ASSESSMENT OF ORAL THERAPY IN DIABETES MELLITUS

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EARLIER trials at Whittington Hospital confirmed the hypoglycaemic effects of tolbutamide (Wolff, Stewart, Crowley and Bloom, 1956), phenformin (Hall, Crowley and Bloom, 1958) and chlorpropamide (Granville-Grossman, Crawford, Crowley and Bloom, 1959). Since the inception of oral therapy, more than 400 diabetics at this hospital have been successfully treated with these agents for more than three months and many have been under continuous treatment in this way for several years. Sufficient experience has accrued to make useful a review of the outcome of treatment with these drugs, and in particular to inspect the extent to which relapse occurs in diabetics at first well controlled on this oral therapy.

There is general agreement that oral therapy is most likely to offer effective control in those developing diabetes in adult life ("maturity onset"), in those of average or above average weight and in those whose urine is free from acetone. To put it another way, oral therapy is regarded as unlikely to be successful in young diabetics, in underweight diabetics or in those displaying ketoacidosis. However, more recent studies have demonstrated that in some more severe diabetics phenformin and chlorpropamide were more effective when taken together than when taken separately (Bloom and Richards, 1961). In view of this, a prospective series of newly diagnosed diabetics has been treated with a combination of phenformin and chlorpropamide in an endeavour to determine the extent to which this combination can widen the effective range of oral therapy.

Material and Analysis

Patients studied have been attending the Diabetic Clinic since 1955 when oral hypoglycaemic agents became available. The series excluded patients who attended before that time and also those suffering from carcinoma of pancreas, pancreatitis, haemochromatosis, acromegaly, Cushing's syndrome or receiving steroids for another disease. In all, 1408 cases notes were surveyed and 404 patients were still receiving oral therapy at their last recorded attendance. 212 patients were taking chlorpropamide; 62 tolbutamide; 112 chlorpropamide and phenformin combined; 11 phenformin; and seven were taking other oral hypoglycaemic drugs. It should be stated that in analyses to follow, some patients were transferred from one form of therapy to another and so appear more than once.

The choice of treatment in the new diabetic was determined by the type of diabetes and by the age of the patient. Mild diabetics, particularly when overweight, were treated by simple dietary restriction. Where hyperglycaemia persisted despite loss of weight and an adequate trial of diet, oral therapy was introduced and a suitable diet maintained. Chlorpropamide has been regarded as the drug of choice in recent years, since it is more effective than tolbutamide and need only be given once a day. Tolbutamide has been reserved for the very elderly in view of the dangers in these patients of hypoglycaemia when chlorpropamide is used. A combination of chlorpropamide and phenformin was employed when patients responded inadequately to chlorpropamide alone. As appears later, more recently this combination has also been used as initial therapy in patients thought unlikely to respond to oral therapy by reason of youth, ketoacidosis or because they were underweight.

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In analysing the results of therapy, no attempt has been made to determine the extent of primary failures (i.e. those who failed initially to respond to tablets or relapsed within the first three months). Of those successfully treated with tablets for more than three months, the majority have been maintained on the original therapy for the period of observation. Some of the remainder have relapsed and required more effective therapy, while others have remitted and have been managed on dietary restriction alone.

Those maintained on oral hypoglycæmic therapy have been analysed for degree of control. Patients attended the Diabetic Clinic usually at one to three monthly intervals, depending on the degree of control and other factors. Patients tested their own urine for sugar (using Clinitest) and a specimen was tested at each clinic attendance. A venous blood sample was taken at each attendance in the early afternoon, usually one to three hours after lunch. Blood sugar estimations were by the Hagedorn and Jensen method until 1961, and since then by the auto-analyser, using ferro-ferricyanide oxidation-reduction reaction.

A patient was considered to show good control when the post-prandial blood sugar levels were consistently below 190 mg./100 ml. and the urine was consistently sugar free. Control was regarded as fair when the majority of blood sugars were below 190 mg. but occasional blood sugars were between 190 and 240 mg./100 ml., and as unsatisfactory or variable when occasional blood sugars were more than 240 mg./100 ml. with sporadic glycosuria.

