the time of the study only two drugs were used—chlorpromazine and reserpine—and, though some comparison between them was made in the results, the aim was not to compare the effectiveness of different drugs. For this purpose something other than the clinical diagnosis may well be required, such as the "target symptom" approach originally proposed by Professor Freyhan, or the more recent "target function" concept of Irwin (1968). What, I think, was shown by the comparison between the two treatment eras was that, as a group, patients treated with drugs had a better short-term outcome, and that whereas with earlier somatic treatments, such as deep insulin, the patients who responded favourably were probably those "destined for a more benign course of illness" (Freyhan, 1955), pharmacotherapy seemed to be effective in a wider range of patients, including those who showed less hopeful prognostic features.

It is, however, in relation to the long-term prognosis that most of the theoretical difficulties arise. As it happens, the comparison of the two groups showed no difference in this respect, but Professor Freyhan asks on what theoretical basis any long-term effects could be expected from short-term drug treatment. He states, "This leaves us in the highly peculiar situation where the historical association of a given treatment, administered at a particular point in time is regarded as the determining influence on the short- and long-term outcome." This, together with his statement that "the anticipation of permanent therapeutic results can only be based on the evidence of permanently produced changes in biological systems", seems to imply a belief in a solely somatic basis for the illness or group of illnesses that we call schizophrenia.

As far as neurotic illness is concerned, rather than a highly peculiar situation there is a widely held view that the historical association of given psychological events or circumstances at a particular point in time does have a determining influence on subsequent liability to illness. With schizophrenia, an increasingly widely accepted view is that we are dealing with a group of disorders in which somatic and psychological factors contribute in varying proportions. Thus, a combination of a genetically determined predisposition with certain adverse psychological experiences in childhood may, with exposure to some current stress, result in an illness which may be further aggravated by the distortion of reality which is produced. If the latter is speedily reduced or removed, then may there not be less psychological damage and perhaps less likelihood of subsequent illness? Professor Freyhan himself has earlier expressed this view—"It seems, furthermore, justified to assume that course and prognosis are favourably influenced by the speed of resocialization, which somatic and psychological therapies facilitate through rapid reduction, or removal, of disturbing symptoms that disorganize the inner continuity of the schizophrenic individual" (Freyhan, 1955).

In short, to deny that short-term treatment might have long-term effects seems to imply a static somatic approach and ignores the dynamic interplay of aetiological factors which probably determines the manifestation of this illness. In such a complex nexus, alteration of one element could theoretically have far reaching and long-term effects.

Finally, may I be permitted to draw attention to a regrettable statistical error on p. 1347 of my first paper? The first χ^2 should read 7·96, which gives $p<0·05$, but fortunately this does not affect the conclusions of the study.

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5-HYDROXYTRYPTAMINE IN THE HINDBRAIN OF DEPRESSIVE SUICIDES

DEAR SIR,

I have read with great interest the paper by Drs. Shaw and Camps and Mr. Eccleston (*Journal*, December, 1967, pp. 1407-1411).

While I feel that their work is important I wish to comment on their interpretation of the data and on the assumptions underlying the work.

It is true that the figures quoted do show a just significant difference between the 5-hydroxytryptamine (5-HT) contents of depressed v. control hindbrains if Student's t test is used ($p<0·05$).

However, if the control and depressed groups are pooled and the two groups are distributed above and below the median value of the pooled figures the following results:

	Above Median	Below Median	
Controls	10	7	$\chi^2= 2·67$
Depressives	3	8	$p>0·1$

The really disappointing feature of their results (on which they do not comment) is the lack of any difference between the 5-HT levels of the depressed Suicides v. the other Suicides ($t = 1·42$, $p>0·1$). This is the critical comparison to make if one is to

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feel justified in relating brain 5-HT levels to the pathophysiology of depression, as they do.

I am also intrigued by their decision to examine the brain stem rather than the forebrain. Vascular stripping of the forebrain does take some little time, but the rate of disappearance of 5-HT from a pre-cooled brain in the 3 or 4 minutes needed would not be significant.

While Dr. Shaw and his colleagues are cautious (with good reason) in the discussion of their results, I am unable to accept their implication that a dubious "finding" in the hindbrain tissue may be causally related to limbic lobe function and affective disorder.

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Dear Sir,

The most suitable statistical test for our data was Student's t test, which showed that the difference between control and depressed groups was significant at the 5% level. The χ^2 test is certainly not appropriate in this situation. It is relatively insensitive and is wasting some of the available information.

There was little or no point in comparing the results in the depressed subjects with those of the alcoholic or schizophrenic individuals. The numbers in the subgroups were small and any comparisons would have been open to the criticism that any differences could have been due to alcohol or to long-term treatment with phenothiazines. No attempt was made to pool these data for the same reason, and we were also aware of the possibility that severe depressive illness could have been a secondary diagnosis in a proportion of the subjects suffering from alcoholism or schizophrenia. With these unknown variables in mind, the findings in the subgroup of Table II in the paper were published without comment.

The decision to use the brain stem was based on practical considerations. It is much easier to obtain a reproduceable piece of tissue by taking the brain stem than to dissect out the hypothalamus, and our technique was not sensitive enough to measure 5-HT in homogenate of whole brain.

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THE LOGICAL REQUIREMENTS OF RESEARCH INTO SCHIZOPHRENIA

Dear Sir,

I am writing this letter in response to the stimulating article by D. Bannister (*Brit. J. Psychiat.*, **114** : *118*, 1968), in which he discusses, among other matters, new strategies for achieving a breakthrough in the study of schizophrenia and suggests that the field has thus far failed to advance. I feel that it may be of value to present a somewhat different point of view about the present status of schizophrenia research, since, in my estimation, research in this area is anything but static. In fact, I think that a remarkable number of fundamental discoveries have given great forward momentum to the field and that it should be necessary to detail only a few advances to demonstrate this point.

It may have been the re-introduction of the drug reserpine as an anti-psychotic agent that initiated this revolution in psychiatry. In any event, this was one of the first in a series of developments which have resulted in tremendous advances in our basic understanding of the biological substratum of mental processes. Among these accomplishments has been the elucidation of the metabolic pathways of enzymes involved in the metabolism of catecholamine neurohormones, resulting from studies carried out by Blashko, Armstrong, Axelrod, Von Euler and a large number of other investigators. Extremely important basic studies of tryptamine and serotonin metabolism have also been carried out by Page, Wooley, Udenfriend, Himwich and many others. A new science of psychopharmacology has been developed which has produced so many important works as to make it impossible to decide which are the most important. Among these must surely be included the dramatic improvement in the treatment of psychotic patients resulting from the use of new drugs. The clinical effects of hallucinogens have been very closely studied, and through the work of many investigators, including Daly, Shulgin, Zeller and Charalampous, to name a few, it is possible to design certain hallucinogenic molecules with some assurance about their potency and duration of action.

One of the most dramatic observations has been the finding that all effective anti-psychotic agents have the potential for producing parkinsonian symptoms. The elaboration of a possible metabolic disturbance in dopamine metabolism in parkinsonism by Hornykiewicz and Barbeau has also illuminated a possible mechanism of action of the anti-psychotic agents themselves. In another area, a great advance in epidemiological and genetic studies in mental illness has been generated by Kallmann, Slater, Gottesman