The Effects of Long-term Therapy with Oral Hypoglycemic Agents on the Oral Glucose Tolerance Test Dynamics in Male Chemical Diabetics

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SUMMARY

The effect of fixed doses of oral hypoglycemic agents and placebo (diet alone) on the blood glucose, serum insulin, triglyceride, and cholesterol responses during oral glucose tolerance tests done annually for up to four years' follow-up was studied, in a double-blind manner, in five groups of mild male chemical diabetics. The drugs used were chlorpropamide (100 mg. O.D.), tolbutamide (500 mg. b.i.d.), phenformin (50 mg. O.D.), acetohexamide (250 mg. O.D.), and placebo. Each subject was given an individualized diet aimed at attaining and maintaining ideal weight.

Comparison by chi-square analysis between the placebo group and each of the drug groups showed (a) no significant differences with regard to the number of subjects with normal glucose tolerance in each of the tests and (b) no change in the insulin secretion dynamics. Comparison between the initial test and each of the subsequent tests within each group showed (a) a greater number of subjects with normal glucose tolerance in the first follow-up test in the chlorpropamide group only, (b) no change in the insulin secretion dynamics except in the chlorpropamide group, where there was an increased insulin/glucose ratio in the first follow-up test, and (c) no change in the fasting serum triglyceride and cholesterol levels.

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A goal in the detection of the early stages of diabetes mellitus is the hope that prompt therapeutic intervention may retard the clinical manifestations of the later stages of the disease. Both remission of the disease[1,2] and improvement of the carbohydrate tolerance[3-16] following the use of oral hypoglycemic agents have been reported. Some groups reported the improvement of the carbohydrate tolerance to be associated with increased insulin secretion,[4-7] while others indicated otherwise.[8-16] A lowering of fasting serum lipid levels in diabetics treated with oral hypoglycemic agents has also been reported.[5,10,17-20] Most of the above studies were performed after relatively short-term (weeks to months) therapy with the oral hypoglycemic agents. One study[1] reported the effect of tolbutamide therapy on glucose tolerance in young chemical diabetics for up to seven years. No data on insulin secretion were presented, however. The present study reports on the effect of long-term (up to four years) therapy with fixed doses of oral hypoglycemic agents and diet on (a) the glucose tolerance, (b) the insulin secretion dynamics, and (c) the lipid dynamics during oral glucose tolerance tests of chemical diabetics.

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METHODS

Over a six-year period, 365 mild chemical diabetics participated, with informed consent, in a double-

blind prospective study to determine the influence of fixed doses of oral hypoglycemic agents and proper diet on the natural history of the disease. Each of them was asymptomatic and had normal fasting blood glucose levels but had two abnormal oral glucose tolerance tests prior to entering the study. They were randomly assigned to four groups, each group taking a different drug. In each group one out of every four subjects was placed on a placebo. The drugs used were chlorpropamide (100 mg. daily), tolbutamide (500 mg. twice daily), phenformin (50 mg. daily), and acetohexamide (250 mg. daily). Drug adherence was assessed by history during the follow-up visits every three months. Each subject was given an individualized diet aimed at attaining and maintaining ideal weight as defined by the Metropolitan Life Insurance Company—1959. It is noted that the placebo group was actually on diet therapy. All patients received diet instruction, which was reviewed periodically. This consisted of a weight-reduction diet for those overweight or a weight-maintenance or weight-gain diet for those of ideal weight or the underweight, respectively. No diet was particularly high or low in carbohydrate. The diet prescription, instructional sessions, and review were similar to the procedures used in the Joslin Clinic for patients with more severe degrees of diabetes.

In this preliminary report, only *male* subjects who had at least two tests and complete data (namely, glucose, insulin, cholesterol, and triglyceride values) in the initial (test 1) and subsequent tests (tests 2-5) were included (n = 120). As shown in table 1, there were 37 in the placebo group, 18 in the chlorpropamide group, 28 in the tolbutamide group, 23 in the phenformin group, and 14 in the acetohexamide group. As the follow-up years increased, the number of subjects in each group decreased.

