MEDICINE GRAND ROUNDS
UNIVERSITY OF TEXAS SOUTHWESTERN
MEDICAL CENTER AT DALLAS

AUGUST 1, 1996

THE ORAL THERAPY OF NON-INSULIN DEPENDENT DIABETES MELLITUS

"SOMETHING OLD, SOMETHING NEW, SOMETHING BORROWED AND SOMETHING BLUE"

PHILIP RASKIN, M.D.

Non-insulin dependent diabetes mellitus is not just a "touch of sugar" as many patients and physicians think. Rather, it is a serious chronic illness with health care costs in the billions of dollars, annually. In the United States, diabetes ranks as the leading cause of new blindness in adults and it is the leading cause of end stage renal failure. Diabetes is also the leading cause of non-traumatic amputation. Amputation is usually the end result of diabetic neuropathy with resulting foot ulceration.

Fortunately, most individuals with diabetes never go blind, do not end up on dialysis or have an amputation. What does cause diabetic individuals the majority of their problems and is so expensive is the macrovascular disease that occurs at such a high frequency in diabetic people. Strokes are four times more common in diabetic individuals than in people without diabetes. The presence of peripheral vascular disease complicates the management of foot ulcers, and contributes to the high amputation rate. The big killer is coronary artery disease, however. Men with diabetes are twice as likely to have coronary artery disease than men of the same age who don't have diabetes. Women are four to five time more likely to have coronary artery disease than non-diabetic women of the same age. Why women with diabetes are at such a high risk for coronary artery disease is unknown. Mortality rates for insulin dependent diabetic patients are five to seven times that of the general population for men and nine to twelve times that for women. Life expectancy for people with insulin dependent diabetes is reduced by 15

rate that is twice that of adults in the general populations. Life expectancy is reduced five to 10 years and is greater in women than in men.

Diabetes is a much more common disease today than it has been in the past. Figure 1 shows Maureen Harris' data on the increasing peak prevalence of diabetes from 1976 to 1980. In this survey the prevalence of diagnosed diabetes was approximately 6%. Of great interest, is the fact that another 6% of the population also had diabetes, but it was undiagnosed. The failure to diagnose diabetes is an important problem and explains why many individuals (approximately 20%) with NIDDM already have chronic complications at the time their diabetes is discovered.

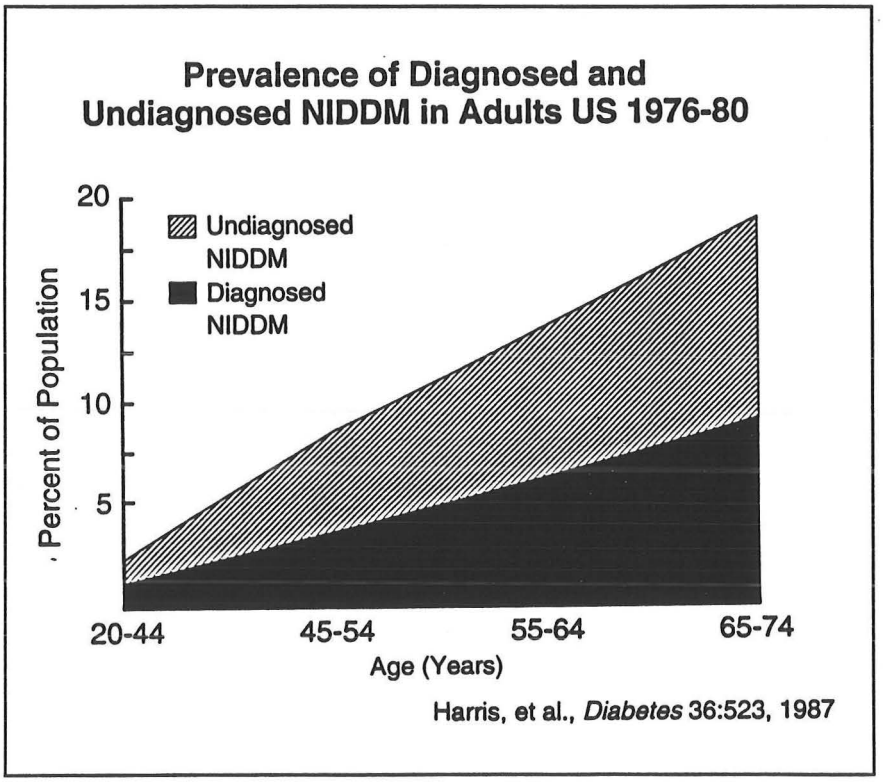

Figure 1

There are two main types of diabetes, insulin dependent and non-insulin dependent. Although the precise diagnosis is not always apparent, the major difference between insulin dependent and non-insulin dependent diabetes is the ability to secrete insulin. Individuals with insulin dependent diabetes mellitus have no endogenous insulin secretory capacity and thus are dependent upon the daily administration of insulin for their survival. Individuals with non-insulin dependent diabetes, although insulin deficient, can secrete some insulin. Although approximately 60% of individuals with this type diabetes, require insulin treatment to control hyperglycemia, they can "survive" in its absence. The major clinical features of both types of diabetes are presented in Table 1 and Table 2.

Table 1

INSULIN DEPENDENT DIABETES MELLITUS

- Insulinopenic
- Dependent to Exogenous Insulin
- Prone to Ketoacidosis
- Usually Lean, but not always
- Recent Weight Loss
- Abrupt Onset of Symptoms, often before age 30
- May Occur at Any Age

Table 2

NON-INSULIN DEPENDENT DIABETES MELLITUS

- May Be Free of Classic Symptoms
- May Require Exogenous Insulin
- Not Prone to Ketoacidosis
- Family History of Diabetes Mellitus
- Usually Obese
- Usually Diagnosed after Age 30, but not always

Figure 2 shows the pathogenesis of non-insulin dependent diabetes. Non-insulin dependent diabetes is a heterogeneous disorder with two major pathogenic features. First of all, there is insulin deficiency. All individuals with diabetes have defective insulin secretion. Individuals with insulin dependent diabetes have an absolute insulin deficiency. Those with non-insulin dependent diabetes have a relative insulin deficiency. In addition to insulin deficiency, most patients with non insulin dependent diabetes have some degree of insensitivity to insulin, more commonly referred to as "insulin resistance". Both the liver and muscle tissue are "resistant" to the effects of insulin. This results in an increase in hepatic glucose production at times when the liver should not be releasing glucose into the circulation and defective glucose uptake in muscle. The combination of increased glucose entry into the circulation and decreased glucose utilization by muscle results in hyperglycemia. Although most individuals with NIDDM are somewhat insulin resistant, insulin resistance is really related to body mass index. The fatter someone is the

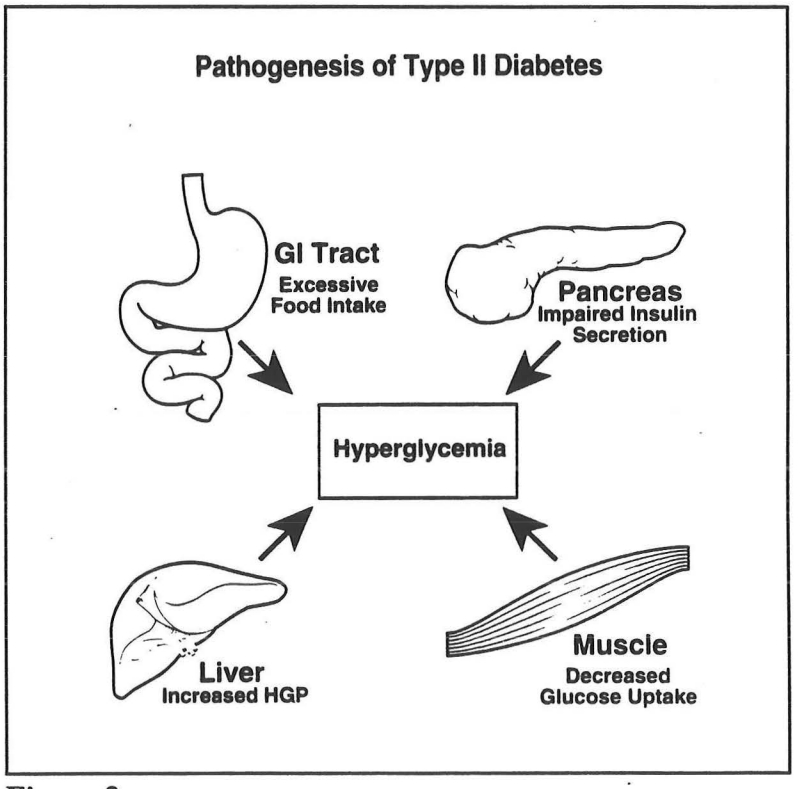

Figure 2

more insulin resistant they will be.

The rationale for the management goals for NIDDM include the fact that good glycemic control will reduce the microvascular complications of diabetes and that careful management of associated cardiovascular risk factors (hypertension, hyperlipidemia, etc), so common in individuals with non-insulin dependent diabetes, will reduce macrovascular disease. Finally, given today's climate, appropriate early health care can reduce overall health care costs.

