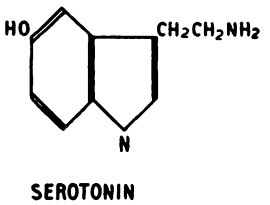
IN the past few years papers have appeared in the U.S.A. and in Europe which discuss the role played by 5 hydroxy-tryptamine (serotonin) in cerebral metabolism, both in health and disease. The aim of this paper is to report a trial of a benzyl analogue of serotonin, a serotonin antagonist, and to shed some light upon its possible side-effects.

Reserpine is said to reduce the concentration of serotonin in the tissues, possibly by displacing the latter from its receptors. Serotonin causes the smooth muscle in arteries and viscera to contract, hence it may be an aetiological factor in the production of hypertension. Only about 1 per cent. of the serotonin content is found in the brain, most being found in the spleen and in the tissues forming the gastro-intestinal tract. Patients suffering from a malignant tumour of the chromaffin cells called carcinoid disease often show high levels of blood serotonin, for which reason Davies and Rimington (1) and other workers have tried serotonin antagonists in cases of carcinoid disease. In one such case B.A.S. was used but the condition was controlled only to a very limited extent. An incidental but highly interesting observation made at the time was that the patient, previously depressed, anxious and often tearful, became placid, cheerful and, in the fullest sense of the word, "tranquillized" while on the drug.

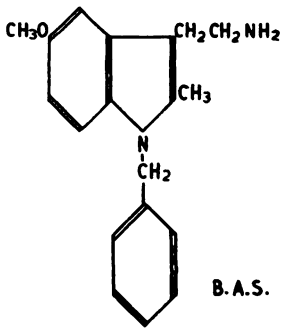
This observation, together with a tentative hypothesis that B.A.S. might act by blocking the action of serotonin in cerebral metabolism, led the author to undertake a small-scale trial with the drug on a limited number of female psychotic patients, to compare the efficacy of the drug with chlorpromazine in the management of agitation, restlessness and anxiety.

## B.A.S.

B.A.S. was first synthesized by Shaw and Woolley (2) who showed this compound, 1-benzyl-2-5-dimethylserotonin, to be a very potent anti-metabolite of serotonin both *in vitro* and *in vivo*.




SEROTONIN




B.A.S.



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B.A.S. has been administered to man for the treatment of hypertension by Wilkins (3, 4) and very recently, while the trial described herein was in progress, a paper has been published in the U.S.A. by Rudy (5) showing that it has been employed for the treatment of schizophrenic patients.

## METHOD

Initially twenty female psychotic patients were selected for the trial, all of whom were considered to have a poor prognosis. Most exhibited behaviour disorders, warranting regular maintenance E.C.T. in order to render them manageable.

All the patients had previously had a course of chlorpromazine. This was useful since any new drug should be compared with existing preparations and chlorpromazine was deemed a suitable yardstick for the present purposes.

All medication was discontinued for a period of 4 weeks to avoid confusion by overlap of chlorpromazine treatment. This treatment-free period was followed in all cases by 4 weeks' therapy with B.A.S. As will be seen, this part of the trial was not completed by all patients due to marked side-effects arising in some cases. After the trial period another treatment-free interval of 4 weeks was reinstated. This was done in order to detect any after-effects of treatment, and it was also hoped to obtain some idea of how long a remission would last. After this 4-week period free of treatment patients were replaced on chlorpromazine if necessary.

The trial group consisted of: 7 schizophrenics, 6 paraphrenics, 1 schizophrenic reaction superimposed upon a psychopathic personality, 1 melancholic, 2 epileptic psychotics, 2 manic-depressive psychotics and 1 mental defective exhibiting behaviour disorders.

The patients were all nursed in the same ward and were fully and frequently observed by the nursing staff. All patients attended the occupational therapy department and frequent reports were obtained on the patients' progress from the therapists. Before the trial commenced full physical and psychiatric examinations were carried out and recorded, together with a preliminary blood count.

Blood pressures were recorded daily at the same time of day, and at weekly intervals body weights were noted.

B.A.S. was supplied in the form of 50 mg. tablets, scored for division into 25 mg. segments. All patients commenced treatment with 50 mg. t.d.s. Some patients were withdrawn from the trial due to serious side-effects after a total dosage of 300 mg. The remainder had their dosage reduced to 25 mg. t.d.s. and then slowly increased to 50 mg. t.d.s. over a period of 2 weeks.

In 6 cases B.A.S. had to be discontinued due to profound side-effects and in one case a patient was transferred to another institution. The 7 cases who fell by the wayside were replaced by a further 7 suitable cases. The assessment was made on the psychiatric condition of the patient, the following factors being considered in all cases:

(*a*) Florid symptoms; hallucinations, delusions, etc.

(*b*) Behaviour; violence, controllability, submissiveness, etc.

(*c*) Accessibility, including degree of retardation.

(*d*) Affective response.

For the purposes of recording, however, a simple numerical record was made as follows:

1. Recovery.
2. Much improved.
3. Improved.
4. Unimproved.
5. Deterioration in the psychiatric condition.

All patients when being treated with chlorpromazine were assessed as category (4).