Each subject had an oral glucose tolerance test (100 gm. dextrose) at the beginning of the study (test 1) and then annually during the follow-up years. Each subject followed his usual diet, which contained 100-200 gm. carbohydrate, and took no medication on the day of the test. Each test was done after an overnight fast and begun between 0800 and 0900 hours. Blood samples were obtained by venipuncture prior to and at 30, 60, 120, and 180 minutes after ingesting the glucose. Blood glucose was measured by Hoffman's method as modified for the Auto-Analyzer.[21] Serum insulin was assayed by the double-antibody method of Soeldner and Slone.[22] Serum cholesterol and triglycerides were measured by the Technicon AutoAnalyzer method.[23]

TABLE 2

Demographic features of the subjects in each group at the initial test

Group	Mean age (yrs.)	Number with per cent ideal weight: 121 or more	120 or less
Placebo	46.1 ± 2.1	10	27
Chlorpropamide	42.3 ± 2.7	5	13
Tolbutamide	43.8 ± 2.3	8	20
Phenformin	45.7 ± 2.7	3	20
Acetohexamide	44.4 ± 3.9	4	10

The criteria for an abnormal oral glucose tolerance test are those used in the Joslin Clinic. A test was judged abnormal if any one blood glucose value at a given time interval exceeded the following: Fasting = 100 mg./dl., 30 minutes = 160 mg./dl., 60 minutes = 160 mg./dl., 120 minutes = 120 mg./dl., and 180 minutes = 110 mg./dl.

The criteria for normal fasting serum cholesterol and triglycerides are those of Goldstein et al.[24]

Statistical analyses were done by chi square and paired and unpaired Student's *t*-tests, as indicated.

RESULTS

Comparison of the Groups at the Beginning of the Study

The placebo group did not differ significantly from each of the treated groups in mean age and per cent ideal weight at the beginning of the study and in subsequent years (tables 2 and 3). The percentage of obese subjects in each group was also comparable, except in the phenformin group, where only 13 per cent of the subjects were obese as against 27 per cent

TABLE 1

Number of subjects in each test and group

Group	Initial test 1	Follow-up tests (years): (1) = Test 2	(2) = Test 3	(3) = Test 4	(4) = Test 5
Placebo	37	37	29	21	19
Chlorpropamide	18	18	17	13	11
Tolbutamide	28	28	25	21	17
Phenformin	23	23	21	18	16
Acetohexamide	14	14	12	10	7

TABLE 3

Body weights (lb.) and ideal weight (per cent) in study groups

Test	Group	N	Weight Mean	Weight S. D.	Ideal weight Mean	Ideal weight S. D.
Initial						
(Pl)	Placebo	37	177.6	26.7	110.5	12.9
(C)	Chlorpropamide	18	180.8	29.3	114.4	16.5
(T)	Tolbutamide	28	175.5	36.0	107.7	19.2
(P)	Phenformin	23	170.2	27.9	103.9	14.7
(A)	Acetohexamide	14	172.2	30.3	108.4	16.0
Second						
(Pl)		37	175.1	27.8	108.9	12.8
(C)		18	175.9	29.7	111.2	17.6
(T)		28	172.3	34.5	105.5	18.6
(P)		23	164.5	27.1	100.2	14.0*
(A)		14	169.2	28.2	106.1	14.6
Third						
(Pl)		29	174.0	24.3	108.5	11.1
(C)		17	180.9	34.6	114.4	19.9
(T)		25	174.3	36.2	106.7	19.4
(P)		21	168.2	29.1	101.9	14.5
(A)		12	164.8	28.8	102.9	14.2
Fourth						
(Pl)		21	177.2	27.5	110.4	12.2
(C)		13	178.3	29.1	111.7	17.4
(T)		21	172.1	31.1	106.1	17.9
(P)		18	168.3	32.4	102.8	16.5
(A)		9	166.3	28.6	103.1	14.9
Fifth						
(Pl)		19	174.8	26.3	110.6	12.2
(C)		11	178.0	27.2	109.9	17.4
(T)		17	170.8	33.9	106.2	19.2
(P)		16	160.6	28.1	98.2	14.9
(A)		7	163.6	21.8	101.7	13.6

