TUCKER

Oral Antidiabetic Therapy 1956-1965

ORAL ANTIDIABETIC THERAPY 1956-1965: WITH PARTICULAR REFERENCE TO TOLBUTAMIDE (ORINASE)

By

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Preface

According to Ellenberg and Rifkin,* "The introduction of the oral hypoglycemic agents has had a great impact on therapy [of diabetes mellitus] and has been a stimulus to certain types of investigations." For these reasons it was thought worthwhile to compile this annotated bibliography. The *therapy* of diabetes mellitus must be the concern of nearly every physician, regardless of his specialty. And because of the pragmatic nature of the treatment of this disease, every newly discovered diabetic marks the beginning of an *"investigation."* Will diet and weight reduction suffice, for example? Will control be adequate with dietary management and oral chemotherapy? Must insulin be used from the outset? What type? What dosage?

The experienced clinician—whether family physician, surgeon, internist, or of whatever other specialty—will surely recognize these statements as self-evident. Then why, he might ask, go back so many years and abstract or cite articles that already seem hopelessly out of date? There were two reasons for doing so, one scientific, the other personal.

Scientifically, oral sulfonylurea therapy represents a remarkable "case history" in drug development. Without going into detail, in the 1930's and 1940's, oral therapy for diabetes had justifiably fallen into disrepute. Then Janbon and his coworkers* reported that 2254 RP (p-aminobenzene-sulfamidoisopropyl-thiodiazol) produced lowering of the blood sugar in patients with typhoid fever. Serendipity, perhaps, but keen clinical observation, certainly. Then Loubatières (see abstracts 66 and 67, 1956) and others did fine work at the animal level and, by 1946, therapeutic human trials were proposed. After a delay of nearly

*Ellenberg, M., and Rifkin, H. (Eds.): *Clinical Diabetes Mellitus*, New York, Blakiston Division, McGraw-Hill Book Co., Inc., 1962, p. xii.

*Janbon, M., Chaptal, J., Vedel, A., Schaap, J.: Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP). *Montpellier méd.*, *21/22*:441-444 (1942).

ten years, these went ahead well in Europe, with particular attention being given to tolbutamide (Hoechst) and carbutamide (Boehringer). By the mid-1950's, both drugs were on the market on the Continent . . . and essentially unknown in the United States.

But in 1955 a new era arose in the management of diabetes mellitus and a new means of obtaining a better understanding of this metabolic disease. A member of the Medical Staff of The Upjohn Company alertly noted a reference to these agents in the Detroit Free Press, and almost immediately arrangements were formalized and supplies of tolbutamide obtained. Cornelius J. O'Donovan, M.D., as clinical monitor, did a masterful and definitive piece of work in setting up and evaluating the clinical investigations; it was a privilege to have a ringside seat. Tolbutamide was finally marketed in this country in 1957, and the experience over the intervening years has documented fully Dr. O'Donovan's conclusions and recommendations. And this is true even though—as perusal of this volume will show—investigations have perhaps become more sophisticated and reports more convincing in recent than in the earlier years.

This work was not done in a vacuum. At the same time, in fact, carbutamide was under intensive study by top-drawer monitors and clinicians. The questions in what was literally a race were simple ones: was the enormous but inestimable potential market for an effective and safe sulfonylurea to be shared? Go to one pharmaceutical house? Or could either obtain clearance from the Food and Drug Administration?

As all workers in the field know, carbutamide was associated with untoward side effects and withdrawn from clinical trial. It differed in structure from tolbutamide in one minor detail (an amino instead of a methyl group), and such a happening should give pause to those who berate the pharmaceutical industry for "molecule manipulation."