The data, that improved glycemic control will reduce the development and progression of the microvascular complications are irrefutable. These data come from the DCCT which showed an appropriate 50-60% reduction (Table 3) in the risk of the development and progression of diabetic retinopathy, nephropathy and neuropathy in those individuals randomized to the intensive treatment group. Perhaps even more importantly, the risk of the development of macrovascular events was reduced by 44%. Although this risk reduction did not reach statistical significance , because there were too few events, I believe that improved glycemic control will help reduce the very

Table 3

DCCT

INTENSIVE DIABETES TREATMENT REDUCED

• Retinopathy	63%
• Nephropathy	54%
• Neuropathy	60%
• Macrovascular Events	44%

high frequency of macrovascular disease seen in diabetic individuals.

Although the DCCT studied individuals with insulin dependent diabetes, the DCCT study group concluded that the data obtained in the DCCT on individuals with insulin dependent diabetes could be extrapolated to all individuals with diabetes. Thus, the goal of therapy for all individuals with diabetes is a glycosylated hemoglobin level in the range of individuals without diabetes. It makes no real difference whether one measures a total glycosylated hemoglobin (as we do at Parkland and the Aston Center), a HbA1 or a HbA1c. Other than the absolute value obtained, there is little clinical difference. What is important for the laboratory to provide is the reference range for individuals without diabetes. Other treatment goals for individuals with non-insulin dependent diabetes are listed in Table 4.

Table 4

TREATMENT GOALS IN NON-INSULIN DEPENDENT DIABETES

- Clinical Well-Being
- Glycated Hemoglobin in Range of Individuals without Diabetes
- Normal Lipid Levels
- Body Weight Stable and as Close to Normal as Possible

Thus, please understand, that whenever possible , the health care provider, and their patients should strive to achieve a glycosylated hemoglobin level in the range of individuals without diabetes. The relationship between glycosylated hemoglobin and diabetic complications (Figure 3) is curvalinear and not unlike the relationship between serum cholesterol levels and myocardial infarction and blood pressure levels and strokes. There is no plateau. Thus, there is a measurable and relatively stable reduction in the risk of all the diabetic complications for every 10% reduction in the level of glycosylated hemoglobin. Table 5 shows the reduction in risk for the development of diabetic retinopathy for individuals in the intensive treatment group in the DCCT for those with HbA1c levels above and below 8%. Please note that the reduction in risk for each 10% reduction in HbA1c is the same whether or not the HbA1c was above or below 8%. Thus, the closer to normal your patient's glycosylated hemoglobin, the less likely that complications will develop or progress. However, even if one cannot get the glycosylated hemoglobin to normal, any reduction in the level is of benefit to the patient. This true for nephropathy, neuropathy, as well

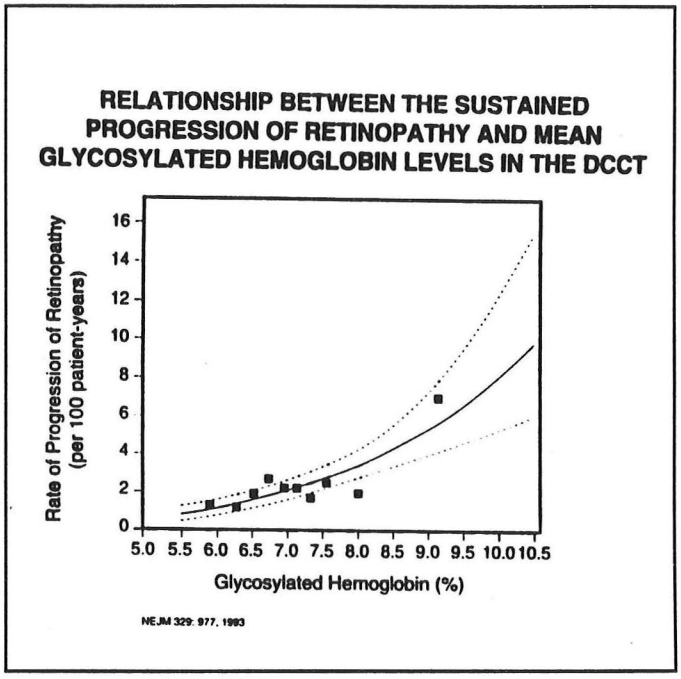

Figure 3

as retinopathy.

Table 5

COMPARISON OF THE RELATIVE RISK REDUCTION FOR RETINOPATHY PROGRESSION ASSOCIATED WITH A 10% LOWER MEAN HbA1c LEVELS BETWEEN HbA1c ABOVE AND BELOW 8%

	HbA1c	
Treatment Group	≤ 8%	>8%
	Risk Reduction %	
Intensive	49	37
Conventional	69	34*
Combined	53	35*

*p= <0.05 vs HbA1c ≤ 8%

The management of non-insulin dependent can now be compared to the way hypertension is managed. Figure 4 shows the algorithm for managing hypertension as recommended by the Joint National Commission. It suggests lifestyle intervention as initial therapy. If this is not successful in achieving the blood pressure goal then some pharmacological intervention is needed. In hypertension, you have

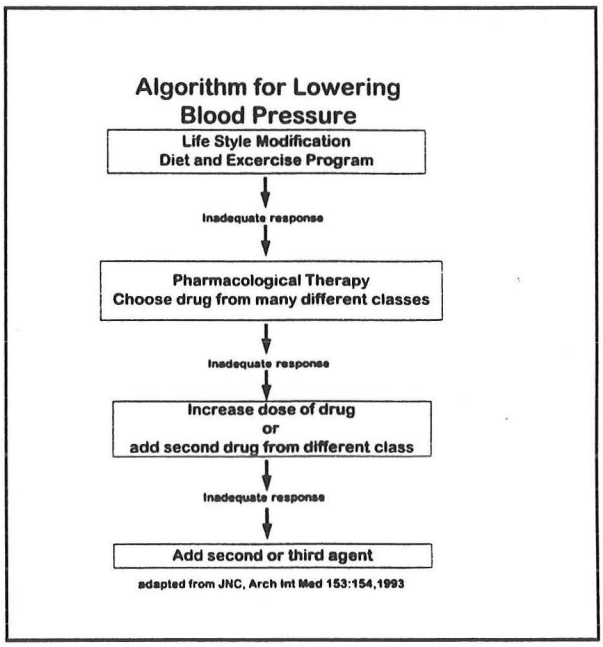

Figure 4

many choices (Figure 5). There are drugs from different classes, with varying mechanisms of action, all of which work together to lower the blood pressure. If the first drug chosen results in an inadequate response, then a drug from a different class is chosen and added to the first.

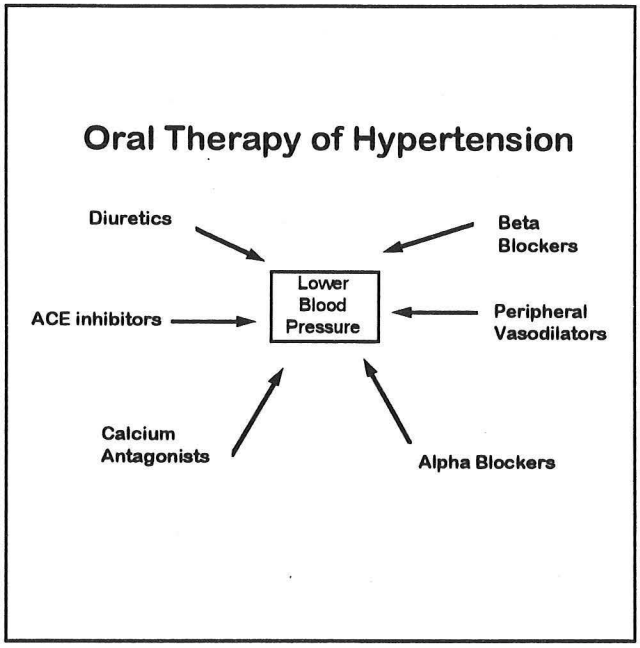

Figure 5

Figure 6 shows the algorithm for the management of non-insulin dependent diabetes that I "borrowed" from the hypertension people. As you can see, the algorithm for the management of non-insulin dependent diabetes is identical to that used in hypertension, except for the drugs that are used.

