

ORAL HYPOGLYCEMIC AGENTSCase 1.

This 57 year old [redacted] woman was first diagnosed as having diabetes mellitus in 1959 when she developed polydipsia and polyuria. The family history was positive in that one sister had diabetes. She was placed on tolbutamide therapy, 1.0 G daily, at the time of diagnosis. In the ten years since she has done exceedingly well. She was hospitalized in 1966 for a cellulitis of the left leg which followed a traumatic injury. She has never had ketoacidosis or hypoglycemia. Her weight on diagnosis was 237 pounds. At one period she lost 41 pounds but currently has gained back to 236 pounds. She has no evidence of retinal or renal disease. She feels well and has no polyuria while taking 1.5 G of tolbutamide daily. At her last clinic visit the ankle reflexes were noted to be slightly depressed with a questionable slowing of return. A PBI was obtained and reported as 7.5  $\mu$ G%.  $T_3$  resin uptake was 27.5%. Fasting blood sugars on the last three clinic visits were 170, 190, and 192 mgs%.

Case 2.

This 46 year old woman was diagnosed as having diabetes mellitus after the onset of symptoms of polyuria in 1965 at the age of 41. Fasting blood sugars were in the 200-300 mg% range. Urinalysis showed strongly positive acetone. The patient was started on tolbutamide and over several weeks was taken to maximal doses of 3.0 G per day. When blood sugars failed to respond, phenformin 100 mg daily was added to the schedule. Despite this, all urines in the clinic showed strongly positive acetone. After two months the patient was switched to insulin with disappearance of ketones in the urine. Blood sugars were erratically controlled with occasional episodes of hypoglycemia. One year after diagnosis she developed frank diabetic ketoacidosis after a period of gastroenteritis. She has subsequently had two more episodes of diabetic acidosis. On [redacted]/69 the fasting blood sugar was 241 mgs% while taking 40 units of NPH insulin daily. She has had one recent hypoglycemic episode.

Case 3.

This 72 year old [redacted] woman was in good health until about 3-4 weeks prior to her first [redacted] admission when she developed polydipsia and increased urine output coupled with easy fatigability. She was seen by her private physician and a diagnosis of diabetes mellitus was made. Treatment was started with diet alone. Five days prior to admission she was seen again by her physician, who found a blood sugar of 167 mgs%. She was started on acetohexamide (Dymelor) 250 mg twice daily. On the day of admission, about 9 hours prior to arrival at the hospital emergency room, she was found unconscious in her home. She had been incontinent of urine and feces. On examination she was found to be a modestly obese, unconscious woman with no localizing neurological signs. B.P. was 180/94, pulse 80 and respirations 16 per minute. She had bilateral cataracts which precluded retinal examination. No other findings of significance were noted, though subsequently she was found to have a moderate sensory loss on the right and an expressive aphasia. A blood sugar drawn on arrival was 40 mgs% by dextrostix and 50 mgs% in the regular lab. She was given 50 cc's of 50% glucose with apparent dramatic response. Additional laboratory workup of interest was a BUN of 50 mgs%, sodium 140 meq/liter, potassium 3.7 meq/liter and  $CO_2$  of 16 meq/liter.

Following the 50% glucose the patient was started on 10% dextrose in water IV. Four hours after admission, having received 125 grams of carbohydrate, the blood sugar was 223 mgs%. Nine hours later after an additional 550 grams of carbohydrate the blood sugar had decreased to 150 mgs. In the next 16 hours she was given 630 grams of glucose, but the blood sugar fell to 80 mgs%. Over the next 8 hour period 300 grams of dextrose was given with the blood sugar remaining 71 mgs%. She thus received 1600 grams of carbohydrate in a 35 hour period. It is of interest that throughout this period the urines had been free of sugar.

On the third hospital day the patient began to spill sugar in the urine and for the first time had an elevated blood sugar of 391 mgs%. She was able to eat. On the fourth hospital day the glucose drip was stopped and the patient carefully watched. The following sequence of events transpired:

<u>Time</u>	<u>Blood sugar</u>
1100	302 mgs%
1200	116 mgs%
1300	74 mgs%
1330	52 mgs% (blurred vision, ↑ confusion)
1400	46 mgs% (glucagon 0.5 mg I.M.)
1430	130 mgs%
1500	138 mgs%
1600	92 mgs%
1700	72 mgs%
1800	62 mgs%

Carbohydrate was restarted at 1800.