Now, a word about the construction of this annotated bibliography. It has been compiled through 1963 from records maintained in the Technical Library of The Upjohn Company. Essentially, the list was originally gathered from *The Upjohn*

Abstracts, Biological Abstracts, Chemical Abstracts, Excerpta Medica, and *Index Medicus.* Where a significant abstract is available in one of the above-mentioned secondary sources, this is noted following the journal citation, through 1963. The following abbreviations have been used to indicate the abstract source:

BA *Biological Abstracts*
CA *Chemical Abstracts*
EM *Excerpta Medica*
II Section 2: Physiology, Biochemistry and Pharmacology
III Section 3: Endocrinology
VI Section 6: Internal Medicine

Journal citations are abbreviated according to the *Index Medicus* method where possible, and *Chemical Abstracts* when not listed in *Index Medicus.*

Selection of particular papers for abstracting depended on their interest at the time of their appearance; thus one may see the changes over the years from "preliminary reports," for example, to articles dealing with thousands of patients followed for several years. A considerable number of abstracts were of reports of the use of sulfonylurea compounds in conditions other than diabetes. Inclusion here should not imply endorsement, acceptance, or approval. In many of these instances, the reader may be intrigued enough to examine the original data. And finally, it should be pointed out that the objective of this collection was to be representative rather than complete, and to have at least some items of interest to every clinician and clinical investigator.

It is a pleasure to acknowledge the expert help of friends in the Technical Library, Frederick J. Bassett, Head Librarian, Virginia Wilcox and her staff of abstractors, from which most abstracts here included have been adapted, and Gloria Wilson and Mildred Philipp, for careful typing and proofreading.

H.A.T.

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ORAL ANTIDIABETIC THERAPY 1956-1965: WITH PARTICULAR REFERENCE TO TOLBUTAMIDE (ORINASE)

ORAL ANTIDIABETIC THERAPY 1956-1965
With Particular Reference to Tolbutamide (Orinase)

1956

1. **Anderson, G. E., Perfetto, A. J., Termine, C. M., Monaco, R. R.:** Hypoglycemic action of Orinase. Effect on output of glucose by liver. *Proc. Soc. Exp. Biol. & Med.*, *92*:340-5 (1956); *CA*, *50*:15904e (1956).

The results of this study suggest that tolbutamide suppresses glucagon production in dogs and therefore reduces the output of glucose by the liver. No evidence was found that it destroys the alpha cells of the pancreas.

The authors have already reported that throughout postabsorption there are aperiodic fluctuations in glucose in hepatic venous blood and that these fluctuations are reflected throughout the major peripheral arterial tree. These fluctuations promptly disappear in both the hepatic vein and peripheral arteries under the influence of tolbutamide, and there is a 33 per cent fall in the rate of output of glucose by the liver in ten minutes after tolbutamide is administered. A small intravenous dose of glucagon immediately reverses this trend, and the normal postabsorptive fluctuations return in exaggerated form. It is suggested that the site of tolbutamide's action is proximal to the phosphorylase enzyme systems and takes the form of a suppression of glucagon production at its source.

Acute signs and symptoms of toxicity were present in a normal dog that had been given very large doses of tolbutamide (200 mg/kg/day) for seventy days, but there were no histopathologic changes in the liver, kidneys, thyroid, adrenals, or pancreas (including alpha-beta cell ratios).

2. Another oral drug for diabetes (Editorial): *Canad. M. A. J.*, *75*:224-5 (1956).

An excellent symposium published in the *Deutsche Medizin-*

ische Wochenschrift for 25 May and 1 June of this year was mainly concerned with Orinase which is known in Germany as D-860, Rastinon, and Artosin. Work by clinicians, pharmacologists, and other research workers from a number of German cities was reported. Thus far, it seems that D-860 in therapeutic doses is a well tolerated and nontoxic substance. It is not a cure for diabetes, and suitable cases must be selected intelligently.

A total of 781 cases studied in various clinics were discussed. The criteria for selection of patients for D-860 treatment were closely similar to those for BZ55 therapy. At least half of those patients over forty years were able to use D-860 alone, as were 80 per cent of those persons whose diabetes had appeared after the age of fifty. The length of the diabetes showed a doubtful correlation with the effectiveness of the drug. The fat, sthenic type of patient did best on D-860, and 75 per cent of them could use D-860 alone, as compared to only 20 per cent of hyperthyroid types. The response was much better in cases with hypertension than in uncomplicated cases or cases with retinopathy alone. The outlook for D-860 treatment was poor in patients requiring more than 40 units per day of insulin and in those who had been on prolonged insulin therapy.