*$P < 0.01$ compared with initial test.

in the placebo group. A comparison of the per cent ideal weight of the subjects in each group between the initial test and each of the subsequent tests was made by paired t analysis. No significant difference was noted except in the phenformin group. In this group there was a significant decrease in per cent ideal weight in test 2 (table 3, $P < 0.01$). The mean changes in body weight and per cent ideal weight are shown in table 4.

The glucose tolerance and insulin secretion dynamics during the initial test showed no significant differences between the placebo and each of the drug-treated groups (figure 1).

In tables 5 to 7, two types of comparisons are made by chi-square analysis. The between-group comparison (shown vertically) compares the placebo group with each of the drug groups in each test. The within-group comparison (shown horizontally) compares test 1 with each of the subsequent four tests in each group. As shown in the tables, each comparison consists of two numerators and one denominator. The two numerators represent the number of subjects with normal values in each test being compared. The denominator of each comparison represents the total number of subjects who had the two tests under consideration.

Comparison of Subjects with Normal Glucose Tolerance

In the between-group comparison, no significant difference was seen in the number of subjects with normal glucose tolerance tests between the placebo and each of the drug groups (table 5). Unpaired t tests showed the glucose values at the various time intervals to be comparable between the placebo and each of the drug groups. The within-group comparisons showed that, compared with the appropriate initial test, there was only one significant difference in the number of subjects with a normal glucose tolerance test. In the chlorpropamide group, a significantly greater number of subjects had a normal glucose tolerance test after one year of treatment than at the beginning. In subse-

quent follow-up years, no such difference was noted. A comparison of glucose levels was done by paired *t* analysis, where each individual's initial test served as the control. The following significant results were obtained ($P < 0.05$ or greater): (a) in the placebo group the blood glucose levels were lower at 30 minutes and 60 minutes in test 2 and higher at 0 and 120 minutes in test 4; (b) in the chlorpropamide group the blood glucose levels were lower at fasting, 30 minutes, 60 minutes, and 120 minutes in test 2 and at 30 minutes and 60 minutes in test 3; (c) in the tolbutamide group the blood glucose levels were lower at fasting, 30 minutes, and 60 minutes in tests 2 and 3; (d) in the phenformin group the blood glucose levels were higher at zero minute and 30 minutes in test 5, and (e) no significant changes were observed in the acetohexamide group.

Comparison of Insulin Secretion

In figure 2 the insulin response to oral glucose was calculated as the total incremental area above fasting for the stated time interval (μU./ml. × min.). Similarly, the insulin response relative to glucose stimulus was calculated as the total incremental area for insulin