After completion of the period of treatment with B.A.S.:

2 cases were placed in category 1
3 cases were placed in category 2
3 cases were placed in category 3
13 cases were placed in category 4
5 cases were placed in category 5

Of the two cases who were up-graded as the result of treatment with B.A.S. to category 1, one was returned to voluntary status and discharged, her condition (paranoid schizophrenia) having remitted; the other who had previously been acutely suicidal and auditorily hallucinated, was able to go out shopping, and allowed leave of absence. After 3 months she was placed on a small maintenance dose (25 mg. t.d.s.) and subsequently required only occasional E.C.T. to maintain her improvement.

One patient, a depressive, requested resumption of treatment with B.A.S. as it improved her condition. She was maintained on 25 mg. t.d.s., and was placed in category 2. In the 8 cases who were improved by treatment with B.A.S. (i.e. categories 1, 2 and 3) it was particularly noticeable that the florid symptoms had disappeared, and insight was gained into the nature of these symptoms.

All 8 cases, because of their improvement, were not replaced on to chlorpromazine during the last period of the trial. Those cases who deteriorated with B.A.S. were replaced after the 4-week treatment-free interval on to chlorpromazine therapy, and dramatic improvement in their condition was seen, but never much beyond their original condition (i.e. category 4).

## Side-Effects

Side-effects resulting from the use of B.A.S. were considerable. In 6 patients they were of such an order that after 6 doses, a total of 300 mg., the drug had to be discontinued and the trial abandoned.

Chiefly amongst these severe side-effects were:

1. *Vertigo.* Six patients complained of profound dizziness to the extent that walking unaided was impossible.
2. *Ataxia.* Four of these patients showed a profoundly ataxic gait, with gross tremor of the hands. Co-ordination of body movements was disturbed, the patients being unable to hold a cup or spoon for feeding. These symptoms occurred after 6 doses, a total of 300 mg. having been administered. Cessation of treatment was followed by a slow recovery, complete in 7 days after stopping the drug.

3. *Abdominal Pain.* Severe and cramp-like abdominal pain occurred in 4 of the 6 cases, accompanied by—
4. *Vomiting*, in 3 cases, which persisted for 2 days after withdrawal of the drug.
5. *Circulatory Collapse.* Occurred in 2 cases associated with hypotension. In the first case the blood pressure fell drastically, the patient became pale, cold, clammy and cyanosed. For 3 days afterwards she was confused, restless, incontinent of urine and faeces, the condition returning to the patient's normal state at the end of this time. In the second case the blood pressure fell, the patient was shocked, pale, sweating profusely and the pulse was impalpable. The lips were cyanosed and gross dysarthria was present. She recovered slowly over 14 days. In both these cases a total of 300 mg. B.A.S. had been given over a period of 2 days and treatment had to be discontinued.
6. *Bradycardia.* A marked and persistent fall in pulse rate during treatment was noticed in one patient (from 72–54) and this was associated with the usual hypotension. This patient also complained of giddiness but recovered slowly after a period of 3 days after withdrawing B.A.S.

Other side-effects associated with B.A.S. were:

7. *Weight Loss.* This occurred in every case which was treated with B.A.S. except one. The weight loss varied from 1 pound–15 pounds, the average weight loss per patient being 7 pounds.
8. *Hypotension*, to a small degree was noticed in every case. The average overall blood pressure during treatment with B.A.S. was 100/78. The systolic blood pressure fell 20–30 mm. of mercury in many cases, but once treatment was maintained, patients appeared to suffer no ill effects from the hypotension. Only when circulatory collapse ensued as has been described in the above two cases was it found necessary to withdraw B.A.S.
9. *Sedation.* Sleepiness was rarely encountered. Only in one case was it noted to any excessive degree.

## Discussion

The results obtained on the whole with B.A.S. in this group totalling 26 chronic psychotic female patients of middle age were disappointing. In 8 cases a satisfactory response was obtained, but in 18 cases the response was negative. Side-effects when they occurred were dramatic and alarming, both to the patient and the clinician. The results of this trial make it tempting to suggest that there might be two opposing conditions both leading to psychoses. In one state one can postulate an excess of serotonin in the cerebral tissues and in the other condition a deficiency of the substance. Because of the paucity of knowledge relating to the distribution of serotonin in free and combined forms in the brain it is pointless to speculate whether these serotonin values would be absolute or relative values, i.e. whether there is a true excess of serotonin or whether there is inadequate binding of the substance.

On clinical grounds it is impossible to forecast which patients will do well on B.A.S. and which will deteriorate. In the absence of any means for measuring brain serotonin levels one wonders whether measurements of blood serotonin levels (bound and free) would in any way help in forecasting which patients may warrant a trial with B.A.S. It is just possible that such levels might reflect the state of affairs in the brain although there is no reason to assume such a direct relationship. It is worthy of note in this

connection that those patients who improved on treatment with the drug showed no evidence of serious side-effects developing.

## Summary

Twenty-six chronic psychotic female patients, all nursed in the same ward and whose response to chlorpromazine therapy had been ascertained, were subjected to a trial of a serotonin antagonist, B.A.S. (1-benzyl-2-5-dimethyl-serotonin) in order to ascertain whether this drug should have a place amongst psychotropic therapeutic agents. B.A.S. gave rise to a degree of improvement in 8 cases which was satisfactory, but side-effects, mainly of hypotension, loss of weight, ataxia, and abdominal pain, were frequently seen in those patients whose psychological condition did not improve.

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