Side effects with D-860 appeared to be less marked than with BZ55; urticaria appeared in only seven cases and jaundice in one. Constipation developed occasionally. No deterioration in the cardiovascular system was detected during treatment. A precipitate developed in the acidified urine upon addition of sulfosalicylic or picric acid, but this proved to be a harmless excretion product of D-860. Hypoglycemia rarely appeared during D-860 administration, although mild subjective symptoms were noted in some ambulant patients. Careful study of blood and bone marrow did not reveal toxic changes.

3. **Ashmore, J., Cahill, G. F., Jr., Hastings, A. B.:** Inhibition of glucose-6-phosphatase by hypoglycemic sulfonylureas. *Metabolism,* 5:774-7 (1956); *CA,* 51:12352g (1957).
4. **Bänder, A., Scholz, J.:** Special pharmacological investigations with D-860. *Deutsch. Med. Wschr.,* 81:889-91 (1956); *CA,* 51:5292d (1957).

5. **Balduini, M., Boari, L.:** BZ55 and D-860 in therapy of diabetes mellitus. *Boll. Soc. Medicochir. Cremona, 11*: 37-53 (1956).
6. **Beaser, S. B.:** The use of Orinase in diabetes. *Metabolism, 5*:933-9 (1956); *BA, 31*:21338 (1957).
7. **Bergesi, G., Curatolo, F., Dal Vit, S., Donini, P., Marchetti, E., Montezemolo, R., Puzzuoli, D.:** Pharmacological observations on D-860, a hypoglycemic preparation active by oral administration, free of bacteriostatic effects (glicotron Serono). *Rass. Clin. Ter., 55*:211-24 (1956), *CA, 51*:6849f (1957).
8. **Berthet, J., Sutherland, E. W., Makman, M. H.:** Observations on the action of certain sulfonylurea derivatives. *Metabolism, 5*:768-73 (1956); *CA, 51*:12352d (1957).
9. Blood chemistry: *Deutsch. Med. Wschr., 81*:888 (1956); *CA, 51*:5292c (1957).
10. **Böhle, E., Pfeiffer, E. F., Schöffling, K., Steigerwald, H.:** Blood lipid levels and D-860. *Deutsch. Med. Wschr., 81*:838 (1956); *CA, 51*:5291g (1957).
11. **Braverman, A. E., Drey, N. W., Sherry, S.:** Experience with Orinase in the management of adult diabetes. *Metabolism, 5*:911-8 (1956); *BA, 31*:21343 (1957).

This paper describes: (1) clinical experience with tolbutamide in adult diabetic patients, and (2) an intravenous sodium Orinase screening test that may prove helpful in selecting patients for therapy.

Twenty-six diabetic patients were maintained on Orinase for periods up to twenty-two weeks. Most patients were treated with 1 or 2 gm daily, except that larger doses (2 to 6 gm daily) were employed before the therapeutic regimen was considered to have failed. A good response was observed in sixteen (62 per cent), a partial effect in three (11 per cent), and no benefit in seven (27 per cent). Five of the seven failures occurred in individuals who were fifty years old or younger. Urticaria was observed in one patient.

Injection of intravenous sodium tolbutamide, 1 gm, was evaluated as a screening test to predict responsiveness to Orinase because preliminary studies had shown that significant fall in

blood sugar did not occur for approximately four hours after single oral doses of 1 and 2 gm, and blood sugars in control older diabetics decreased spontaneously over four hours of observation under fasting conditions.

Nondiabetics showed an average fall of 37 per cent in the first thirty minutes after injection, and an almost complete return to normal at the end of two hours.

