Status of Problem of Usage of Tolbutamide
Preliminary Statements

FDA STATEMENT

Friday, May 22, 1970

"The FDA said today it agrees with the recent study which indicated that in the treatment of mild, adult onset diabetes mellitus the use of the drug Orinase (tolbutamide) is no more effective than diet alone.

"In commenting on about-to-be released findings on a long term study of diabetic treatment, the agency said that in the types of patients studied, a regimen employing Orinase was no more effective than diet alone, and as far as death from heart disease and related conditions is concerned, may be less effective than diet or diet and insulin.

"The results of this study, conducted by the University Group Diabetes Program, were reviewed by the Food and Drug Administration and an expert advisory committee. Despite a number of limitations in the study, both the agency and its advisory committee agree with its stated conclusions which are: 'This study provides no evidence that the combination of diet and tolbutamide therapy as described and used for mild non-insulin dependent diabetes is more effective than diet alone. Moreover, the findings suggest that diet plus tolbutamide may be less effective, insofar as cardiovascular mortality is concerned, than diet alone or than diet and insulin combined.'

"The study was started in 1961 and conducted in 12 university medical schools. It is the largest prospective study of this sort and includes over 800 patients, most of whom have been followed for eight years.

"The study compared the results of various treatment regimens in patients with recently diagnosed adult onset mild diabetes who were not insulin dependent and who were expected to live at least five years after entry into the study. All patients were placed on a diabetic diet. Tolbutamide was given to one group in a fixed dosage, insulin was given in a fixed dosage to a second group and in varying dosage to a third and a control group was treated with diet and a placebo.

"The FDA emphasized that the conclusions of this study pertain only to patients with mild, adult onset, non-insulin dependent diabetes and to the specific type agents and dosage schedules used. Further studies and analysis of other ongoing studies will be necessary to determine if similar conclusions are warranted in regard to treatment of other diabetics with more or less severe disease and with other currently available agents or dosage schedules. A determination of the ultimate usefulness of oral antidiabetic agents must await further studies.

"Pending results of such studies the FDA recommends that Orinase (tolbutamide) and other sulfonylurea type agents Dymelor (acetohexamide), Diabinese (chlorpropamide), Tolinase (tolazamide) should be used only in patients with symptomatic adult onset diabetes mellitus who cannot be adequately controlled by diet alone and who are not insulin dependent (i.e., require insulin). In instances where these oral agents are deemed necessary by the physician their dosage should be tailored to the individual patient's needs as recommended in the labeling of these products.

"Other recent studies on this subject have also been analyzed by the FDA. These studies do not alter the validity of the conclusions of the University Group Diabetes study.

"Diabetic patients currently taking tolbutamide or other chemically related sulfonylurea agents who are under adequate medical supervision should continue on their current regimen until advised by their physicians.

"FDA said it will take the following actions:

"1. Require labeling changes for sulfonylurea drugs, to reflect the results of this study.
"2. Inform physicians of the findings of this study.
"3. Require the industry to institute long-term studies on the use of their products in various types of diabetic patients.
"4. Continue to monitor all studies pertaining to the use of anti-diabetic agents in patients with diabetes mellitus of varying severity.
"5. Continue an intensive examination of all new evidence in the field to be able to make prompt reevaluation of these decisions as necessary."

STATEMENT OF CHAIRMAN OF UGDP

Thursday, May 21, 1970

"Premature release of some of the information from reports which are to be presented to the American Diabetes Association in St. Louis on June 14 is most unfortunate, not only from a scientific standpoint, but for the thousands of diabetics in this country who are

vitally concerned about the value of various forms of therapy now in use," said Dr. Max Miller, professor of medicine at Case Western Reserve School of Medicine and chairman of the University Group Diabetes Program (UGDP).

"It subjects to debate in newspapers and other media very serious questions which have been under study for many years, which must be discussed and evaluated first by impartial investigators in the field. Naturally we have been concerned by our findings regarding the efficacy of certain hypoglycemic drugs. Final judgment of the relevancy and significance of the UGDP findings will rest on the detailed analyses by our peers and by comparison with other possibly related studies. Complete provision has been made for review and dissemination of the proceedings of the ADA meeting on June 14. Until that date it would be inappropriate to discuss the UGDP findings."