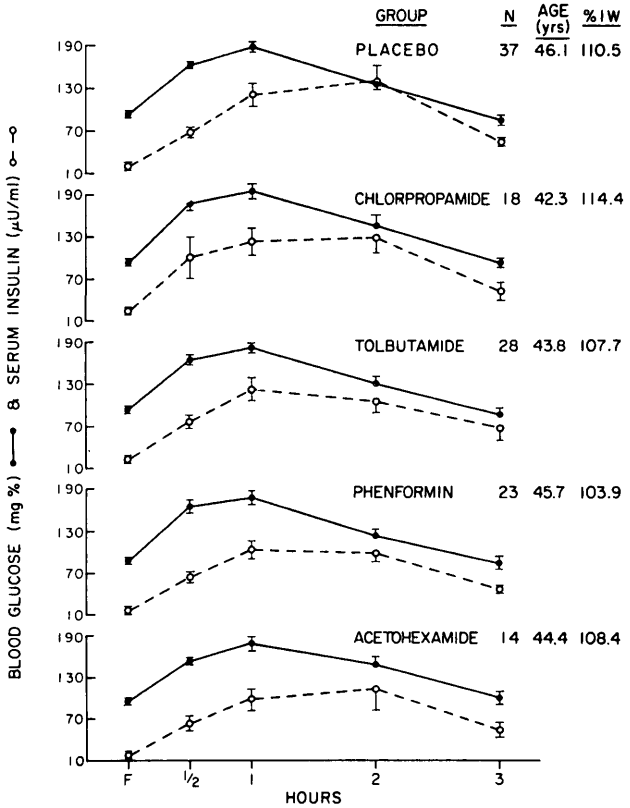

FIG. 1. Mean levels of blood glucose, serum insulin, age, and per cent ideal body weight during initial oral glucose tolerance test. Vertical bars represent standard errors of means.

TABLE 4

Change of body weight (lb.) and ideal weight (per cent) in study groups from initial to follow-up tests

Follow-up test	Group	N	Change in weight Mean	Change in weight S. D.	Change in ideal weight Mean	Change in ideal weight S. D.
Second						
(Pl)	Placebo	37	2.43	9.77	1.57	6.15
(C)	Chlorpropamide	18	4.94	12.77	3.22	8.22
(T)	Tolbutamide	28	3.14	13.36	2.21	7.71
(P)	Phenformin	23	5.70	6.61	3.70	4.01
(A)	Acetohexamide	14	3.00	13.13	2.21	8.06
Third						
(Pl)		29	1.10	8.45	1.00	5.59
(C)		17	−1.29	14.65	−0.24	9.22
(T)		25	0.36	14.87	0.88	8.79
(P)		21	1.71	5.93	1.52	3.70
(A)		12	4.92	13.39	3.92	8.61
Fourth						
(Pl)		21	−0.62	8.85	0.19	5.13
(C)		13	0.31	13.73	0.92	8.85
(T)		21	−1.14	14.72	−0.24	8.80
(P)		18	0.83	8.33	1.22	4.67
(A)		9	2.78	11.96	2.22	7.46
Fifth						
(Pl)		19	0.83	11.41	0.11	8.42
(C)		11	2.64	15.40	2.91	9.87
(T)		17	−5.41	13.71	−2.24	7.85
(P)		16	3.31	7.18	3.06	4.11
(A)		7	6.29	9.90	5.57	7.19

TABLE 5

Comparison between placebo and each of the drug groups for each test and between test 1 and subsequent tests in each group

Number of subjects with normal oral glucose tolerance test indicated

Group	Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	5 vs. 11 / 37	5 vs. 9 / 29	5 vs. 6 / 21	3 vs. 6 / 19
Chlorpropamide	1 vs. 8* / 18	1 vs. 6 / 17	1 vs. 4 / 13	1 vs. 3 / 11
Tolbutamide	5 vs. 11 / 28	5 vs. 12 / 25	5 vs. 7 / 21	4 vs. 4 / 17
Phenformin	4 vs. 5 / 23	4 vs. 5 / 21	3 vs. 4 / 18	3 vs. 2 / 16
Acetohexamide	1 vs. 3 / 14	1 vs. 5 / 12	1 vs. 3 / 10	1 vs. 2 / 8

Degree of significance between test 1 and another test (within-group comparison) is indicated as: * = $P < 0.025$.

TABLE 6

Comparison between placebo and each of the drug groups for each test and between test 1 and subsequent tests in each group*

Number of subjects with normal fasting triglyceride levels indicated

Group	Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	21 vs. 22 / 33	19 vs. 17 / 26	15 vs. 15 / 19	12 vs. 12 / 17
Chlorpropamide	9 vs. 9 / 16	9 vs. 11 / 15	8 vs. 7 / 12	7 vs. 6 / 10
Tolbutamide	21 vs. 23 / 25	19 vs. 20 / 22	20 vs. 20 / 20	17 vs. 16 / 17
Phenformin	16 vs. 18 / 22	15 vs. 18 / 20	13 vs. 14 / 18	12 vs. 12 / 16
Acetohexamide	9 vs. 11 / 11	10 vs. 10 / 11	7 vs. 7 / 8	5 vs. 5 / 7