In eleven diabetics who responsed to Orinase therapy, a slower than normal but progressive fall in blood sugar was seen, averaging 26 per cent (range 15-43 per cent) at two hours. In four diabetics who did not respond to therapy, the blood sugar fall averaged only 7 per cent (range 0 to 14 per cent) at two hours. These limited data suggest that a fall of 15 per cent or greater in the blood sugar two hours after the intravenous administration of 1 gm of sodium Orinase is associated with good response to oral therapy.

12. **Brown, J., Solomon, D. H.:** Effects of tolbutamide and carbutamide on thyroid function. *Metabolism, 5*:813-9 (1956); *CA, 51*:12353i (1957).
13. **Camerini-Davalos, R., Marble, A., Root, H. F.:** Clinical experience with Orinase. A preliminary report. *Metabolism, 5*:904-10 (1956); *EM; VI; 12*:2373 (1958).
14. **Canal, N., Garattini, S., Tessari, L.:** A new hypoglycemizing drug: 1-sulfanilyl-3-butylurea. II. Peripheral mechanism of action. *Clin. Ter. (Roma), 11*:472-6 (1956); *CA, 51*:16952e (1957).
15. **Canal, N., Garattini, S., Tessari, L.:** The peripheral activity of some new urea derivatives on the hypoglycemic action. *Boll. Soc. Ital. Biol. Sper., 32*:491-4 (1956); *CA, 51*:3844d (1957).
16. **Cappelli, V., Dozio, G., Noli, S.:** Mechanism of action of hypoglycemic sulfamides. *Boll. Soc. Ital. Biol. Sper., 32*:916-8 (1956); *CA, 51*:9937b (1957).
17. **Cavallero, C., Malandra, B.:** Hypoglycemic activity of the new drugs, BZ55 and D860. *Boll. Soc. Ital. Biol. Sper., 32*:745-8 (1956); *CA, 51*:6876g (1957).
18. **Clarke, W. T. W.:** Clinical experience with U-2043 (Orinase). *Canad. M. A. J., 74*:998 (1956).

During a period of three months, the author has tried tolbutamide in six diabetic patients. Orinase (0.5 gm two or four times daily) without insulin showed a hypoglycemic effect on three patients aged fifty-one to sixty-eight years who had been diabetic for two or three years.

Vague symptoms of lightheadedness and indigestion caused one patient to discontinue Orinase, although they may not have been due to the drug. Orinase had no hypoglycemic effect in two patients; one was a twenty-seven-year-old woman who was diabetic for two years and other was a thirty-seven-year-old man who had been diabetic for twenty years. Orinase was effective in a seventeen-year-old boy who had been diabetic for two years and who had remained well but underweight on a restricted diet without insulin; after starting tolbutamide he became aglycosuric with a fasting blood sugar level of 95 mg per cent and he gained weight as a result of being able to increase his diet.

19. **Colwell, A. R.:** Oral antidiabetic sulfonamides. *Diabetes*, 5:62-3 (1956).

Two new oral antidiabetic arysulfonylureas, N_1-sulfanilyl-N_2-n-butylcarbamide (BZ55) and N_1-p-tolylsulfonyl-N_2-n-butylurea (U-2043 or D860), are under intensive investigation. These substances in single oral doses will lower the blood sugar promptly and substantially in normal men, dogs, and rabbits; hypoglycemic effects occur within an hour or two (earlier when given with alkali) and persist for hours. Abnormal glycosuria and hyperglycemia can be reduced or eliminated by these compounds in many patients with mild or moderately severe diabetes mellitus; Franke and Fuchs reported eight cases where this happened, and they claim similar results were obtained in 80 per cent of fifty diabetics treated in Berlin for periods up to one year. Bertram, Bendfeldt, and Otto reported the successful control of diabetes following the use of a sulfonamide in twenty-five of twenty-eight older patients with mild diabetes who were not using insulin and in twenty-eight of thirty-eight patients in which the compound was substituted for insulin. The sulfonamide had no effect in younger patients with severe forms of diabetes.