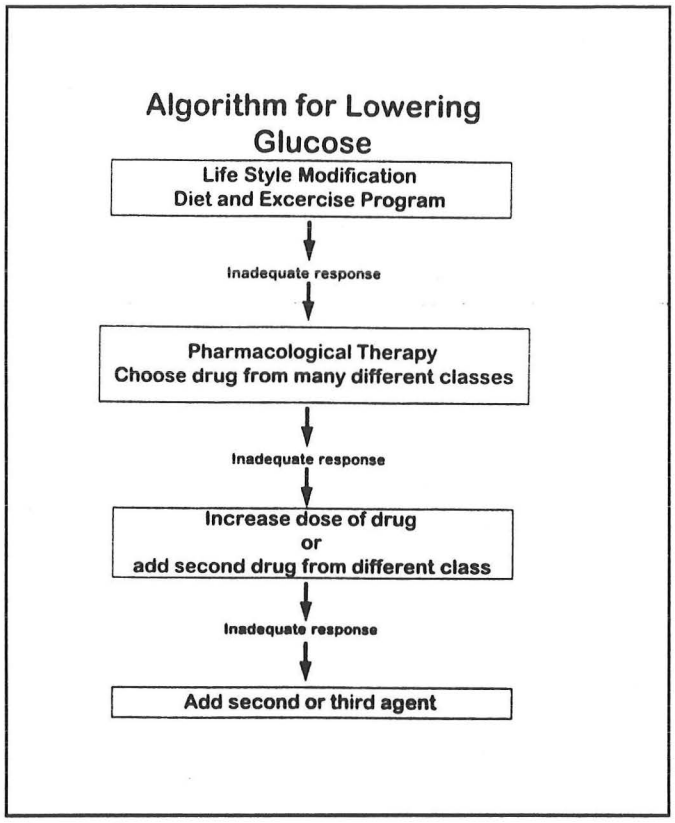

Figure 6

For the management of non-insulin dependent diabetes, we now have multiple oral agents, that have different mechanisms of action, and all lower blood glucose levels (Figure 7). The remainder of this discussion will be directed at the clinical management of non-insulin dependent diabetes and the use of this algorithm.

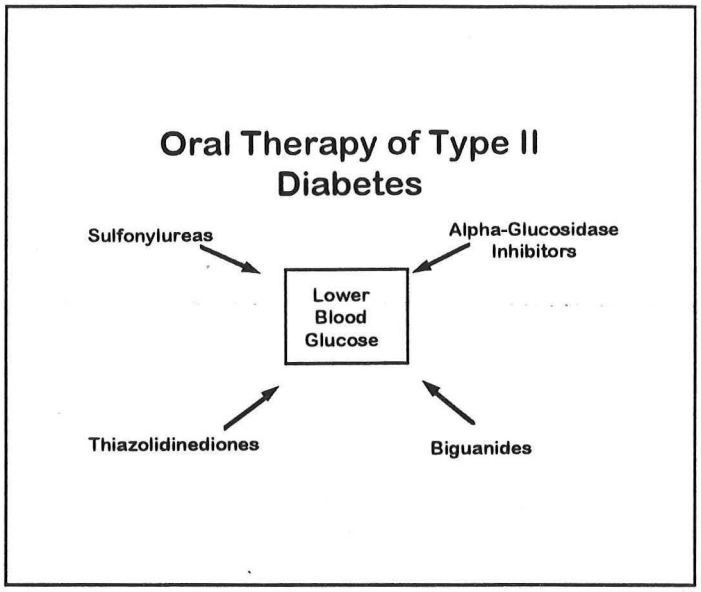

Figure 7

Table 6 shows the treatment options for the management of non-insulin dependent diabetes mellitus.

Table 6

TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS

- **Diet and Exercise Program**
- **Oral Agents**
  - **Sulfonylureas**
  - **Biguanides**
  - **Alpha glucosidase inhibitors**
- **Insulin**
- **Combination Therapy**

DIET AND EXERCISE

The cornerstone of the management of non-insulin dependent diabetes mellitus is a diet and exercise program. To be successful, the meal plan must be individualized with the patient and his or her family. The member of the health care team best qualified to help with this area of patient care is the dietitian. The diabetes nurse clinician can help as well. In my opinion, the member of the health care team least capable of helping with diet, is the physician. Diet therapy is time consuming and most physicians don't have or won't take the time. The diet prescription is simple. It is a "heart healthy diet", with a nutrient content as listed in Table 7.

Table 7

ADA RECOMMENDED MEAL PLAN

Nutrient	% of Daily Calorie Intake
Protein	12-20
Carbohydrates	50-60
Fats	<30

- Saturated Fat <10% Total Calories
- Cholesterol Intake <300 mg
- Fiber Intake 30-45 g

As many patients with diabetes are overweight, the goal of diet therapy is weight loss. It is difficult for anyone to loose weight with diet alone. Thus, an exercise program must be incorporated into the treatment plan. Some care must be taken when recommending an exercise program to individuals with NIDDM. Many are older and often they have other medical problems. In some, but certainly not all, a cardiac evaluation should be done prior to initiating an exercise program. Most often the exercise program recommend should be brisk walking, starting very slowly and gradually increasing distance as the individual becomes more fit. The benefits of diet and exercise therapy are considerable. Exercise clearly improves insulin sensitivity as does weight loss.

ORAL AGENTS

SULFONYLUREAS

When a diet and exercise program are not effective in normalizing the glycosylated hemoglobin level, some pharmacological intervention is needed. The most widely used oral agents are sulfonylureas, as they have been in use in the United States for forty years. A list of sulfonylurea drugs available for use in the United States are given in Table 8.

Table 8

SULFONYLUREA DRUGS

Generic Name	Brand Name	Dosage (mg)	Duration of Action (h)
GLYBRIDE	Diabeta Micronase	1.25-20	16-24
	Glynase PresTab	0.75-12	12-24
GLIPIZIDE	Glucotrol	2.5-40	12-24
	Glucotrol XL	5-60	24
GLIMEPIRIDE	Amaryl	1 - 8	24
CHLORPROPAMIDE	Diabinase	100-500	60

For all practical purposes all sulfonylurea drugs are the same. There are some minor differences with respect to duration of action, metabolism and excretion. Of the "second generation" drugs, only glipizide XL and glimepride are truly once a day drugs.

Sulfonylureas increase insulin secretion. Thus, they are only effective in individuals with residual endogenous insulin secretory capacity. Sulfonylureas work, it is thought, by binding to specific beta cell plasma membrane receptors. These binding receptors are coupled to ATP-dependent K+ channels and binding results in the closure of these potassium channels blocking efflux from the cell. Inhibition of potassium efflux from the beta cell depolarizes the plasma membranes.

This leads to gating of voltage-dependent plasma membrane calcium ion channels results in the facilitated influx of calcium ion into the beta cell. The increase in the cytosolic calcium ion concentration activates a cytosolic system which is responsible for the translocation of insulin secretory granules to the cell surface and extrusion of insulin via exocytosis.

When initiating therapy with sulfonylureas one should strive to use the lowest effective dose. Start with a small dose and raise it every few weeks until optimal control is achieved. There is considerable data to suggest (see Figures 8 & 9) that if half the maximum daily dose of a sulfonylurea is not effective in achieving normoglycemia increasing the dose to the maximum allowable dose is not any more effective. Thus, when normoglycemia is not achieved on half maximum dose of a particular sulfonylurea agent, one should consider adding another drug from a different class.

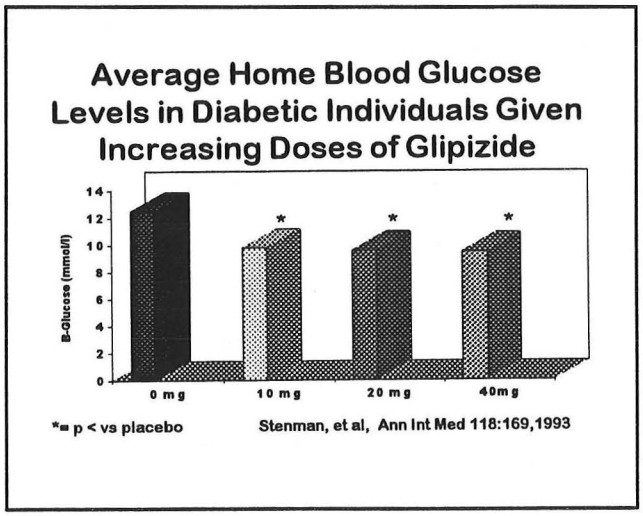

Figure 8

Plasma Insulin Response to a Mixed Meal in Diabetic Individual Given Increasing Doses of Glipizide

Glipizide dose	Area under Insulin Curve (mmol/l)	
mg/day	0 - 240 min	0 - 90 min
0	219 ± 46	90 ± 17
10	278 ± 40*	126 ± 19*
20	286 ± 42*	118 ±17*
40	239 ± 32*	101 ± 12**

* =p<0.01 vs Placebo ** =p< 0.02 vs 10mg dose

Stenman, et al, Ann Int Med 118:169,1993

Figure 9

In general, sulfonylurea therapy is effective, at least in the short term in 70-75% of patients. About 10-20% of individuals fail to respond initially, (so called "primary failures). Individuals who are thin rarely respond to sulfonylureas or to other oral agents, for that matter. These individuals often need to be treated with insulin. About 5-10% of patients who seem to be doing well on sulfonylureas seem to "fail" each year, so called "secondary failures". The longer an individual has non-insulin diabetes the less likely sulfonylureas will be successful as monotherapy. The addition of other oral agents from other drug classes in "secondary failures" is an appropriate course of action.

The major side effect of sulfonylurea therapy is hypoglycemia. Individuals who present with sulfonylurea induced hypoglycemia to the

emergency room should not be released immediately after correction of the hypoglycemia as can be done with individuals with insulin induced hypoglycemia. "Twenty-three hour observation " is appropriate.