*There were no significant differences between placebo and drug groups.

divided by the total incremental area for glucose for the stated time interval. In the between-group comparisons by unpaired *t* test, no significant difference was noted between the placebo and each of the drug groups in each of the five tests for the four variables shown. The mean (± S.E.M.) time of peak insulin during the initial test for the five groups were placebo = 93.2 (± 5.7) minutes, chlorpropamide = 96.6 (± 11.8) minutes, tolbutamide = 85.4 (± 7.9) minutes, phenformin = 99.1 (± 9.5) minutes, and acetohexamide 87.9 (± 9.1) minutes. The placebo group did not differ significantly from each of the drug groups in all five tests in the mean time of peak insulin. In the within-group comparisons by paired *t* analysis, the only significant differences between test 1 and each of the subsequent tests of the above variables was seen in the chlorpropamide and acetohexamide groups. In the former group the 0-60-minute and 0-180-minute insulin/glucose area ratios were significantly higher in test 2 than in test 1. In the latter group, the 0-180-minute insulin/glucose area ratio of test 3 was higher than that in test 1. These differences were due not to an increase in insulin secretion but to a decrease in glucose area.

Comparison of Fasting Lipid Levels

Table 6 shows the number of subjects with normal fasting serum triglyceride levels in each test and group. As a group, only 76 of the 116 chemical diabetics tested had normal fasting triglyceride levels in the initial test. In the between-group comparison by chi-square analysis no significant changes between

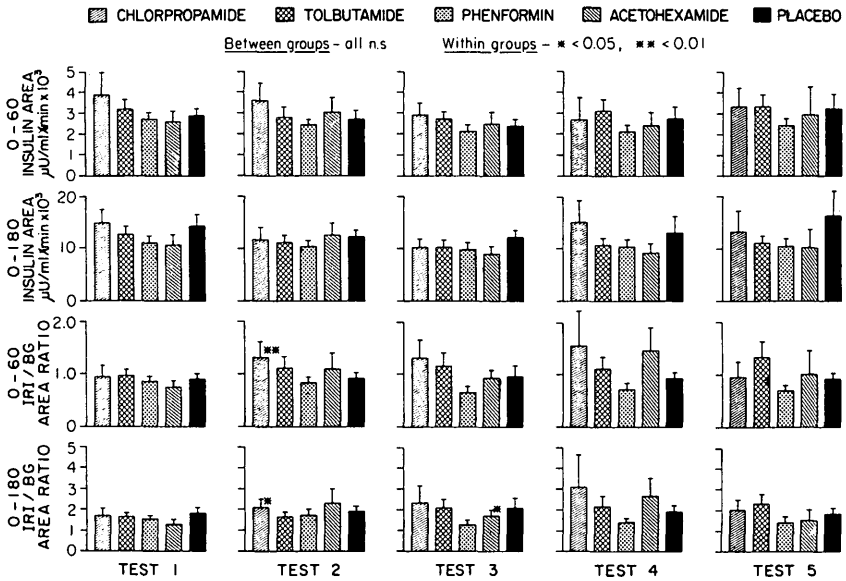

FIGURE 2

The absolute and relative insulin responses in each group for each of the five sequential oral glucose tolerance tests.

placebo and each of the drug groups were present. Unpaired *t* analysis indicated that, compared with the placebo group, the tolbutamide group showed lower fasting triglycerides in tests 4 and 5 while the other groups showed no differences. In the within-group comparison by both chi-square analysis and the paired *t* test, no significant differences were seen between the fasting triglyceride levels in test 1 and each of the follow-up tests in all five groups.

A discrepancy exists between the total number of subjects in the study and the number of subjects compared in tests 1 and 2 in each group. This is because some of the subjects did not have fasting lipid levels measured because of insufficient quantities of serum in some tests. In the chlorpropamide group, two subjects did not have fasting serum lipids measured in test 1. In the tolbutamide group, three subjects did not have fasting lipids measured in test 2 and one of these three subjects also had no fasting serum lipids measured in test 1. In the phenformin group, one subject did not have fasting lipids measured in test 2. In the acetohexamide group, three subjects did not have fasting lipids measured in test 2. In the placebo group, one subject in test 1 and three subjects in test 2 did not have fasting lipids measured.