Toxic side effects seem to be negligible with the compounds, and the LD_{50} dosages in animals are high. Skin reactions may occur, but hematologic, hepatic, and renal effects are seldom noted. Therapeutically effective blood sulfonamide levels of 10 to 15 mg per 100 ml can be obtained with approximately 1 gm per day, following larger priming doses for the first day or two. Blood levels fall slowly for days after withdrawal of the drug.

Investigators agree that the compounds are totally ineffective in "pancreatectomy diabetes" and relatively ineffective in alloxan diabetes.

No compounds of this type are on the U.S. market at the present time and intensive investigations concerning indications, mechanism of action, and particularly dangers from continued use are being carried on by two pharmaceutical firms which are testing the compounds in diabetic patients in selected clinics and laboratories. Probably these more convenient forms of medication for diabetes will be available for use by the end of this year, if their safety is verified by the investigators.

20. **Colwell, A. R., Jr., Colwell, J. A., Colwell, A. R., Sr.:** Intrapancreatic perfusion of the antidiabetic sulfonylureas. *Metabolism,* 5:749-56 (1956); *CA,* 51:12351i (1957).
21. **Cox, R. W., Henley, E. D., Fergus, E. B., Williams, R. H.:** Sulfonylureas and diabetes mellitus. I. Clinical evaluation. *Diabetes,* 5:358-65 (1956); *CA,* 52:11276g (1958).

Supplementary insulin was not required to control diabetes adequately in half of fifty-six patients treated with tolbutamide or carbutamide. Good responses to the sulfonylureas can be predicted in patients who are over forty years of age, endomorphic, require less than 30 units per day of insulin, have had diabetes for less than five years, have received insulin for less than one year, and do not have severe diabetic complications. These drugs are indicated in essentially all diabetic patients of the maturity-onset type without a history of sulfonamide sensitivity, suggestion of collagen disease, or severe allergic responses of other types. Patients in acidosis and those subjected to severe stress should

be treated with insulin, either alone or combined with an arylsulfonylurea.

Serious toxicity was not observed in this series. Nausea, giddiness, drowsiness, and paresthesias appeared in a few patients when therapy was begun.

Therapeutic doses of sulfonylureas did not alter the metabolic responses to insulin, glucagon, and epinephrine.

22. **Cox, R. W., Henley, E. D., Williams, R. H.:** Sulfonylureas and diabetes mellitus. II. Preliminary studies of the mechanism of action. *Diabetes, 5*:366-77 (1956); *CA, 52*:12207g (1958).
23. **Creutzfeldt, W.:** D-860: a new oral antidiabetic drug; pharmacological experimental and clinical studies (Review section). *German Med. Monthly, 1*:253-6 (1956).
24. **Creutzfeldt, W.:** Pancreatic findings in diabetic patients after treatment with D-860. *Deutsch. Med. Wschr., 81*:841-4 (1956); *CA, 51*:5291i (1957).
25. **Creutzfeldt, W., Böttcher, K.:** D-860 and alloxan diabetic rabbits. *Deutsch. Med. Wschr., 81*:896-9 (1956); *CA, 51*:5292h (1957).
26. **Creutzfeldt, W., Ehrhart, H., Marx, R., Maske, H., Mohnike, G., Pfeiffer, E. F., Schlagintweit, St., Schöffling, K., Seidler, I., Steigerwald, H., Stich, W., Stötter, G., Ulrich, H.:** Treatment of diabetes with D-860; a joint report of clinical results in 781 patients. *German Med. Monthly, 1*:246-51 (1956).

Clinical results with D-860 in 781 diabetic patients are reported jointly by five groups of workers at hospitals and clinics. Cases of diabetes of different types and of varying severity were represented, and the patients were of all ages. Daily doses of 3 gm were generally used initially, and they were reduced gradually by 0.5 gm to a maintenance dose of 0.5 to 1.5 gm per day.

A total of 330 patients were selected, i.e., they seemed suitable for treatment with D-860. There were twenty-seven failures in this group.

A study was made of the factors affecting the success of treatment with D-860 in the 451 unselected cases. There was a posi-