BIGUANIDES

Biguanides represent the next class of available oral agents for use in the treatment of non-insulin dependent diabetes mellitus. There is only one drug available, metformin. This drug, although in use in the rest of the world for the past 20 years, was released for use in the United States by the FDA in May, 1995. Metformin works by increasing insulin sensitivity. It has no effect on insulin secretion. The drug decreases hepatic glucose production (Figure 10) more than it increases peripheral glucose utilization (Figure 11).

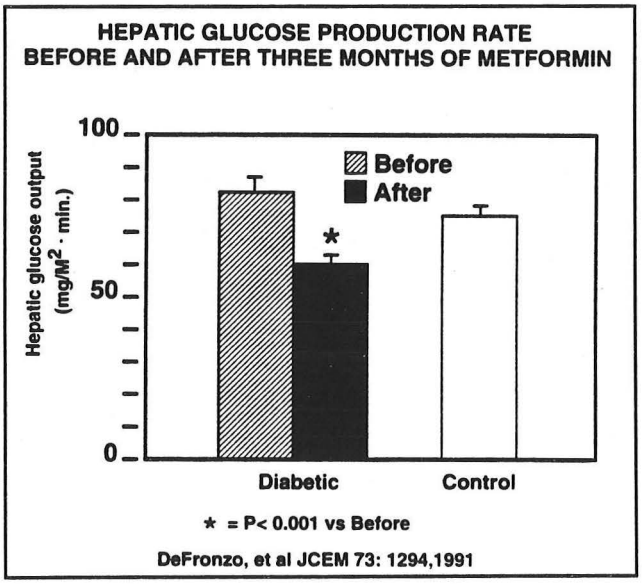

Figure 10

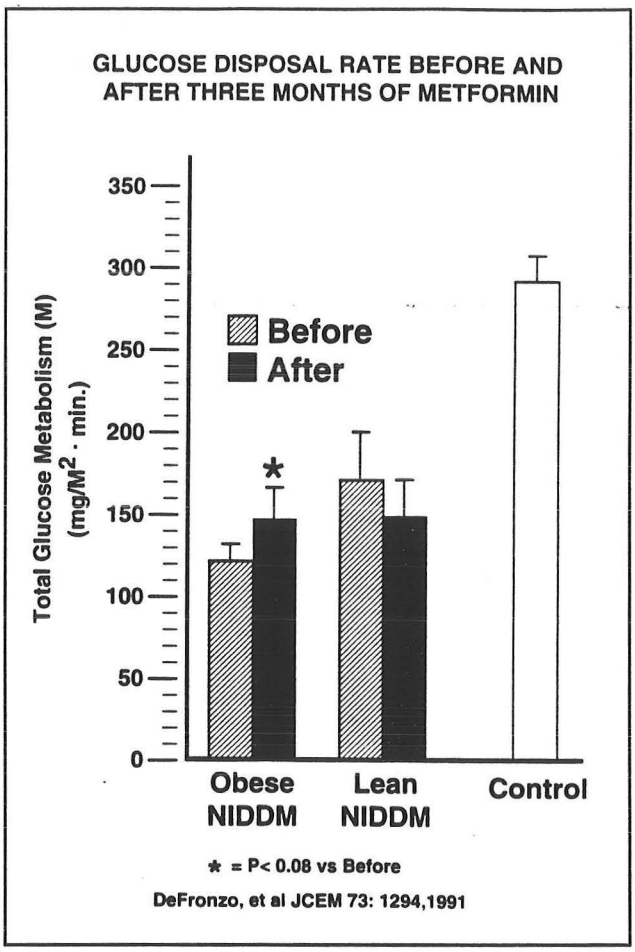

Figure 11

Clinically, metformin reduces hyperglycemia by reducing hepatic glucose production and increasing glucose utilization. Interestingly, it is said that when given alone, metformin will not cause hypoglycemia even if given to non-diabetic individuals. This is not the case with sulfonylureas. Metformin also improves the lipoprotein profile and does not cause weight gain. In fact, it might even result in a few pounds of weight loss.

Metformin can be used as monotherapy, i.e., the first choice of oral agent

when a diet and exercise program are not successful in normalizing the glycosylated hemoglobin. Again, since this drug works by increasing insulin sensitivity it is usually more effective in obese individuals than in normal weight or thin ones. However, the way it is used most often is in combination with sulfonylureas. Usually it is added to the sulfonylurea, in cases of "sulfonylurea failure", but there is no reason that sulfonylureas could not be added to metformin in cases of "metformin failure". Finally, although there is not yet an indication for the use of metformin in poorly controlled insulin treated individuals with non-insulin dependent diabetes, I feel this will turn out to be an effective use of this drug. We are currently engaged in a clinical trial comparing the effects of the addition of metformin or placebo in such individuals.

The maximum daily dose of metformin is 2.5 gm daily. The usual starting dose is 500 mg two or three times daily with meals. The dose should not be increased for at least six weeks. If the effect on blood glucose control is not seen by this time the dose can be slowly increased until a maximum of 850 mg three times a day with meals. It is also reasonable to give it in doses of 1000 mg with breakfast, 500 mg with lunch and 1000 mg at dinner. Figure 12 shows the effectiveness of metformin as monotherapy.

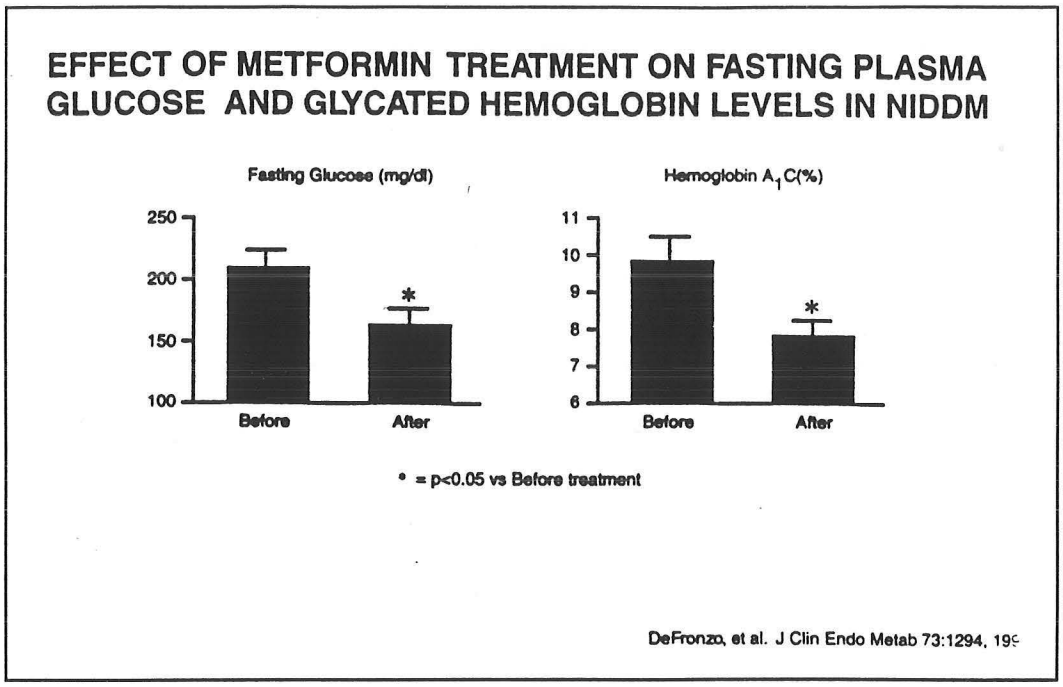

Figure 12

The side effects of metformin are listed in Table 9. The major side effects are gastrointestinal. Patients often complain of nausea, abdominal pain and diarrhea. Giving the medication with meals either directly before or even the middle or after the meal, greatly reduces the gastrointestinal side effects. The gastrointestinal side effects are greatly reduced by starting at a low dose (even 250 mg [1/2 tablet] once a day with a meal) and very slowly increasing the dose.

Table 9

METFORMIN
SIDE EFFECTS

Abdominal Discomfort
Nausea
Anorexia
Diarrhea
Metallic Taste
Decreased Absorption of Folate and B_{12}
Lactic Acidosis
Hypoglycemia with Sulfonylureas

Also, the side effects tend to disappear with continued use. The other major concern about metformin is the development of lactic acidosis. Lactic acidosis is 100 times less frequent with metformin use than with phenformin (Table 10), a biguanide drug taken off the market in 1977 by the FDA because of a high frequency of lactic acidosis. The contraindications for the use of metformin are given in Table 11.

Table 10

RISK OF LACTIC ACIDOSIS WITH BIGUANIDE THERAPY

Phenformin	0.6 per 1000 patient years
Metformin	0.08 per 1000 patient years

(Clin Endo Metab 2:455, 1988)

Table 11

METFORMIN

Contraindications

- Renal Disease
- Hepatic Disease
- Pregnancy
- Cardiac Insufficiency
- Hypoxic Condition
- Insulin Dependent Diabetes

ALPHA GLUCOSIDASE INHIBITORS

Alpha glucosidase inhibitors are a new class of antidiabetic drugs available in the Unites States. Approved for use by the FDA in December, 1995, they have been used in Europe and elsewhere for several years. Acarbose is the single agent available at present from this class. Acarbose inhibits the enzymatic digestion of carbohydrate in the intestinal lumen. Thus, it delays the digestion of starch and sucrose. Clinically it decreases post prandial glucose excursions (Figure 13) and reduces HbA1c levels (Figure 14). It has no effect on fasting plasma glucose levels or plasma lipid profiles.