Table 7 shows the number of subjects with normal fasting serum cholesterol levels. In the initial test, 85 out of the total 116 chemical diabetics tested had normal fasting cholesterol levels. In the between-group comparison by chi-square analysis no signifi-

TABLE 7

Comparison between placebo and each of the drug groups for each test and between test 1 and subsequent tests in each group*

Number of subjects with normal fasting cholesterol level indicated

Group	Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	22 vs. 22 / 33	18 vs. 19 / 26	12 vs. 13 / 19	10 vs. 12 / 17
Chlorpropamide	12 vs. 15 / 16	11 vs. 12 / 15	9 vs. 10 / 12	7 vs. 9 / 10
Tolbutamide	21 vs. 21 / 25	18 vs. 19 / 22	16 vs. 16 / 20	14 vs. 14 / 17
Phenformin	19 vs. 19 / 22	17 vs. 16 / 20	15 vs. 18 / 18	13 vs. 11 / 16
Acetohexamide	11 vs. 11 / 11	11 vs. 11 / 11	8 vs. 8 / 8	7 vs. 7 / 7

*There were no significant differences between placebo and drug groups.

cant changes between placebo and each of the drug groups were present. Comparisons made by unpaired *t* test indicated that only the acetohexamide group differed from the placebo group, and only in tests 1, 2, and 3. The within-group comparison by chi-square analysis showed no significant difference between test 1 and each of the follow-up tests in all five groups. However, by paired *t* analysis, the phenformin group showed higher fasting cholesterol levels in tests 3 and 5 than in test 1. None of the other groups showed any significant differences.

Lipid Dynamics During Oral Glucose Tolerance Test

Figure 3 shows the serum cholesterol and triglyceride changes during the initial test for the entire group. By paired *t* analysis, there was a significant increase over baseline (7-12 per cent) in the serum triglyceride at one-half and one hour, followed by a significant decrease (6 per cent) at three hours after the ingestion of glucose. On the other hand, the serum cholesterol showed a significant decrease at one, two, and three hours after the ingestion of glucose. This pattern of change in serum triglyceride and cholesterol was seen in all five groups and in all five tests.

Mortality

During the study period, the following deaths occurred in the entire group of 365 patients: In the placebo group, two males died with myocardial infarction and one male by automobile accident. In the chlorpropamide group, one female died of uremia. In the tolbutamide group, one male died by automobile accident and one female by reticulum cell sarcoma. In the phenformin group, one male died with carcinoma of the lung and one female with myocardial infarction. In the group of males in the placebo group in this study, the only deaths noted were of two males, who died of myocardial infarction.

DISCUSSION

In this study the number of subjects with normal glucose tolerance was significantly greater only in the chlorpropamide group after one year of treatment. This improvement was not related to weight loss in these subjects.

Improvement of glucose tolerance in chemical diabetics on placebo therapy has been reported by Wilansky and Shochat.[2] This was also reported in diabetics by Turtle,[8] but not by Arky and Abramson.[5] This current study shows no such improvement in the placebo (diet therapy) group.