Tolbutamide was given usually as a dose of 0.5 g. three times a day, occasionally as 1 g. twice a day or 0.5 g. twice a day. Chlorpropamide was given as a single morning dose, usually at an initial level of 500 mg. or 375 mg., and reducing to 350 mg., 250 mg., 200 mg. or even less if the response warranted it. When combined therapy was used, the object was to give the maximum dose likely to be well tolerated. Phenformin, 100 mg. was administered as "timed-disintegration" capsules, two

of each; and chlorpropamide, 500 mg. was given at the same time. As soon as there was good response, the dose of chlorpropamide was reduced to 350 mg. or less; phenformin usually was maintained at 100 mg., but occasionally reduced to 50 mg.

Tolbutamide

Ninety-four patients have been under observation for more than three months while taking tolbutamide.

Forty-seven patients were maintained on tolbutamide. Of these 23 have been well controlled and 11 fairly well controlled for a length of observation up to seven years. In a further 13 patients, control has been variable. For example, one patient observed for over six years had two blood sugar levels over 190 mg./100 ml., one of them 288 mg./100 ml. Nevertheless, in these 47 patients, control of the diabetes while taking tolbutamide has not warranted change of treatment. The patients have been symptom-free and the weights satisfactory. The duration of observed treatment is set out in Table 1.

In 41 patients, control with tolbutamide became inadequate and other therapy was substituted. The cause of this secondary failure was usually not apparent. In three patients the deterioration was precipitated by an acute infection. Dietary indiscretion was always suspected and the patient admonished in this respect before therapy was changed: occasionally stricter attention to diet led to improvement and offered an explanation for the variability of control already noted. Of these 41 cases of secondary failure to tolbutamide, 25 were subsequently controlled by chlorpropamide, 13 by chlorpropamide and phenformin together, two by tolbutamide and phenformin together and one by insulin. The time and rate of this relapse is set out in Table 2.

Six patients showed remission of their diabetic state and tolbutamide was discontinued after periods ranging from one to five years.

TABLE 1
LENGTH OF MAINTENANCE THERAPY
(Omitting remissions and secondary failures)

	3-6 months	6-12 months	1-2 years	2-3 years	3-4 years	4-5 years	5-6 years	6-7 years
Tolbutamide	5	8	10	5	10	7	1	1
Chlorpropamide	18	37	64	45	14	5	—	—
Phenformin plus Chlorpropamide	18	13	26	5	6	1	—	—
Number of cases								

TABLE 2
RELAPSE RATE %
(Secondary failures)

	3-6 months	6-12 months	1-2 years	2-3 years	3-4 years	4-5 years	5-7 years	Total
Tolbutamide (94 cases)	7.4	4.3	9.6	10.7	9.6	2.1	0	43.7%
Chlorpropamide (234 cases)	2.1	3.4	5.1	0.4	0.9	0	—	11.9%
Phenformin plus Chlorpropamide (95 cases)	2.1	4.2	5.3	1.1	0	0	—	12.7%

Note. All patients in this category were successfully controlled by oral therapy for at least 3 months, thus excluding primary failures.

Chlorpropamide

Two hundred and thirty-four patients have been treated with chlorpropamide for more than three months.

One hundred and eighty-three patients have been maintained on chlorpropamide (Table 1) with steady weights and freedom from symptoms. Of these, 108 have shown good control and 42 fair control for up to five years. In 33, control has been variable and unsatisfactory, though in many for obvious reasons. Six patients were careless in their eating habits; six probably failed to take their tablets regularly; five became irregular because of concurrent ailments. In the remaining 16, blood sugars showed fluctuations for no obvious reasons, though the general control was regarded as sufficiently satisfactory to warrant continuation of this therapy: in several there was only one blood sugar over 240 mg./100 ml. during a period of observation of several years.

In 28 patients, treatment had to be changed (Table 2). Two developed toxic reactions probably due to chlorpropamide. Two went out of control during an acute infection. In the remaining 24, no obvious cause of the relapse was apparent. Of these cases of secondary failure to chlorpropamide, 16 were subsequently controlled by chlorpropamide plus phenformin, one by phenformin alone, three by tolbutamide and eight by insulin.

Twenty-three patients showed remission of their diabetic state and were able to be controlled by diet alone after periods of treatment with chlorpropamide up to two years.

Chlorpropamide plus Phenformin

Ninety-five patients have taken this combination of tablets for at least three months.

Sixty-nine cases have been maintained on this therapy (Table 1). Forty-two patients have been well controlled and 14 fairly well controlled for up to four years. In 13, control has been variable or unsatisfactory. Of these, one

patient refuses insulin, two do not take the tablets regularly, five have conditions other than diabetes which make control erratic and the remaining five show fluctuations in the blood sugar levels, the majority being in the satisfactory range. These 69 patients are free from diabetic symptoms, their weight remains satisfactory and there has been no pressing indication to change therapy.

