appearance (differences which provide the basis for clinical diagnosis), and although they show subtle differences in many biochemical properties, the consistent pattern demonstrated here in the distribution of protein among the various parts of the cell indicates that, within their cells, all of the tumors studied possess the same basic architecture.

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2. The four additional malignant human tumors were obtained through the kind efforts of William S. Walsh of the Tumor Service, Hines Veterans Administration Hospital, Hines, Ill. The work reported here was performed under the auspices of the U.S. Atomic Energy Commission.
3. The desirability of expressing the quantities of cell constituents in terms of the amount per unit of DNA rather than the amount per gram of tissue, and thus recognizing the cell rather than the gram as the basic unit of protoplasm, has been well presented by J. N. Davidson and I. Leslie, *Cancer Research* 10, 587 (1950). See also J. M. Price and A. K. Laird, *ibid.* 10, 650 (1950).
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Antiserotonins in Hypertension and the Antimetabolite Approach to Chemotherapy

In 1944, as a result of experiments with antimetabolites of vitamins and purines, Woolley (*1*) suggested that useful pharmacological agents could be made which would control specific noninfectious diseases. This could be accomplished by use of the antimetabolite idea coupled with knowledge of vitamin or hormone deficiencies. Thus, a disease arising from an excess of one of the hormones present in an animal might logically be controlled by production of a structural analog of this hormone that would act antagonistically to it. This idea was an extension of that of Woods (*2*) and Fildes (*3*) regarding the mechanism of control of bacterial infections by sulfanilamide.

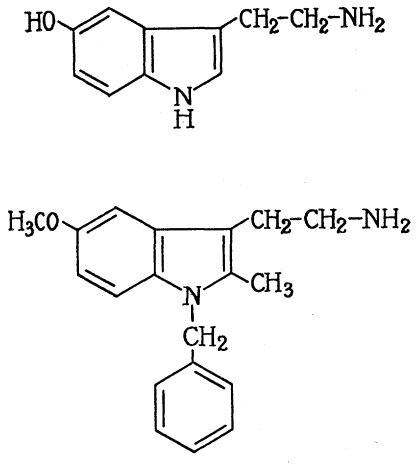

Fig. 1. Structures of serotonin (top) and 1-benzyl-2,5,dimethyl-serotonin or BAS.

The prospect that was thus raised of a rational chemotherapy of both noninfectious and infectious disorders through the use of antimetabolites has, in the intervening years, been viewed with considerable skepticism by many investigators. These have reminded us that penicillin and other wondrous agents have not been discovered in this fashion but rather have been found empirically—for example, by screening programs. Because this opposing view has enjoyed such acceptance, we would like to record the following facts as an interesting case in which the antimetabolite approach has led to the development of a new series of pharmacological agents capable of checking a common human disease.

In 1952 we (*4*) suggested that essential hypertension might arise from an excess of serotonin. We also saw that if this were so, the disease might be controlled with a suitable antimetabolite of serotonin. The first antiserotonins were thus envisioned and produced. We have pursued this idea and have made a member of this series of antiserotonins which is apparently suitable.

The compound in question is 1-benzyl-2,5-dimethyl serotonin, a benzyl analog of serotonin, or BAS. The structures of BAS and of serotonin are shown in Fig. 1. This antimetabolite was synthesized in the manner described previously (*5, 6*) and was found to be highly effective by the oral route in protecting dogs from the pressor action of serotonin (*6, 7*). However, it was not merely a hypotensive agent, because, in normal dogs and in one normotensive human being, it did not lower blood pressure significantly. What it did do was to protect these animals against the pressor effects of injected serotonin.

As a result of these findings, the aid of Robert Wilkins of the Massachusetts Memorial Hospital was sought in order that a clinical trial of this antimetabolite could be made. Preliminary findings reported by Hollander, Michelson, and Wilkins (*8*) have shown that BAS will bring about reduction in blood pressure of patients with hypertension. Only small doses were needed, and these did not seem to cause harmful side-effects.

Several problems arose during the discovery of BAS, and some are worthy of comment here. (i) It was realized at the outset that a drug, to be useful in this disease, must be orally effective. (ii) The drug should also have a low inhibition index, and it should be an irreversible antagonist of serotonin (*9*). This was desirable so that the serotonin that is constantly being produced in the body would not readily nullify the effects of the drug. (iii). The compound must not affect the central nervous system so as to cause mental disturbances. This was a very real problem, because early in the investigation of antiserotonins we had found (*10*) that some of them do disturb the mind. It was therefore necessary to design one that would not elicit this kind of effect.

The antiserotonin, BAS, was so designed that it met these requirements. For example, the benzyl group was introduced to help with points i and ii. The validity of this can be seen from the fact that the corresponding debenzylated compound was shown to lack the high activity by the oral route and to lack some of the irreversible character (*7*). The primary aliphatic amino group was retained in the molecule to deal with point iii. Several compounds with the amino group either attached at other points or otherwise modified caused profound behavioral changes in animals (*10*).

The findings of Wilkins and his collaborators (*8*) show that a suitably constructed antimetabolite of serotonin such as BAS can bring about a reduction in the blood pressure of many hypertensive patients and can do this without causing obvious harmful side-effects. Whether or not such a compound will be a useful drug remains to be seen. It is quite probable that further alteration of the structure of serotonin to give other members of this series of antimetabolites will be needed in order to achieve the best agent. Nevertheless, present facts indicate that the original hypotheses are worthy of attention. These hypotheses are (i) that a new series of drugs may be discovered with the antimetabolite idea, and (ii) that serotonin may be causally related to essential hypertension.

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