Improvement in glucose tolerance during

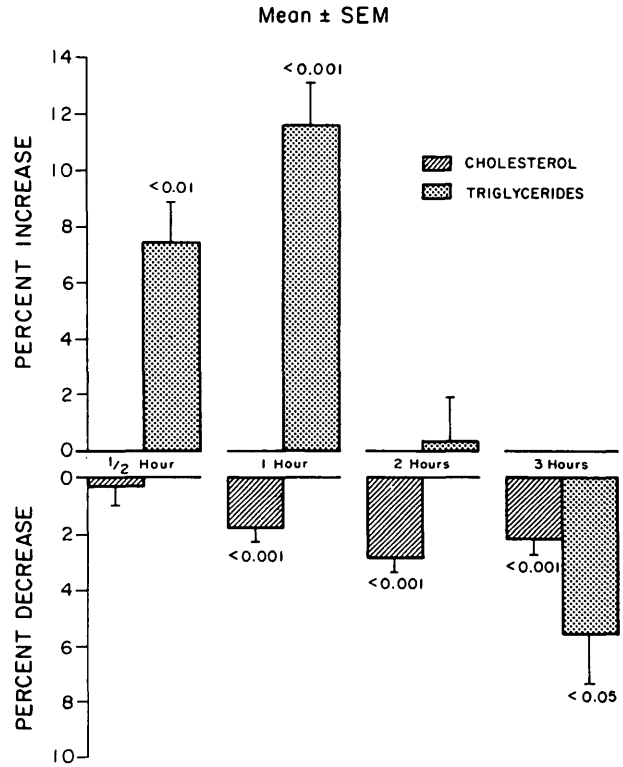

FIG. 3. The per cent change of serum cholesterol and triglyceride levels during the oral glucose tolerance test (n = 116).

chlorpropamide,[5,7,9,14-16] tolbutamide,[1,3,4,14] acetohexamide,[6] tolazamide,[8] and glibenclamide[10-13] therapy has been reported previously, and this study corroborates one of these findings. It is feasible that in the chlorpropamide group the improvement seen during the first year of therapy may be due to diet and the effect of the drug. The lack of improvement in the tolbutamide group does not support the findings of other investigators.[1,3,4,14] Nor does this study confirm the finding that chemical diabetics or mild diabetics, when treated with phenformin, improved their glucose tolerance.[2,5,25] This apparently is not because the subjects in this study are on fixed doses of phenformin (50 mg. daily), as Wilansky and Shochat's subjects were on a similar dose. Another possible explanation for the lack of improvement of glucose tolerance following treatment with oral hypoglycemic agents is that most of the subjects in this study were over 35 years of age (chlorpropamide group 15/18, tolbutamide 21/28, phenformin 18/23, acetohexamide 12/14, and diet therapy 32/37 over age 35 years). Two previous studies[1,26] suggested that patients younger than 35 years of age responded better to therapy.

A possible explanation for the improved glucose tolerance in chemical diabetics treated with chlor-

propamide is the increased insulin secretion in response to glucose. Indeed, several groups have demonstrated an increase in insulin secretion during the glucose tolerance tests in diabetics after short-term therapy with sulfonylureas—i.e., one week of therapy,[14] three weeks,[5] four weeks,[16,27] seven weeks,[7] and eight weeks.[4,6] Two other groups[15,28] reported higher insulin secretion in diabetics when they were on sulfonylurea therapy than when they were off therapy.

In the present study, improvement in glucose tolerance was seen in the chlorpropamide group. This improvement was not associated with an increase in insulin secretion during the glucose tolerance test. Improvement in glucose tolerance unassociated with increased insulin secretion has been reported by many groups.[8-13,29] The discrepancy is most likely due to the timing of the test after initiation of drug therapy. An increase in insulin secretion during oral or intravenous glucose tolerance tests is observed when the tests are performed after one to eight weeks of therapy. Despite this improvement in glucose tolerance, tests done after three months of therapy in diabetics almost invariably show no increase in insulin output when compared with the initial test. Indeed, four of the studies[6,14,16,27] that demonstrated increased insulin output during glucose tolerance test after short-term therapy with sulfonylureas could not demonstrate the same finding when the tests were repeated after three months of therapy. In the present study, the first follow-up test was performed after one year of therapy.