On the 5th hospital day the patient was found to be able to maintain normal blood sugars on oral feedings alone. She subsequently recovered without difficulty. Blood sugars remained normal and no diabetic medications were required.

<u>Fasting blood sugar</u>	<u>Percent of total patients</u>	
	<u>Oral agents</u>	<u>Insulin</u>
< 100		11
100-149		9
150-199		21
200-300		26
> 300		30

PARKLAND MEMORIAL HOSPITAL DIABETIC CLINIC

Active patients: 1556

TABLE I

Treatment	Percent of total patients
Diet alone	6
Oral hypoglycemic agents*	76
a. Tolbutamide	46
b. Tolbutamide + phenformin	30
Insulin <sup>†</sup>	18

\* 3% previously treated with insulin.

† 22% previously treated with oral agents.

TABLE II

Fasting blood sugar	Percent of total patients	
	Oral agents	Insulin
< 100	1	11
100-149	15	9
150-199	29	21
200-300	43	28
> 300	12	30

TABLE III

Weight	Percent of total patients	
	Oral agents - diet*	Insulin†
< 100	1	6
100-149	32	46
150-199	54	37
200-249	17	11
250-300	7	--
* Mean weight of patients on oral agents or diet		170
† Mean weight of patients on insulin		152

# REFERENCES

## Reviews

1. Davidoff, F. F. Oral hypoglycemic agents and the mechanism of diabetes mellitus. New England J. Med. 278:148, 1968.
2. Loubatieres, A. The hypoglycemic sulfonamides: history and development of the problem from 1942 to 1955. Ann. N.Y. Acad. Sci. 71:4, 1957.
3. Madsen, J. Extrapankreatic and intrapancreatic action of antidiabetic sulphonylureas. A review. Acta. Med. Scand. Suppl. 476:110, 1967.

## Insulin secretion and mechanism of action of the sulfonylureas

4. Arky, R. A. and Abramson, E. A. Insulin response to glucose in the presence of oral hypoglycemics. Ann. N.Y. Acad. Sci. 148:768, 1968.
5. Bressler, R., Cordon, M. V. and Brendel, K. Studies on the role of adenylyclase in insulin secretion. Arch. Int. Med. 123:248, 1969.
6. Chu, P. C., Conway, M. J., Krouse, H. A. and Goodner, C. J. The pattern of response of plasma insulin and glucose to meals and fasting during chlorpropamide therapy. Ann. Int. Med. 68:751, 1968.
7. Grodsky, G. M., Bennett, L. L., Smith, D. and Nemecek, K. The effect of tolbutamide and glucose on the timed release of insulin from the isolated perfused pancreas. In Tolbutamide After Ten Years. W. J. H. Butterfield and W. Van Westering, editors. Excerpta Medica Foundation. New York, 1967. p 11.
8. Hirata, Y. and Blumenthal, H. T. Blood sugar and antiinsulin serum levels of actively and passively immunized rabbits. Diabetes 11 (Suppl.):26, 1962.
9. Loubatieres, A., Mariani, M. M., Alric, R. and Chapal, J. Antagonistic mechanism of action of tolbutamide and diazoxide on insulin secretion. Tolbutamide After Ten Years, op.cit.p 100.
10. Malaisse, W. J., Malaisse-Lague, F., Mayhew, D. A. and Wright, P. H. Effects of sulfonylureas upon insulin secretion by the rat's pancreas. Tolbutamide After Ten Years, op.cit. p 49.
11. Pfeiffer, E. F. Dynamics of insulin secretion in normal, obese and diabetic subjects

