EDITORIAL

COMMENTS ON BENZIMIDAZOLE: ILLUSTRATING A METHOD OF APPPROACH TO THE INTRODUCTION OF NEW DRUGS *

THIS is a brief report on some aspects of benzimidazole, a drug which has been known as an important commercial chemical for many decades but whose interesting biological properties appear to have remained unknown until discovered by Goodman (1) in 1943. He found that benzimidazole when parenterally administered produced paralysis of the skeletal muscles. Its action and safe use in the human subject were first tested by Goodman, Bourne and Lehmann in Montreal in 1943. Since that time the biological properties of the drug have been studied extensively by Hosein (2, 3), Denstedt and Bourne in the Departments of Biochemistry and Anaesthesia at McGill University.

Benzimidazole is a colorless crystalline compound, fairly soluble in warm water but sparingly soluble at room temperature. Like other imidazole derivatives it forms salts with acids. The hydrochloride is readily soluble in water and a solution of this salt in concentration of about 100 mg. per milliliter, when neutralized, is suitable for parenteral use.

A fairly large dose of the drug is necessary to produce paralysis. It has been found that when sodium pentothal[2] is administered to rats and rabbits simultaneously with benzimidazole, the dosage of benzimidazole needed is much smaller than when the drug was used alone.

Benzimidazole is strongly antagonistic to the convulsive action of strychnine. Since strychnine is known to act on the motor neurons of the spinal cord, it is suspected that benzimidazole acts on the same neurons as does strychnine. The site of action of benzimidazole is probably similar to that of myanesin. The paralytic action is thus of central rather than peripheral origin.

The drug is rapidly destroyed in the liver, very slowly by the brain and not at all by the kidney. There is also evidence that the drug is evenly distributed after injection, there being no particular tissue which contains more of the drug on a weight-drug concentration basis.

One phase of the investigation was to determine to what extent the presence of the drug in the body of the animal produced any effect on the normal metabolic state. The purpose of this study was to determine some method of measuring toxicity. Since it is known that the presence of almost any agent in tissues can produce a disturbance

* Read before the Annual Meeting of the American Society of Anesthesiologists, Inc., Seattle, Washington, October 7, 1953.

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of the normal enzymatic mechanisms operating, it was decided to investigate the effect of the drug on various enzyme systems in the body, using the Warburg respirometer. This apparatus was designed to measure either the oxygen consumed or the carbon dioxide produced by certain enzymatic systems. Tissue slices (0.5 mm. thick) or homogenates derived from fresly killed animals were used in these studies.

Aerobic studies on tissues indicated that the drug produced its greatest inhibitory effect on brain tissue metabolism.

Benzimidazole has been found to produce its inhibitory action on dehydrogenases and the DPN-cytochrome-C-reductase system, components of the system responsible for the consumption of oxygen.

The drug has been found to inhibit choline dehydrogenase, carbonic anhydrase, xanthine oxidase and the oxidation of ascorbic acid.

Kinetic studies indicate that the inhibitory action of the drug is of the noncompetitive type, which means that the inhibition can be reversed.

It was observed that the drug inhibited a variety of enzyme systems. This seems to indicate that after the injection of the drug and the animal has become paralyzed, there are quite a number of vital enzymatic mechanisms which are being "slowed down" by the presence of the drug. It was also determined that the inhibition produced by the drug was of the reversible type, indicating that although there was some inhibition of enzyme systems, it was possible for the animal to survive the side effects of the drug since they are of a reversible nature.

Several factors have limited the clinical use of benzimidazole up to the present. All we have done is to give it to 4 patients undergoing simple abdominal operations in order to get some idea of the dose required to obtain muscle relaxation. When used in combination with light cyclopropane this dose is apparently quite large. The relatively poor solubility of benzimidazole means that for relaxation a large volume of solution must be given. This is a disadvantage when the drug is compared with succinylcholine, for instance, which produces such easily controllable relaxation when given in comparatively small quantity by continuous intravenous drip.

We have satisfied ourselves that benzimidazole will produce muscle relaxation in human subjects under anesthesia, with rapid recovery and no discernible after effects. We intend to use it in a larger series of cases in combination with moderate doses of pentothal, to examine its potentiating possibilities, but our clinical results would not have justified us in bringing this drug to the attention of anesthesiologists at the present time.

It is the method of study of benzimidazole by examining its effect on enzyme systems which seems to us to be worthy of report. This is a measure of toxicity that could and should be applied to many other drugs used in anesthesiology. Gillies (4) has coined the term "physio-

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logical trespass" to describe many of the valuable procedures of modern anesthesiology. Sometimes we commit physiological trespass almost nonchalantly with powerful drugs of which the long range toxic effect on the body is quite unknown. We believe that examination of these drugs by a study of their effects on enzyme systems would contribute to their clinical evaluation.

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