An alternative explanation for the lack of change in insulin levels is the heterogeneity of insulin responses in a group of subjects. It has been shown that, in latent diabetics, the insulin responses to glucose may be quite variable. Those with low insulin responses had an increase in the early insulin response with sulfonylurea after many years of therapy, while those with high insulin responses had a decrease. If these groups are combined, no change in insulin levels would be found.[30]

The absence of an increased insulin output to account for the improved glucose tolerance would suggest that the sulfonylureas have some extrapancreatic effects that facilitate the disposal of a glucose load. Several mechanisms have been postulated: (a) an acquired loss of insulin antagonism;[6] (b) an increased biologic activity of the endogenous insulin;[31] (c) an enhancement of the sensitivity of the beta cell without affecting its total response,[32] and/or (d) an increased secretion of insulin coupled with an increased degradation by the liver of the secreted insulin.[9]

Before attributing the improvement of glucose tolerance in diabetics on long-term sulfonylurea therapy to extrapancreatic effects of the drugs, two "pancreatic factors" must be considered. These are the influence of sulfonylureas on glucagon secretion and on the early phase of insulin secretion after a glucose load. Experience is too limited to speculate on the role of glucagon in the mechanism of action of the sulfonylureas. In normal humans, oral administration of chlorpropamide[33] and gliburide[34] did not suppress plasma glucagon levels, whereas, in the only reported study in diabetics, therapy with chlorpropamide for 12 days in six maturity-onset diabetics reduced the levels of circulating glucagon.[35]

Recent observations of the regulation of diabetes in dogs and man by an artificial pancreas suggested the importance of the early phase of insulin secretion.[36,37] An absent or reduced early phase would decrease the effectiveness of insulin, while a restored first phase could lower the subsequent hyperglycemia after a glucose load without increasing the late phase of insulin secretion. In the present study the time of peak insulin was not corrected by diet with or without drug therapy. Three other groups reported similar findings,[10,26,29] while another three groups reported a correction of the delay in the peak insulin.[8,16,32] In one of the latter groups,[16] a highly significant increase in the early phase of insulin release was shown at five minutes after rapid intravenous glucose administration in diabetics on drug therapy.

Previous studies on the effect of phenformin on glucose tolerance tests in diabetics showed improvement of glucose tolerance associated with a decrease in insulin secretion.[5,25] Recently, the suggestion was put forth that phenformin's primary action is the enhancement of peripheral glucose assimilation and that the changes in insulin secretion are secondary to this.[38] The present study demonstrated neither an improvement in glucose tolerance nor a decrease in insulin secretion. This apparent discrepancy may be due to the subjects used and/or to the dose of phenformin given. In the two studies quoted, all subjects were obese and a higher dose of phenformin was used. In addition, the subjects were studied after a very short period of therapy.

The need to redetermine periodically the necessity of long-term therapy with oral hypoglycemic agents in diabetics was recently raised.[39,40] The present study also raises the same question because a group of

chemical diabetics on placebo therapy did not differ significantly from another group on drug therapy as far as glucose tolerance was concerned. Two points need to be emphasized. First, the chemical diabetics treated with drugs were on a *fixed* dose of drugs, no attempt being made to regulate the hyperglycemia closely. Second, on an individual basis, more chemical diabetics seem to respond better to a combination of diet and chlorpropamide therapy than to diet alone during the first year of therapy.

Both sulfonylureas and biguanides have been known to lower serum cholesterol and triglyceride.[5,10,17-20] In the present study the number of subjects with normal fasting cholesterol or triglycerides was not significantly changed when the number in the initial test was compared with each of the subsequent tests. A comparison of the mean fasting values in the initial test with each of the subsequent tests also did not show any difference. The reason for this is not apparent.

The patterns of changes in serum triglycerides and cholesterol during the oral glucose tolerance test are similar to those of normal subjects (data not shown). The early increase in serum triglycerides may be due to two possible causes: (a) increased endogenous triglyceride synthesis from fatty acids, which are not utilized as fuel when glucose is available and insulin is present, and (b) conversion of glucose to triglycerides. A later decrease in serum triglycerides has been reported previously.[41] This is most likely due to decreased substrate (fatty acids) availability due to decreased lipolysis in adipose tissue and to increased triglyceride removal secondary to an increase in lipoprotein lipase.[42] A decrease in serum cholesterol following prolonged glucose feeding has also been reported recently.[43] This study demonstrates the acuteness of the effect. The mechanism responsible for the change remains to be elucidated.

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