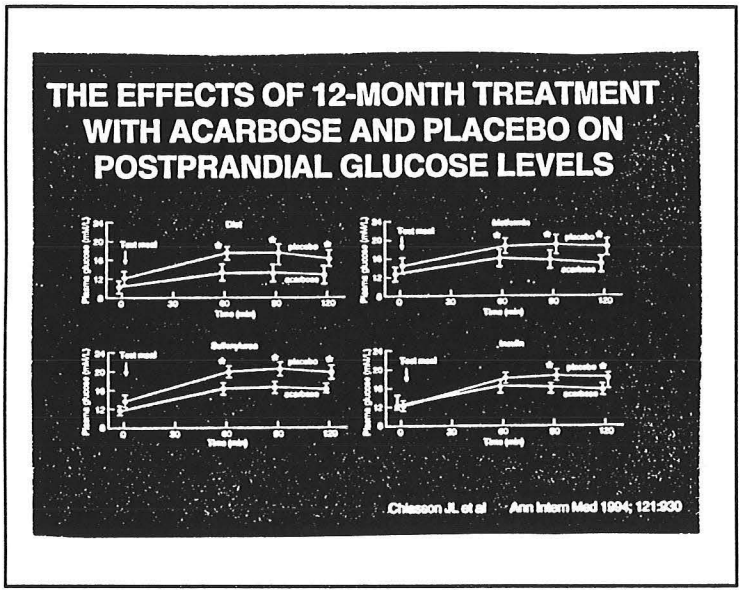

Figure 13

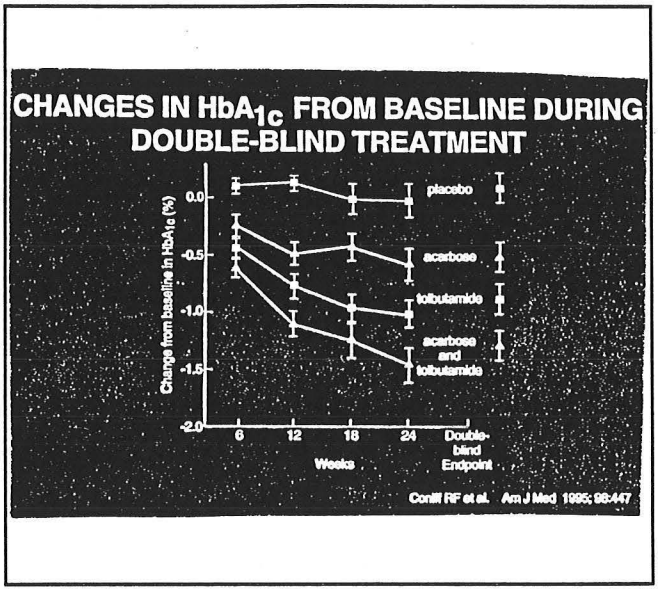

Figure 14

The initial dosage schedule for acarbose is 25 mg three times a day with meals; slowly increasing the dosage to 100 mg three times a day if adequate control is not achieved with a lower dose.

The major side effects of acarbose are gastrointestinal. As the drug is not absorbed there are no systemic side effects, known. It causes local gastrointestinal effects such as flatulence, loose stools, and abdominal discomfort due to the induction of carbohydrate malabsorption. Starting with a low dose and very slowly increasing the dose when needed helps reduce the frequency of the gastrointestinal side effects.

DRUGS IN DEVELOPMENT

THIAZOLIDINEDIONES

There are several drugs in this class that are presently in various stages of development. The drug that is closest to use is troglitazone, that was developed by Sankyo and licensed in the United Sates and Europe to Parke-Davis. Although the precise molecular mechanism is unknown, troglitazone is also an insulin sensitizer. Although it has some similarities to metfomin in this regard, troglitazone has more of an effect on increasing glucose utilization in muscle (Figure 15) than it does in reducing hepatic glucose production (Figure 16). This difference in tissue sensitivity suggests that metformin and troglitazone could, after appropriate study, be used in combination.

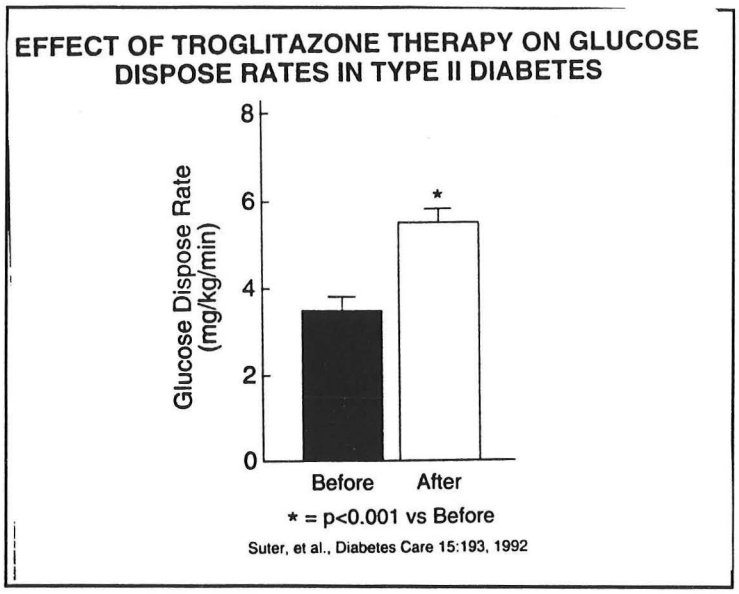

Figure 15

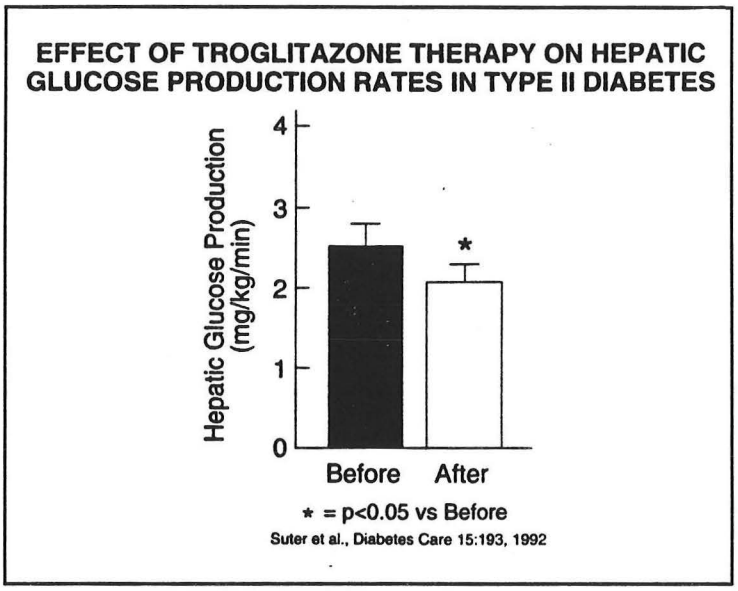

Figure 16

Clinically, although there have only been a few published clinical trials, troglitizone has been shown to reduce fasting plasma glucose levels (Figure 17) and reduce insulin levels (Figure 18), as well as decrease HbA1c in "sulfonylurea failures" (Figure 19)

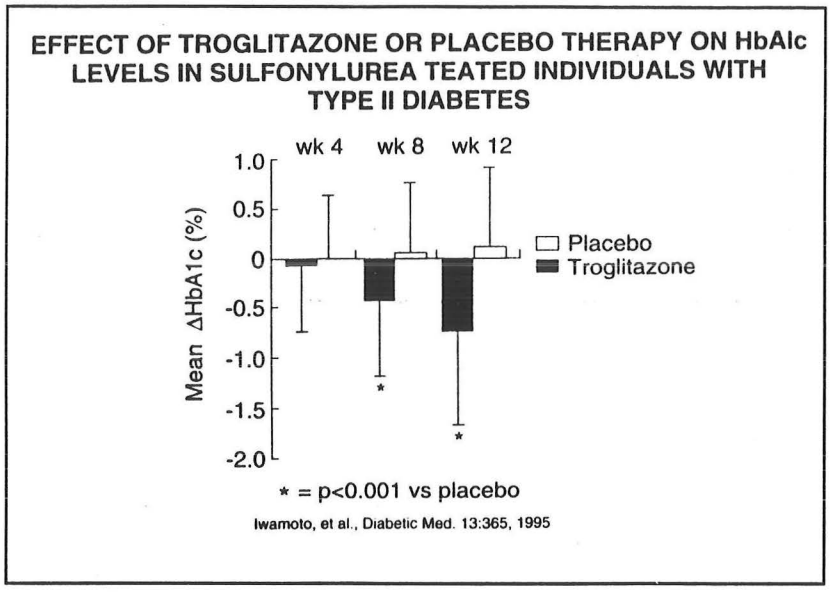

Figure 17

NON-SULFONYLUREA INSULIN SECRETAGOGUES

BTS 67-582

BTS-67 582 is presently being developed by Knoll Pharmaceuticals. This compound is a non-sulfonylurea, insulinotropic compound with a morpholinoguandine chemical structure. BTS-67 582 affects the potassium ATP channel in the beta cell but at a different binding site than the sulfonylureas. BTS-67 582 in several dosage levels has been shown to be effective in reducing fasting plasma glucose levels and fructosamine levels during a four week dosing period.