Twelve patients relapsed and were transferred to insulin (Table 2). Six patients developed persistent weight loss or ketosis while taking the tablets, and there was an immediate improvement when insulin was administered. In some patients, however, transfer to insulin led to variations in the blood sugar levels wider than those observed when on oral therapy and in addition, hypoglycæmic attacks were observed. Some were maintained on a moderate daily dose of insulin (about 30 units) but in others there has been a steady increase of insulin requirements.

In 14 cases, some remission or amelioration of the diabetic state was observed after periods up to three years. In two cases diet alone became adequate for good control, in one chlorpropamide was discontinued and in 11 phenformin was discontinued with maintenance of good control.

The overall outcome of therapy (using tolbutamide, chlorpropamide or combined chlorpropamide and phenformin) is set out in Table 3.

Late Toxic Effects

Toxic reactions occurring after the first three months of therapy were both mild and unusual. One patient taking chlorpropamide developed a generalised rash which cleared when the drug was discontinued. One patient developed gastric symptoms when taking phenformin, which improved when therapy was changed. Three other patients were recorded as having symptoms doubtfully attributed to therapy. One patient complained of giddiness

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TABLE 3

and headache and another of palpitations while taking chlorpropamide. One patient felt tired and unwell while on phenformin therapy.

Range of Therapeutic Effectiveness

In order to evaluate the extent to which combined oral therapy (chlorpropamide plus phenformin) could control successfully the diabetic state, a scheme of treatment was devised (Table 3) and studied in a prospective series of 100 consecutive newly diagnosed cases. All patients presented with a history of diabetic symptoms and the diagnosis was confirmed in all but very severe cases by an oral glucose tolerance curve. Diabetes secondary to a known underlying disease was excluded.

The series thus defined consisted of 48 males and 52 females, with ages ranging from three to 82 years (average 51.5). The period of follow-up was from six to 22 months (average 14.7). The response to treatment was considered satisfactory if the patient felt well, if the body weight approximated to normal, if repeated random blood sugars were less than 190 mg./100 ml., and if there was no ketonuria.

Patients were treated initially according to the criteria set out in Table 3. The assessment

of body weight was based on the comparison of the initial weight with the expected mean (Kemsley 1951). Ketonuria was regarded as significant when "Acetest" was strongly positive in repeated specimens.

Of these 100 patients, 33 responded well to simple dietary restriction (Group A) and have remained satisfactorily controlled without further therapy.

Twenty-eight patients failed to respond to dietary restriction alone but became satisfactorily controlled when chlorpropamide was given (Group B).

Group C contained 23 patients who were controlled by a combination of chlorpropamide and phenformin. Of these, five had shown an inadequate response to chlorpropamide alone but became satisfactorily controlled when phenformin was added. Eighteen were given combined treatment from the start: these were patients who were underweight (6), ketonuric (6) or both (6), and hence regarded as unlikely to respond to chlorpropamide alone.

Sixteen patients out of the 100 were given insulin. Six were children under 16. One patient showed a primary failure to respond to tablets. One patient developed exfoliative dermatitis soon after starting oral therapy and so was transferred to insulin. Two patients were so unco-operative about taking their tablets that insulin was regarded as a safer alternative. One patient had pulmonary tuberculosis and so was given insulin as initial treatment. One patient failed to gain weight while on the tablets: unfortunately he remained equally skinny when transferred to insulin. Four patients relapsed while taking combined chlorpropamide and phenformin. The relapse was relatively sudden, within a few weeks, and after a period of successful control varying from seven months to 22 months. Two of these patients were under 30 years old, the other two were over 73 years old. They each required about 40 units of insulin for control.