- following beta cell stimulation. Tolbutamide After Ten Years, op.cit. p 127.
12. Reaven, G. and Dray, J. Effect of chlorpropamide on serum glucose and immunoreactive insulin concentrations in patients with maturity onset diabetes. *Diabetes* 16:487, 1967.
  13. Porte, D. Jr., Sympathetic regulation of insulin secretion. *Arch. Int. Med.* 123:252, 1969.
  14. Seltzer, H. S. Comparative insulinogenic potencies of glucose and sulfonylurea compounds. *Diabetes* 11 (Suppl):11, 1962.
  15. Seltzer, H. S., Allen, E. W., Herron, A. L. Jr. and Brennan, M. T. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. *J. Clin. Invest.* 46:323, 1967.
  16. Seltzer, H. S. and Crout, J. R. Modification of diazoxide inhibition of insulin secretion by tolbutamide. *Tolbutamide After Ten Years, op.cit.* p 114.
  17. Sheldon, J., Taylor, K. W., and Anderson, J. The effects of long term acetohexamide treatment on pancreatic islet cell function in maturity onset diabetes. *Metabolism* 15:874, 1966.
  18. Sussman, K. E., Stjernholm, M. and Vaughan, G. D. Tolbutamide and its effect upon insulin secretion in the isolated perfused rat pancreas. *Tolbutamide After Ten Years, op.cit.* p 22.
  19. Weber, G., Singhal, R. L., and Srivastava, S. K. Insulin: Suppressor of biosynthesis of hepatic gluconeogenic enzymes. *Proc. Nat'l. Acad. Sci.* 53:96, 1965.

#### Extrapancreatic effects of sulfonylureas

20. Bewsher, P. D., Mayhew, D. and Ashmore, J. Studies on the antiketogenic effects of tolbutamide. *Tolbutamide After Ten Years, op.cit.* p 208.
21. DeBeer, L. and De Schepper, P. J. Metabolic effects of hypoglycemic sulfonylureas. II. In vitro effect of sulfonylureas on cell free protein synthesis and energy metabolism in rat tissues. *Biochem. Pharm.* 16:2355, 1967.
22. DeSchepper, P. J. Metabolic effects of hypoglycemic sulfonylureas I. In vitro effect of sulfonylureas on leucine incorporation and metabolism and on respiration of rat tissues. *Biochem. Pharm.* 16:2337, 1967.
23. Feldman, J. M. and Lebovitz, H. F. Appraisal of the extrapancreatic actions of sulfonylureas. *Arch. Int. Med.* 123:314, 1969.
24. Hershman, J. M. and Konerding, K. Effects of sulfonylurea drugs on the thyroid and serum binding of thyroxine in the rat. *Endocrinology* 83:74, 1968.
25. McGavack, T. H., Seegers, W., Haar, H. O., Enzinger, J. and Erk, V. O. Thyroid function of diabetic patients as influenced by the sulfonylureas. *Ann. N.Y. Acad. Sci.* 71:268, 1957.
26. Schless, G. L. and Lee, C. T., Jr. Oral hypoglycemic therapy and associated hypothyroidism. *Ann. N.Y. Acad. Sci.* 148:813, 1968.
27. Signorelli, S. Tolerance for alcohol in patients on chlorpropamide. *Ann. N.Y. Acad. Sci.* 74:900, 1959.
28. Stone, D. B. and Brown, J. D. Effect of sulfonylurea drugs on plasma free fatty acids and blood glucose concentration in man. *Diabetes* 15:314, 1966.
29. Stone, D. B. and Brown, J. D. The in vitro effects of tolbutamide on adipose tissue. *Tolbutamide After Ten Years, op.cit.* p 202.

#### Mechanism of action of phenformin.

30. Altschuld, R. A. and Kruger, F. A. Inhibition of hepatic gluconeogenesis in guinea pig by phenformin. *Ann. N.Y. Acad. Sci.* 148:612, 1968.
31. Beckmann, R. The fate of biguanides in man. *Ann. N.Y. Acad. Sci.* 148:820, 1968.
32. Grodsky, G. M., Karam, J. H., Pavlatos, F. C. and Forsham, P. H. Reduction by phenformin of excessive insulin levels after glucose loading in obese and diabetic subjects. *Metabolism* 12:278, 1963.
33. Kreisberg, R. A. Kinetics of glucose utilization in obesity: the effect of phenformin. *Ann. N. Y. Acad. Sci.* 148:743, 1968.