INSULIN THERAPY

When diet, exercise, and the maximal doses of combination oral agents fail to achieve a glycosylated hemoglobin level in the range of individuals without diabetes, consideration of initiation of insulin therapy is appropriate. Table 12 shows the other indications for the use of insulin in individuals with non-insulin dependent diabetes mellitus.

Table 12

INSULIN THERAPY IN NIDDM
Indications

- Significant Hyperglycemia at Presentation
- Hyperglycemia Despite Diet, Exercise, and Maximal Doses of Oral Agents
- Weight Loss and Worsening Glycemia
- Acute Stress
  Surgery, Infection, Injury
- Pregnancy
- Allergy to Oral Agents

When initiating treatment with insulin a good starting point is a dose of between 0.4 and 0.7 units/kg/day. Usually it is appropriate to begin with at least two daily injections of a mixture of intermediate and short acting insulin before breakfast and supper. The use of blood glucose monitoring is appropriate as in any individual who uses insulin. Often larger doses are needed to control hyperglycemia and often individuals

with non-insulin dependent diabetes require multiple daily injections of insulin and innovative treatment programs, not dissimilar to individuals with insulin dependent diabetes.

CONCLUSION

Non-insulin dependent diabetes mellitus is a serious illness that afflicts a large percentage of our population. The glycemic treatment goal is a glycosylated hemoglobin level in the range of individuals without diabetes. Over the past year or so, new treatment options have become available and more are on the way and thus, the treatment of non-insulin dependent diabetes is becoming more complicated. We must be aggressive in dealing with our patients because it is clear that with appropriate treatment we can reduce the long term complications of diabetes. In addition to attending to the glycosylated hemoglobin levels the astute health care provider will also carefully monitor plasma lipid levels and deal with rising blood pressure levels. Finally, no matter how well your patient seems to be doing, all diabetic individuals need regular ophthalmological care and assessment of albuminuria. Immunizations should be up to date and feet examined regularly.

BIBLIOGRAPHY

Aguilar C, Reza A, Garcia JE, Rull JA: Biguanide Related Lactic Acidosis: Incideuce (sic) and Risk Factors. Archives of Medical Research 23(1):19-24, 1992

Arauz-Pacheco C, Lackner C, Ramirez LC: Lipoprotein (a) Levels in Diabetic Patients and Its Correlation with the Metabolic Control. Ann. Int. Med. 117:42-47, 1992.

Assan R, Heuclin CH, Ganeval D, Bismuth CH, George J, Girard JR: Metformin-induced lactic acidosis in the presence of acute renal failure. Diabetologia 13:211-217, 1977

Bailey CJ: Biguanides and NIDDM [Review]. Diabetes Care 15(6):755-72, 1992

Bailey CJ: Hypoglycaemic, Antihyperglycaemic and Antidiabetic Drugs. Diabetic Medicine 9:482-3, 1992

Bailey CJ: Metformin--an update. [Review]. General Pharmacology 24:1299-1309, 1993

Benzi L, Trischitta V, Ciccarone A, Cecchetti P, Brunetti A, Squatrito S, Marchetti P, Vigneri R, Navalesi R: Improvement With Metformin in Insulin Internalization and Processing in Monocytes From NIDDM Patients. Diabetes 39:844-9, 1990

Bischoff H: The Mechanism of α-Glucosidase Inhibition in the Management of Diabetes. Clin Invest Med 18:303-11, 1995

Björntorp P, Carlström S, Fagerberg SE, Hermann LS, Holm AGL, Scherstén B, Östman J: Influence of Phenformin and Metformin on Exercise Induced Lactataemia in Patients with Diabetes Mellitus. Diabetologia 15:95-8, 1978

Bonora E, Cigolini M, Bosello O, Zancanaro C, Capretti L, Zavaroni I, Coscelli C, Butturini U: Lack of Effect of Intravenous Metformin on Plasma Concentrations of Glucose, Insulin, C-peptide, Glucagon and Growth Hormone in Non-Diabetic Subjects. Current Medical Research and Opinion 9:47-51, 1984

Butterfield J: The Circulation in Diabetes, from HL523 to the NO Era. Lancet 342:533-6, 1993

Campbell IW: Management of Type 2 Diabetes Mellitus with Special Reference to Metformin Therapy. Diabete et Metabolisme 17: 191-6, 1991

Campbell IW, Menzies DG, McBain AM, Brown IRF: Effects of Metformin on Blood Pressure and Microalbuminuria in Diabetes Mellitus. Diabete & Metabolisme 14:613-7, 1988

Caspary WF: Biguanides and Intestinal Absorptive Function. Acta Hepato-Gastroenterol 24:473-80, 1977

Caspary WF, Creutzfeldt W: Analysis of the Inhibitory Effect of Biguanides on Glucose Absorption: Inhibition of Active Sugar Transport. Diabetologia 7:379-385, 1971

Cavallo-Perin P, Aluffi E, Estivi P, Bruno A, Carta Q, Pagano G, Lenti G: The Hyperlactatemic Effect of Biguanides: a Comparison Between Phenformin and Metformin During a 6-Month Treatment. Rivista Europea Per Le Scienze Mediche e Farmacologiche 11:45-9, 1989

Chaiken RL, Eckert-Norton M, Pasmantier R, Boden G, Ryan I, Gelfand RA, Lebovitz: Metabolic Effects of Darglitazone, an Insulin Sensitizer, in NIDDM Subjects. Diabetologia 38:1307-1312, 1995

Chakrabarti R, Hocking ED, Fearnley GR: Fibrinolytic Effect of Metformin in Coronary Disease. Lancet 2:256-9, 1965

Chan JC, Tomlinson B, Critchley JA, Cockram CS, Walden RJ: Metabolic and Hemodynamic Effects of Metformin and Glibenclamide in Normotensive NIDDM Patients. Diabetes Care 16(7):1035-8, 1993

Chiasson J-L, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH, Wolever TM: The Efficacy of Acarbose in the Treatment of Patients With Non-Insulin -dependent Diabetes Mellitus: A Multicenter Controlled Clinical Trial. Ann Intern Med 121:928-35, 1994

Clarke BF, Duncan LJ: Comparison of Chlorpropamide and Metformin Treatment on Weight and Blood-Glucose Response of Uncontrolled Obese Diabetics. Lancet 1(534):123-6, 1968

Clarke BF, Campbell IW: Comparison of Metformin and Chlorpropamide in Non-Obese, Maturity-Onset Diabetes Uncontrolled by Diet. Br Med J 2:1576-8, 1977

Clarke BF, Duncan LJ: Biguanide Treatment in the Management of Insulin Independent (Maturity-Onset) Diabetes: Clinical Experience with Metformin. Research and Clinical Forums 1:53-63

Collier A, Watson HH, Patrick AW, Ludlam CA, Clarke BF: Effect of Glycaemic Control, Metformin and Gliclazide on Platelet Density and Aggregability in Recently Diagnosed Type 2 (Non-Insulin-Dependent) Diabetic Patients. Diabete et Metabolisme 15:420-5, 1989

Colwell JA: Is It Time to Introduce Metformin in the U.S.? Diabetes Care 16:653-5, 1993

Coniff RF, Shapiro JA, Seaton TB, Bray GA: Multicenter, Placebo-Controlled Trial Comparing Acarbose (BAY g 5421) with Placebo, Tolbutamide, and Tolbutamide-Plus-Acarbose in Non-Insulin-Dependent Diabetes Mellitus. The American Journal of Medicine 98:443-51, 1995

Coniff RF, Shapiro JA, Robbins D, Kleinfield R, Seaton TB, Beisswenger P, McGill JB: Reduction of Glycosylated Hemoglobin and Postprandial Hyperglycemia by Acarbose in Patients With NIDDM. Diabetes Care 18:817-24, 1995

Coscelli C, Palmari V, Saccardi F, Alpi O, Bonora E: Evidence That Metformin to Insulin Induces and Amelioration of Glycemic Profile in Type I (Insulin-Dependent) Diabetes Mellitus. Curr Ther Res Clin Exp 35:1058-64, 1984

Czyzyk A, Tawecki J, Sadowski J, Ponikowska I, Szczepanik Z: Effect of Biguanides on Intestinal Absorption of Glucose. Diabetes 17:492-8, 1968

DeFronzo RA, Tobin JD, Andres R: Glucose Clamp Technique: A Method for Quantifying Insulin Secretion and Resistance. Am J Physiol 232:E214-23, 1979

DeFronzo RA: The Trimuirate: P Cell, Muscle Liver: A Collusion Responsible for NIDDM Lilly Lecture 1987. Diabetes 37:667-87, 1987