The following abstracts of the UGDP studies appeared in DIABETES:*19*, Supplement 1, the Program of the Thirtieth Annual Meeting of the American Diabetes Association:

"The University Group Diabetes Program: The Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult Onset Diabetes 1. Design and Methods," Martin G. Goldner, Brooklyn, N.Y., and Thaddeus E. Prout, Baltimore, Md., page 387.

"The University Group Diabetes Program: The Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult Onset Diabetes 2. Findings at Baseline," Thaddeus E. Prout, Baltimore, Md., and Martin G. Goldner, Brooklyn, N.Y., page 374.

"The University Group Diabetes Program: The Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult Onset Diabetes 3. Course and Mortality," Thaddeus E. Prout, Baltimore, Md., and Martin G. Goldner, Brooklyn, N.Y., page 375.

ABSTRACTS

Aharonson, Z.; Shani Mishkinsky, J.; and Sulman, F. G. (Dept. of Applied Pharmacology, Sch. of Pharmacy, Hebrew Univ., Jerusalem, Israel): HYPOGLYCAEMIC EFFECT OF THE SALT BUSH (ATRIPLEX HALIMUS)— A FEEDING SOURCE OF THE SAND RAT (PSAMMOMYS OBESUS). Diabetologia 5:379-83, 1969.

Verbatim summary. The fact that the so-called "sand rat" (Psammomys obesus) is highly susceptible to diabetes, and succumbs to it while changing its food from green leaves to laboratory pellets, puzzled us for a long time. Several hypotheses for this phenomenon were suggested, based on the idea that the sand rats are predisposed to diabetes, and that diabetes occurs when the rats are fed on a high caloric diet. In addition to this, it was noticed that the diabetic rats have high plasma insulin levels, which indicated an impairment in their peripheral utilization of glucose. Assuming that the green leaves which the sand rats find in nature prevent their becoming diabetic, we examined the main feeding source of the sand rats in Israel for possible hypoglycemic activity. Press juice from green leaves of Atriplex halimus, as well as their water extract and dialysate, were fed to normal and to alloxan diabetic albino rats, and showed a significant hypoglycemic effect without any decrease in appetite. Moreover, their food and water intake was increased by 50 to 800 per cent within five hours after treatment. The effect was also preserved in the ash of the dialysate. The composition of the hypoglycemic principle is now under study. It is not based on the presence of cations, since the active extracts contained K, Na, Ca, Mg and Al only.

Allison, S. P.; Chamberlain, M. J.; Miller, J. E.; Ferguson, R.; Gillett, A. P.; Bemand, B. V.; and Saunders, R. A. (Depts. of Med. and Experimental Path., Univ. of Birmingham, Birmingham, England): EFFECTS OF PROPRANOLOL ON BLOOD SUGAR, INSULIN AND FREE FATTY ACIDS. Diabetologia 5:339-42, 1969.

Verbatim summary. Three types of experiments were carried out in normal subjects to determine the effect of therapeutic doses of oral propranolol on (1) the blood sugar, plasma insulin and free fatty acids (FFA) during prolonged fasting and exercise, (2) intravenous glucose tolerance and the rise in insulin level after intravenous glucose, and (3) the intravenous glucose tolerance on exercise. Propranolol caused only slight lowering of the blood sugar in normals, even after twenty-four-hour fasting. This was most noticeable during exercise. There was no significant effect of propranolol on fasting insulin levels, on glucose tolerance at rest or exercise, or on the response of plasma insulin levels to intravenous glucose. Lowering of plasma FFA levels was found in all subjects when taking propranolol particularly during and after exercise. Possible mechanisms of hypoglycemia in those cases reported in the literature are discussed. It is concluded that hypoglycemia is not a major problem in propranolol therapy.

Andreani, Domenico; Menzinger, Guido; Fallucca, Francesco; Aliberti, Giuseppe; Tamburrano, Guido; and Cassano, Cataldo (Instituto di II. Clinica Medica, Università degli Studi di Roma and Cattedra di Terapia Medica Sistematica, Università Cattolica del S. Cuore, Rome, Italy): INSULIN LEVELS IN THYROTOXICOSIS AND PRIMARY MYXOEDEMA: RESPONSE TO INTRAVENOUS GLUCOSE AND GLUCAGON. Diabetologia 6: 1-7, 1970.

Verbatim summary. Glucose disappearance, insulin-like activity (ILA) and serum immunoreactive insulin (IRI) were studied after intravenous injection of glucose or glucagon in patients suffering from thyrotoxicosis or primary myxedema. A group of normal subjects was also investigated.