### Therapy of diabetes mellitus with oral agents

34. Barrett, J. C. and Boshell, B. R. Tolbutamide in the therapy of insulin resistance. *Diabetes* 11(Suppl):35, 1962.
35. Benner, E. J., Partridge, J. W. and Holcomb, B. An evaluation of long-term chlorpropamide therapy. *J.A.M.A.* 193:107, 1965.
36. Bernhard, H. Long-term observations on oral hypoglycemic agents in diabetes. *Diabetes* 14:59, 1965.
37. Camerini-Davalos, R., Lozano-Castaneda, O. and Marble, A. Five years experience with tolbutamide. *Tolbutamide After Ten Years*, op.cit. p 74.
38. Clarke, B. F. and Duncan, L. J. P. Comparison of chlorpropamide and metformin treatment on weight and blood glucose response of uncontrolled obese diabetics. *Lancet* 1: 123, 1968.
39. Galloway, J. A., McMahan, R. E., Culp, H. W., Marshall, F. J. and Young, E. C. Metabolism, blood levels, and rate of excretion of acetohexamide in human subjects. *Diabetes* 16:118, 1967.
40. Hickman, J. W. and Kirtley, W. R. Five years experience with Dymelor. *J. Ind. State Med. Assoc.* 61:1114, 1968.
41. Horton, E. S., Scheikhoulislam, B. M. and Bressler, R. Combined sulfonylurea-phenformin therapy of the dysinsulinism of early diabetes. *Ann. N.Y. Acad. Sci.* 148:778, 1968.
42. Krall, L. P. and Balodimos, M. C. Combined sulfonylurea - biguanide therapy of diabetes mellitus. *Tolbutamide After Ten Years*, op.cit. p 303.
43. Mehnert, H. Clinical and experimental findings after five years treatment of diabetes with sulfonylureas. *Tolbutamide After Ten Years*, op.cit. p 80.
44. Meinert, C. L. and Schwartz, T. B. The relationship of treatment to weight in a randomized study of maturity onset diabetes. *Ann. N. Y. Acad. Sci.* 148:875, 1968.
45. Moorhouse, J. A. A comparison of the effects of tolazamide and tolbutamide upon blood glucose and serum insulin and lipid levels in diabetic subjects. *Canad. Med. Assoc. J.* 96:536, 1967.
46. Sherwood, G. and Bressler, R. Comparison of chlorpropamide with tolazamide in the treatment of diabetes mellitus. *Current Therap. Res.* 10:399, 1968.
47. Singer, D. L. and Nurwitz, D. Long term experience with sulfonylureas and placebo. *New Eng. J. Med.* 277:450, 1967.
48. Unger, R. H., Madison, L. L., and Carter, N. W. Tolbutamide-phenformin in ketoacidosis resistant patients. *J.A.M.A.* 174:2132, 1960.

### Sulfonylurea induced hypoglycemia

49. Alexander, R. W. Prolonged hypoglycemia following acetohexamide administration. *Diabetes* 15:362, 1966.
50. Bauer, H. G. Severe and prolonged hypoglycemic shock during sulfonylurea treatment. *Metabolism* 14:220, 1964.
51. Coates, J. R. and Robbins, J. J. Severe hypoglycemic shock due to chlorpropamide. *J.A.M.A.* 170:941, 1959.
52. Cushman, P., Dubois, J. J., Dwyer, E. and Izzo, J. L. Protracted tolbutamide hypoglycemia. *Amer. J. Med.* 35:196, 1963.
53. Davies, D. M., McIntyre, A., Millar, E. J., Bell, S. M. and Mehra, S. K. Need for glucagon in severe hypoglycemia induced by sulphonylurea drugs. *Lancet* 1:363, 1967.
54. Lampe, W. T., II. Hypoglycemia due to acetohexamide. Treatment by peritoneal dialysis. *Arch. Int. Med.* 120:239, 1967.
55. Marri, G., Cozzolino, G., and Palumbo, R. Glucagon in sulfonylurea hypoglycemia? *Lancet* 1:303, 1968.
56. Soeldner, J. S. and Steinke, J. Hypoglycemia in tolbutamide-treated diabetes. *J.A.M.A.* 193:398, 1965.