DeFronzo RA, Barzilai N, Simonson DC: Mechanism of Metformin Action in Obese and Lean Noninsulin-Dependent Diabetic Subjects. Journal of Clin Endocrin & Metab 73:1294-1301, 1991

DeFronzo RA, Goodman AM and Multicenter Metformin Study Group: Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. New Engl J Med 333:541-49, 1995.

deGrauw WJC, van de Lisdonk EH, van den Hoogen HJM, et al: Cardiovascular Morbidity and Mortality in Type 2 Diabetic Patients: A 22-Year Historical Cohort Study in Dutch General Practice. Diabetic Medicine 12:117-22, 1995

Descovich G, Mantaguti U, Ceredi C, Cocuzza E, Sirtori CR: Long Term Treatment with Metformin in a Large Cohort of Hyperlipidemic Patients. Artery 4:348-59, 1978

Duhault J, Lavielle R: History and Evolution of the Concept of Oral Therapy in Diabetes. Diabetes Research and Clinical Practice 14:S9-S14, 1991

Dunne MJ, Kane C, Harding EA, Jagger J, Ashcroft SJH: BTS 67 582: A Novel Glucose Lowering Agent. Diabetic Medicine 12(Suppl 1):531-2, 1995

Eriksson J, Widen E, Saloranta C: Metformin Improves Insulin Sensitivity in Insulin Resistant Normoglycemic Relatives of Patients with Non-Insulin Dependent Diabetes Mellitus. Diabetes 39(Suppl 1):1099, 1990

Fantus GI, Brosseau R: Mechanism of Action of Metformin: Insulin Receptor and Postreceptor Effects *in Vitro* and *in Vivo*. Journal of Clinical Endocrinology and Metabolism 63:898-905, 1986

FDA drug bull: Phenformin: Removal from general market, Volume 7 Number 3 August, 1977

Fölsch UR: Clinical Experience with Acarbose as First Line Therapy in NIDDM. Clin Invest Med 18:312-7, 1995

Forster O, Rudas B: The Uptake of Orally Administered Trioleate^{14}C in Normal and Diabetic Rats with and without Butylbiguanide Application. Pharmacology 6:81-8, 1971

Gan SC, Barr J, Arieff AI, Pearl RG: Biguanide-Associated Lactic Acidosis: Case Report and Review of the Literature. Archives of Int Med 152:2333-6, 1992

Gin H, Messerchmitt C, Brottier E, Aubertin J: Metformin Improved Insulin Resistance in Type 1, Insulin-Dependent, Diabetic Patients. Metabolism 34:923-5, 1985

Gin H, Freyburger G, Boisseau M, Aubertin J: Study of the Effect of Metformin on Platelet Aggregation in Insulin-Dependent Diabetics. Diabetes Research and Clinical Practice 6:61-7, 1989

Giugliano D, Quatraro A, Consoli G, Minei A, Ceriello A, DeRosa N, D'Onofrio F: Metformin for Obese, Insulin-Treated Diabetic Patients: Improvement in Glycaemic Control and Reduction of Metabolic Risk Factors. European J of Clin Pharmacology 44:107-12, 1993

Groop L, Widen E, Franssila-Kallunki A, Ekstrand A, Saloranta C, Schalin C, Eriksson J: Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 non-insulin dependent) diabetes mellitus. Diabetologia 32(8):599-605, 1989

Groop LC, Ratheiser K, Luzi L, Melander A, Simonson DC, Petrides A, Bonadonna RC, Widén, DeFronzo RA: Effect of Sulphonylurea on Glucose-Stimulated Insulin Secretion in Healthy and Non-Insulin Dependent Diabetic Subjects: A Dose-Response Study. Acta Diabetologica 28:162-8, 1991

Guntafson A, Bjorntorp P, Fahlen M: Metformin Administration in Hyperlipidemic States. Acta Med Scand 190:491-4, 1971

Hamann A, Benecke H, Greten H, Matthaei S: Metformin Increases Glucose Transporter Protein and Gene Expression in Human Fibroblasts. Biochemical and Biophysical Research Communications 196:382-387, 1993

Hermann LS: Metformin: A Review of Its Pharmacological Properties and Therapeutic Use. Diabete & Metabolisme 5:233-45, 1979

Hermann LS: Biguanides and Sulfonylureas as Combination Therapy in NIDDM. Diabetes Care 13(Suppl 3):37-41, 1990

Hermann LS, Scherstén B, Melander A: Antihyperglycaemic Efficacy, Response Prediction and Dose-Response Relations of Treatment with Metformin and Sulphonylurea, Alone and in Primary Combination. Diabetic Medicine 11:953-60, 1994

Higginbotham L, Martin FIR: Double-Blind Trial of Metformin in the Therapy of Non-Ketotic Diabetics. Med J Aust 2:154-6, 1979

Hoffmann J, Spengler M: Efficacy of 24-Week Monotherapy With Acarbose, Glibenclamide, or Placebo in NIDDM Patients: The Essen Study. Diabetes Care 17:561-6, 1994

Hollenbeck CB, Johnston P, Varasteh BB, Chen YD, Reaven GM: Effects of Metformin on Glucose, Insulin and Lipid Metabolism in Patients with Mild Hypertriglyceridaemia and Non-Insulin Dependent Diabetes by Glucose Tolerance Test Criteria. Diabete et Metabolisme 17:483-9, 1991

Hollobaugh SL, Rao B, Kruger FA: Studies on the Site and Mechanism of Action of Phenformin. I. Evidence for Significant "Nonperipheral" Effects of Phenformin on Glucose Metabolism in Normal Subjects. Diabetes 19:45-9, 1970

Howlett HC: Metformin in the management of type 2 diabetes [letter; comment]. Diabetic Medicine 6:179-80, 1989

Hundal HS, Ramlal T, Reyes R, Leiter LA, Klip A: Cellular Mechanism of Metformin Action Involves Glucose Transporter Translocation from an Intracellular Pool to the Plasma Membrane in L6 Muscle Cells. Endocrinology 131(3):1165-73, 1992

Iwamoto Y, Kuzuya T, Matsuda A, Awata T, Kumakura S, Inooka G, Shiraishi I: Effect of New Oral Antidiabetic Agent CS-045 on Glucose Tolerance and Insulin Secretion in Patients With NIDDM. Diabetes Care 14(11):1083-86, 1991

Iwamoto Y, Kosaka K, Kuzuya T, Akanuma Y, Shigeta Y, Kaneko T: Effect of Combination Therapy of Troglitazone and Sulphonylureas in Patients With Type 2 Diabetes Who Were Poorly Controlled by Sulphonylurea Therapy Alone. Diabetic Medicine 13:365-70, 1996

Jackson RA, Hawa MI, Jaspan JB, Sim BM, DiSilvio L, Featherbe D, Kurtz AB: Mechanism of Metformin Action in Non-Insulin-Dependent Diabetes. Diabetes 36:632-640, 1987

Johnson AB, Argyraki M, Heseltine L, Sum CF, Taylor R: The impact of metformin therapy upon skeletal muscle glycogen synthase activity and hepatic glucose output in obese NIDDM patients. Diabetes 39(Suppl 1):109A, 1990

Klein W: Sulfonylurea-Metformin-Combination Versus Sulfonylurea-Insulin-Combination in Secondary Failures of Sulfonylurea Monotherapy. Results of a Prospective Randomized Study in 50 Patients. Diabete et Metabolisme 17(1 Pt 2):235-40, 1991

Klip A, Leiter LA: Cellular Mechanism of Action of Metformin. Diabetes Care 13(6):696-704, 1990

Klip A, Sarabia V, Ramlal T, Bilan PJ, Leifer LA: Glucose Transport in Human Muscle Cells in Culture: Stimulation by Insulin and Metformin. Diabetes 39(Suppl 1):82A, 1990

Kolterman OG, Gray RS, Griffin J, Burstein P, Insel J: Receptor and Postreceptor Defects Contribute to the Insulin Resistance in Non-Insulin Dependent Diabetes Mellitus. J.C.I. 68:957-69, 1981

Lalau JD, Vermersch A, Hary L, Andrejak M, Isnard F, Quichaud J: Type 2 Diabetes in the Elderly: An Assessment of Metformin (Metformin in the Elderly). Intl Journal of Clin Pharmacology, Therapy, & Toxicology 28(8):329-32, 1990

Landin K, Tengborn L, Smith U: Treating Insulin Resistance in Hypertension with Metformin Reduces Both Blood Pressure and Metabolic Risk Factors. Journal of Internal Medicine 229:181-7, 1991

Lebovitz HE: Oral Antidiabetic Agents: The Emergence of α-Glucosidase Inhibitors. Drugs 44(Suppl 3):21-8, 1992

Lebovitz HE: Stepwise and Combination Drug Therapy for the Treatment of NIDDM. Diabetes Care 17(12):1542-1544, 1994

Lorch E: Inhibition of Intestinal Absorption and Improvement of Oral Glucose Tolerance by Biguanides in the Normal and in the Streptozocotocin Diabetic Rat. Diabetologia 7:195-203, 1977