Discussion

Oral therapy for diabetes appears both practicable and efficient over many years. Toxic effects are unusual and reversible, but the main disadvantage appears to be that many patients, initially well controlled, relapse into hyperglycemia after a time. Patients controlled by tolbutamide appeared particularly susceptible in this respect, since nearly half of them had required other treatment within five years: the relapse rate was about 10% for each of the first four years. Chlorpropamide seemed to

TABLE 4
SCHEME OF TREATMENT IN 100 CASES OF DIABETES

MAIN FEATURES		TREATMENT
GROUP A 33%	a. Onset in adult life	Dietary restriction alone.
	b. Weight average or above	Diet varying from 800 cal. to 1200 cal.
	c. No ketonuria	daily according to degree of overweight.
GROUP B 28%	a. Onset in adult life	<i>Chlorpropamide</i> 500 mg. daily reducing to
	b. Weight average or near average	350 mg. or less if adequate response
	c. No ketonuria	OR
	d. Inadequate response to dietary restriction alone.	<i>Tolbutamide</i> (especially in very elderly) 1 g. twice daily reducing to 0.5 g. t.d.s. or b.d. Diet: 1500-1800 cal.
GROUP C 23%	a. Any age except children	Combined daily
	b. Normal weight or underweight	<i>Chlorpropamide</i> 500 mg. reducing to 350 mg.
	c. Ketonuria present	PLUS
	d. Inadequate response to chlorpropamide or tolbutamide	<i>Phenformin</i> 100 mg. Diet: 1500-2200 cal.
GROUP D 16%	a. Children	Insulin
	b. Severe infection	Diet: 2000-2800 cal.
	c. Severe ketoacidosis with danger of coma.	
	d. Inadequate response to combined chlorpropamide and phenformin.	

be more effective in that the relapse was about 5% for each of the first two years, but less than 1% for the three subsequent years. Of patients controlled by combined therapy (phenformin and chlorpropamide), the relapse rate was similar to that for chlorpropamide, the majority of relapses taking place in the first two years.

The cause of this relapse was uncertain. In some patients the return of hyperglycemia was due to a growing disinclination to continue with a restricted diet and consequent indiscretion at the table. Some elderly patients were forgetful in taking their tablets and glycosuria gradually followed. But in the majority of diabetics who relapsed while on oral therapy, neither of these factors could be blamed. It seems that either these patients had become resistant to the action of the tablets in question, or their diabetic state had deteriorated and less endogenous insulin had become available.

Our experience with a combination of chlorpropamide and phenformin has led us to attempt oral therapy in patients previously regarded as unlikely to respond. Phenformin when given in maximum therapeutic doses is very prone to cause gastrointestinal intolerance (Hall and others 1958) but when given in capsule form (Bloom and Richards, 1961) and at a dose of 100 mg. a day, it is well tolerated by the large majority of diabetics. It exerts an additional hypoglycemic effect to that of the sulphonylureas (Beaser 1958, 1960; Granville-Grossman and others 1959; Bloom and Richards 1961). Hence this combination was used in patients who were underweight, or

ketonuric or both, and insulin was reserved for children, or patients where there was a danger of coma or where there was serious infection. Treatment proved effective in the majority of patients so treated, though some relapsed within a year or two and required insulin. Patients successfully controlled on the combination felt well and either maintained their weight or lost a few pounds. Ketones disappeared from the urine in the early stages of control, in contrast to experience when phenformin was used alone.

Hence it has been demonstrated that many underweight and ketotic young adult diabetics can be successfully controlled on oral therapy, at any rate for some years. What remains doubtful is whether they *should* be so controlled. Fajans and Conn (1960) demonstrated that prolonged administration of tolbutamide to a group of young mild diabetics led to an improved performance of the insulin-producing tissue and suggested that the sulphonylureas could be prophylactic in the very earliest stages of diabetes. It seems likely that even ketotic young diabetics have some islet cell reserve, capable of stimulation and perhaps regeneration in some cases (Taylor, 1963). Ultimately the value of oral hypoglycemic therapy will be determined by the incidence of pathological changes in the eyes, kidneys and arteries in patients so treated, as compared with those in whom insulin has been used from the start. Only careful and prolonged observation can determine which treatment offers the best prognosis for the future.

Finally, our experience leads us to add a

warning. The high relapse rate of patients treated with tablets means that regular supervision is essential. Particularly in the younger age groups, relapse can be rapid; unless close supervision is maintained, this could lead to unfortunate results.

Summary

1. Oral therapy has proved effective and safe in the treatment of certain types of diabetes.
2. Over five years, the relapse rate in dia-

betics treated with tolbutamide was 43.7% with chlorpropamide 11.9% and with a combination of phenformin and chlorpropamide 12.7%.

3. When a combination of chlorpropamide and phenformin was used, oral therapy could be extended successfully to include new diabetics who were young, underweight or showing ketonuria. Relapse sometimes occurred rapidly in such cases so that supervision must be close.

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