57. Wishinsky, H., Glasser, E. J., and Perkol, S. Protein interactions of sulfonylurea compounds. *Diabetes II (Suppl)*:18, 1962.
58. Zucker, P. and Simon, G. Prolonged symptomatic neonatal hypoglycemia associated with material chlorpropamide therapy. *Pediatrics* 42:824, 1968.

#### Sulfonylurea-drug interactions

59. Brook, R., Schrogie, J. J. and Soloman, H. M. Failure of probenecid to inhibit the rate of metabolism of tolbutamide in man. *Clin. Pharm. Therap.* 9:314, 1968.
60. Christensen, L. K., Hansen, J. M. and Kristensen, M. Sulphaphenazole-induced hypoglycemic attacks in tolbutamide-treated patients. *Lancet* 2:1298, 1963.
61. Cooper, A. J. and Ashcroft, G. Modification of insulin and sulfonylurea hypoglycemia by monamine oxidase inhibitor drugs. *Diabetes* 16:272, 1967.
62. Field, J. B., Ohta, M., Boyle, C. and Remer, A. Potentiation of acetohexamide hypoglycemia by phenylbutazone. *New Eng. J. Med.* 17:889, 1967.
63. Kristensen, M. and Hansen, J. M. Potentiation of the tolbutamide effect by dicoumarol. *Diabetes* 16:211, 1967.
64. Poucher, R. L. and Vecchio, T. J. Absence of tolbutamide effect on anticoagulant therapy. *J.A.M.A.* 197:1069, 1966.
65. Soloman, H. M. and Schrogie, J. J. Effect of phenylamidol and bis-hydroxycoumarin on the metabolism of tolbutamide in human subjects. *Metabolism* 16:1029, 1967.

#### Sulfonylureas and the diagnosis of islet cell tumors

66. Floyd, J. C., Fajans, S. S., Knopf, R. I. and Conn, J. W. Plasma insulin in organic hyperinsulinism. Comparative effects of tolbutamide, leucine, and glucose. *J. Clin. Endocr.* 24:746, 1969.
67. Johnston, R., Goetz, F. C. and Zimmerman, B. Insulin secreting tumor of the pancreas; report of a case with an untoward response to tolbutamide and with a study of the possible mechanism of postoperative hyperglycemia. *New Eng. J. Med.* 263:1345, 1960.
68. Maingay, D., DeRuyter, H. A., Touber, J. L., Croughs, R.J.M., Stopman, W. and Lequin, R. M. *Lancet* 1:361, 1967.
69. Samols, E. and Marks, V. Evaluation of the intravenous tolbutamide test in the recognition and differential diagnosis of spontaneous hypoglycemia. *Tolbutamide After Ten Years*, op.cit. p 147.
70. Steinke, J. and Soeldner, J. S. Response of serum insulin to intravenous tolbutamide in patients with hypoglycemia. *Tolbutamide After Ten Years*, op.cit. p 140.

#### Use of sulfonylureas in non-diabetic states

71. Ahmed, I., Ahmad, B. and Hussein, M. F. The use of chlorpropamide in the treatment of Parkinsonism. *Brit. J. Clin. Pract.* 22:293, 1968.
72. Ardumo, F., Ferraz, F. P. J., and Rodriguez, J. Antidiuretic action of chlorpropamide in idiopathic diabetes insipidus. *J. Clin. Endo. Metab.* 26:1325, 1966.
73. Feforzo-Membrives, J., Moledo, L. I., Lanaro, A. E. and Megios, A. Antidiuretic effect of L-propyl-3-p-chlorobenzene sulfonylurea (Chlorpropamide). *J. Clin. Endo. Metab.* 28:332, 1968.
74. Hacken, A. G. and Langson, D. Reduction of free water clearance by chlorpropamide. *Brit. M. J.* 1:355, 1968.