Lucis OJ: Pharmacologic Update. The Status of Metformin in Canada. Can Med Assoc J 128:24-6, 1983

Madison LL, Unger RH: Effect of Phenformin on Peripheral Glucose Utilization in Human Diabetic and Nondiabetic Subjects. Diabetes 9:202-6, 1960

Martenson J: Effect of Guanidine and Synthalin on the Citric Acid Metabolism. Acta Med Scandinav 125:82-94, 1946

Matthaei S, Hamann A, Klein HH, Benecke H, Kreymann G, Flier JS, Greten H: Association of Metformin's Effect to Increase Insulin-Stimulated Glucose Transport With Potentiation of Insulin-Induced Translocation of Glucose Transporters From Intracellular Pool to Plasma Membrane in Rat Adipocytes. Diabetes 40:850-7, 1991

McAlpine LG, McAlpine CH, Waclawski ER, Storer AM, Kay JW, Frier BM: A Comparison of Treatment with Metformin and Gliclazide in Patients with Non-Insulin-Dependent Diabetes. European Journal of Clinical Pharmacology 34:129-32, 1988

McIntyre HD, Ma A, Bird DM, Paterson CA, Ravenscroft PJ, Cameron DP: Metformin Increases Insulin Sensitivity and Basal Glucose Clearance in Type 2 (Non-Insulin Dependent) Diabetes Mellitus. Australian & New Zealand Journal of Medicine 21(5):714-9, 1991

Meyer F, Ipaktch M, Clauger H: Specific Inhibition of Gluconeogenesis by Biguanides. Nature 264:203-4, 1967

Mimura K, Umeda F, Hiramatsu S, Taniguchi S, Ono Y, Nakashima N, Kobayashi K, Masakado M, Sako Y, Nawata H: Effects of a New Oral Hypoglycaemic Agent (CS-045) on Metabolic Abnormalities and Insulin Resistance in Type 2 Diabetes. Diabetic Medicine 11:685-691, 1994

Natrass M, Hinks L, Smythe P, Todd PG, Alberti KGMM: Metabolic Effects of Combined Sulfonylurea and Metformin Therapy in Maturity-Onset Diabetics. Horm Metab Res 11:332-337, 1979

Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J: Improvement in Glucose Tolerance and Insulin Resistance in Obese Subjects Treated With Troglitazone. The New England Journal of Medicine 331:1188-93, 1994

Onbe T, Makino H, Kumagai I, Haramoto T, Murakami K, Ota Z: Effect of Proteinase Inhibitor Camostat Mesilate on Nephrotic Syndrome with Diabetic Nephropathy. The Journal of Diabetic Complications 5(2-3):167-8, 1991

Pagano G, Tagliaferro V, Carta Q, Caselle MT, Bozzo C, Vitelli F, Trovati M, Cocuzza: Metformin Reduces Insulin Requirement in Type 1 (Insulin-Dependent) Diabetes. Diabetologia 24:351-4, 1983

Pedersen O, Nielsen O, Bak J, Richelsen B, Beck-Nielsen H, Sorensen N: The Effects of Metformin on Adipocyte Insulin Action and Metabolic Control in Obese Subjects with Type 2 Diabetes. Diabetic Medicine 6(3):249-56, 1989

Rains SG, Wilson GA, Richmond W, Elkeles RS: The Reduction of Low Density Lipoprotein Cholesterol by Metformin Is Maintained with Long-term Therapy. Journal of the Royal Society of Medicine 82(2):93-4, 1989

Reaven GM, Johnston P, Hollenbeck CB, Skowronski R, Zhang JC, Goldfine ID, Chen YD: Combined Metformin-Sulfonylurea Treatment of Patients with Noninsulin-Dependent Diabetes in Fair to Poor Glycemic Control. J of Clin Endocrinology & Metab 74(5):1020-6, 1992

Riccio A, Del Prato S, Vigili de Kreutzenberg S, Tiengo A: Glucose and Lipid Metabolism In Non-Insulin-Dependent Diabetes. Effect of Metformin. Diabete et Metabolisme 17(1 Pt 2):180-4, 1991

Rodger NW, Chiasson J-L, Josse RG, Hunt JA, Palmason C, Ross SA, Ryan EA, Tan MH, Wolever TMS: Clinical Experience With Acarbose: Results of a Canadian Multicentre Study. Clin Invest Med 18(4):318-24, 1995

Sandouk T, Reda D, Hofmann C: The Antidiabetic Agent Pioglitazone Increases Expression of Glucose Transporters in 3T3-F442A Cells by Increasing Messenger Ribonucleic Acid Transcript Stability. Endocrinology 133:352-359, 1993

Scheen AJ, Castillo MJ, Lefebvre PJ: Combination of Oral Antidiabetic Drugs and Insulin in the Treatment of Non-Insulin-Dependent Diabetes. Acta Clinica Belgia 48(4):259-68, 1993

Siconolfi-Baez L, Banergi MA, Lebovitz HE: Characterization and Significance of Sulfonylurea Receptors. Diabetes Care 13(Suppl 3):2, 1990

Skillman C, Raskin P, Podlecki BL, et al: The Effects of Various Doses of BTS 67 582 as Compared With Placebo in NIDDM Patients. Diabetes 44 (Suppl 1):210, 1995

(Skillman C, Raskin P: A Double-Masked Placebo-Controlled Trial Assessing Effects of Various Doses of BTS 67 582, A Novel Insulinotropic Agent, On Fasting Hyperglycemia in NIDDM Patients. Submitted for Publication)

Sotaniemi EA, Karvonen I: Glucose Tolerance and Insulin Response to Glucose Load Before and after Enzyme Inducing Therapy in Subjects with Glucose Intolerance and Patients with NIDDM Having Hyperinsulinemia or Relative Insulin Deficiency. Diabetes Research 11(3):131-9, 1989

Stenman, S, Melander A, Groop P-H, Groop LC: What Is the Benefit of Increasing the Sulfonylurea Dose? Annals of Internal Medicine 118:169-62, 1993

Sum CF, Webster JM, Johnson AB, Catalano C, Cooper BG, Taylor R: The Effect of Intravenous Metformin on Glucose Metabolism During Hyperglycaemia in Type 2 Diabetes. Diabetic Medicine 9(1):61-5, 1992

Suter SL, Nolan JJ, Wallace P, Gumbiner B, Olefsky JM: Metabolic Effects of New Oral Hypoglycemic Agent CS-045 in NIDDM Subjects. Diabetes Care 15(2)193-203, 1992

Teupe B, Bergis K: Prospective Randomized Tow-Years Clinical Study Comparing Additional Metformin Treatment with Reducing Diet in Type 2 Diabetes. Diabete et Metabolisme 17(1 Pt 2):213-7, 1991

The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 153:154-83, 1993

Trischitta V, Italia S, Mazzarino S, Buscema M, Rabuazzo AM, Sangiorgio L, Squatrito S, Vigneri R: Comparison of Combined Therapies in Treatment of Secondary Failure to Glyburide. Diabetes Care 15(4):539-42, 1992

U.K. Prospective Diabetes Study, A Multicenter Study, Turner RC, et al: Reduction in HbA_{1c} with Basal Insulin Supplement, Sulfonylurea, or Biguanide Therapy in Maturity-onset Diabetes. Diabetes 34:793-8, 1985

Unger RH, Madison LL, Carter NW: Tolbutamide-Phenformin in Ketoacidosis-Resistant Patients. JAMA 174:2132-6, 1960

Vague PH, Vague IJ, Alessi MC, Badier C, Valadier J: Metformin Decreases the High Plasminogen Activation Inhibition Capacity, Plasma Insulin and Triglyceride Levels in Non-Diabetic Obese Subjects. Thromb Haemos 57:326-8, 1987

Watanabe CK: Studies in the Metabolic Changes Induced by Administration of Guanidine Bases. I Influence of Injected Guanidine Hydrochloride upon Blood Sugar Content. J Biol Chem 33:253-265, 1918

Wilson JA, Scott MM, Gray RSA: Comparison of Metformin Versus Guar in Combination with Sulphonylureas in the Treatment of non Insulin Dependent Diabetes. Hormone & Metabolic Research 21(6):317-9, 1989

Wolever TMS, Radmard R, Chiasson J-L, Hunt JA, Josse RG, Palmason C, Rodger NW, Ross SA, Ryan EA, Tan MH: One-Year Acarbose Treatment Raises Fasting Serum Acetate in Diabetic Patients. Diabetic Medicine (7)164-72, 1995

Wu MS, Johnston P, Sheu WH, Hollenbeck CB, Jeng CY, Goldfine ID, Chen YD, Reaven GM: Effect of Metformin on Carbohydrate and Lipoprotein Metabolism in NIDDM Patients. Diabetes Care 13(1):1-8, 1990

Young PW, Cawthorne MA, Coyle PJ, Holder JC, Holman GD, Kozka IJ, Kirkham DM, Lister CA, Smith SA: Repeat Treatment of Obese Mice With BRL 49653, a New and Potent Insulin Sensitizer, Enhances Insulin Action in White Adipocytes. Diabetes 44:1087-92, 1995