EDITORIAL

THE CLINICAL USE OF TOLBUTAMIDE IN DIABETES MELLITUS: A STATEMENT OF THE AMERICAN DIABETES ASSOCIATION*

Tolbutamide (Orinase), a hypoglycemic agent for oral use, recently has been released by the Food and Drug Administration and is being generally distributed for use by prescription. Members of the medical and allied professions should be informed concerning this new drug.

It is a sulfonylurea compound with the empirical formula $C_{12}H_{18}N_2O_3S$. It lowers the blood sugar of normal animals and man and of some, but not all, diabetic patients. The mechanism involved is still unknown, but it seems clear that it is ineffective in the complete absence of insulin. Hence it cannot be considered a true substitute for insulin.

According to the manufacturer, experience with more than 5,000 cases has revealed no deaths clearly attributable to the drug during the 1½ years that it has been employed in this country. Toxic reactions, none of them serious thus far, have occurred in approximately 3 per cent of the cases. They have consisted chiefly of gastrointestinal disturbances, cutaneous eruptions presumably due to hypersensitivity, headache and some intolerance to alcohol.

Tolbutamide is contraindicated in those patients with onset of diabetes in childhood or adolescence, those with unstable diabetes, those with a history of diabetic coma, those undergoing surgical operations, or those with existing complications such as ketosis, acidosis, infection, severe trauma, disease of the liver, thyroid or kidneys, or any other condition that usually increases requirement for insulin. In such situations insulin is essential, and attempts to replace it with tolbutamide would be dangerous. There is little or no published information concerning the effect of this drug in pregnancy.

There is, of course, no point in prescribing the drug when diabetes can be controlled with diet alone.

Tolbutamide is most effective in adult patients with relatively mild diabetes who have required small to moderate doses of insulin. The best test for responsiveness is the administration of the drug for a period of seven days during which insulin is withdrawn gradually and tests of the urine for glucose and ketone bodies are performed three times daily.

The dosage of tolbutamide and the method of attempting its substitution for insulin vary with circumstances. Ordinarily, 3 gm. of the drug are given on the first day, 2 gm. on the second and 1 gm. on the third. This method of initiating treatment is applicable whether the patient has been using insulin or not. Maintenance is provided by divided doses totaling from 0.5 to 1.5 gm. (never more than 2 gm.) daily and must be determined on the basis of experience in each case.

Insulin should never be withdrawn abruptly. In cases in which the previous daily requirement has been less than about 30 units, initiation of treatment with tolbutamide may be accompanied by a simultaneous reduction of 30 to 50 per cent in the dose of insulin, further reductions being made gradually so long as levels of blood and urinary glucose remain satisfactory. Patients who have required more than about 30 units daily may reduce their dose by 20 per cent on the first day of tolbutamide therapy, further reductions being made very cautiously. In daily observation the development, at any stage, of sustained hyperglycemia or glycosuria or any sign of ketosis calls for the abandonment of oral therapy and prompt reversion to maintenance doses of insulin. If the blood sugar remains within reasonable limits, however, oral treatment may be continued, the patient returning for examination at weekly intervals for the first month, then at two-weekly and finally at monthly intervals. The periodic examination should include a urinalysis for glucose and ketone bodies, determination of the blood sugar and a white blood cell count, with a differential count if the latter is low. Determinations of serum alkaline phosphatase and bromsulphalein excretion seem to be the most sensitive tests for suspected hepatic damage.

If not hospitalized, the patient must test the urine at home, informing the physician of any increase in glycosuria. He must be made to understand that close adherence to diet is just as important as when insulin is used.

The patient should be warned about the possibility of hypoglycemia while both insulin and tolbutamide are being taken during the period of stabilization. Combined therapy with both agents for purposes of maintenance is pointless.

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If side reactions, including gastrointestinal symptoms or allergic manifestations, occur the drug should be discontinued in favor of insulin.

Uncertainty as to the mode of action of tolbutamide and the brevity of experience with it when compared with the many years over which diabetes must be treated require that it be prescribed by physicians, dispensed by pharmacists and used by patients with caution. The manufacturer has prepared an excellent leaflet in which safeguards are given appropriate emphasis. The drug has been released by the Food and Drug Administration for sale on prescription only. This means that, in order to avoid violation of the law, pharmacists who are accustomed to dispensing insulin without prescription to patients familiar with its use must resist any temptation to do so with tolbutamide.

During the past few months a guanidine derivative, temporarily designated DBI, is being tested in clinical and experimental diabetes. This substance belongs to a different chemical family from that of Orinase. The available information is too scant as yet to allow even preliminary conclusions.

It is hoped that the investigators working in this field will be given undisturbed and unpressured time to investigate fully any of these drugs so that premature introduction into general use does not occur.

INFORMATIONAL COMMITTEE ON ORAL HYPOGLYCEMIC COMPOUNDS
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Henry Rawle Geyelin
1883-1942

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H. Rawle Geyelin was born in Villanova, Pennsylvania, May 12, 1883. Unlike many of the sons of the old families who obtained their college and even preparatory education away from home, Geyelin received all of his formal education in Philadelphia. He prepared for college at the Haverford Grammar School and in 1902 entered the University of Pennsylvania in the combined course leading to an A.B. degree in 1906 and M.D. in 1909. Following graduation from medical school he served an internship in Philadelphia and was fortunate then to be able to have a period of study in Germany. Here were planted the seeds which stimulated his interest in clinical research, particularly along chemical lines.

Upon his return from abroad Geyelin moved to New York in 1912 to begin his graduate medical career at the Presbyterian Hospital. He was fortunate to have for his chiefs of medical service two men who were not only sympathetic but actively encouraged the new advances in clinical research which were beginning to develop in the metropolitan hospitals of this country. Theodore C. Janeway was Professor of Medicine at Columbia University when Geyelin began his post-internship work. Later, Warfield T. Longcope succeeded Janeway who had left to assume the Professorship of Medicine at Johns Hopkins University. New laboratory methods for the scientific study of clinical problems were being developed rapidly in Germany and both Janeway and Longcope were eager to apply them to clinical problems encountered in the medical service of the Presbyterian Hospital. Geyelin was called upon to undertake this task.

The difficulties of this undertaking are best appreciated when it is realized that Geyelin's general cultural background was about what was considered appropriate for a physician at that time. He had had little training in physics and chemistry in either high school or college and his knowledge of these fields was not appreciably increased during his medical training. The men in the city of New York who knew these fields well enough to be helpful to him were few indeed, and he was forced to rely mainly upon his own resources and diligent study of the literature. But to overcome these handicaps in fundamental scientific training he was filled with an ardent desire to master the new technics. He wanted to develop a critical judgment in applying them to clinical problems, and an ability to ask the right questions and frame the appropriate experiments by which they could be answered by the laboratory methods which were then available. In addition he had