FURTHER EXPERIENCE WITH ORAL THERAPY IN DIABETES

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Tolbutamide has proved to be a successful hypoglycaemic agent in many diabetic patients. It is well tolerated and safe, and it does not lead to severe hypoglycaemic symptoms. Nevertheless, it suffers from two disadvantages. First, its effective action is short-lived (Stowers *et al.*, 1958), and so it has to be given twice daily. Second, it is successful mainly in patients with mild diabetes with onset at maturity (Marble, 1958). Hence there is a need for compounds which are effective in a wider range of diabetics and with a more prolonged action. Short-term trials of a new oral hypoglycaemic agent can determine in what type of diabetic the agent is successful, its length of action, and whether it is well tolerated. Long-term trials are necessary before the possibility of toxic effects can be eliminated with confidence. Carbutamide proved to be a well-tolerated and effective oral hypoglycaemic agent, but it had been in use for over a year in Germany

I. Carbutamide

1-butyl-3-sulphonylurea

II. Tolbutamide

1-butyl-3-*p*-tolylsulphonylurea

III. Chlorpropamide

1-propyl-3-*p*-chlorbenzenesulphonylurea

IV. Metahexamide

1-cyclohexyl-3-*m*-amino-*p*-tolylsulphonylurea

V. Phenethyldiguanide

N-beta-phenethyl formamidine ininourea

VI. Dimethyldiguanide

N.N.-dimethylguanylguanidine

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before reports of toxic effects on the blood began to appear (Duncan *et al.*, 1956; *British Medical Journal*, 1956).

This paper describes trials of three more oral hypoglycaemic agents. Two of these, chlorpropamide and metahexamide, belong to the same group of compounds as tolbutamide—namely, the sulphonylureas (see formulae I–IV). The other compound investigated, dimethyldiguanide (formula V), belongs to the diguanide group of compounds, of which phenethyldiguanide (formula VI) has previously been investigated (Hall *et al.*, 1958). Metahexamide and dimethyldiguanide have been the subject of short-term trials, while chlorpropamide has been used for longer periods. These compounds have been compared with tolbutamide.

Metahexamide

Material and Methods

30 diabetic patients (10 male, 20 female) were admitted to the ward for treatment with metahexamide. Their ages ranged from 34 to 89 years, average 67. The weights of 29 lay in the 5–95 centile range (Kemsley, 1952); one patient was heavier than 95% of her peers. Nine patients were newly diagnosed, seven others had relapsed after a successful period of control by diet alone, and the remaining 14 had been treated at some time previously by either insulin or tolbutamide. Patients with severe diabetes—that is those who were young, underweight, and had a tendency to acetonuria—were excluded from the trial. Those with mild diabetes who responded to dietary restriction were likewise not included. All patients were managed by diet alone for an initial period of at least two weeks (the last week as an in-patient), and metahexamide was introduced only when glycosuria and hyperglycaemia failed to diminish.

The calorific value of the diet was arrived at by consideration of the patient's height, weight, sex, age, and activity, and varied from 1,500 calories (150 g. of carbohydrate, 65 g. of protein, and 70 g. of fat) to 2,200 calories (232 g. of carbohydrate, 82 g. of protein, and 105 g. of fat) a day. This diet was sometimes increased when a satisfactory response to metahexamide was obtained. Preprandial venous blood-sugar levels were estimated in all patients at noon (method of Hagedorn and Jensen) during the last seven days of dietary restriction and during the first seven days of treatment with metahexamide. In 16 patients blood for sugar estimations was also taken while fasting at 8 a.m. and before supper at 6 p.m. on alternate days throughout the control period and the first week of treatment. The urine of all patients was tested four-hourly during the day for sugar content and for acetone.

Metahexamide was given at 8 a.m. daily before breakfast after the specimen for fasting blood-sugar estimation had been taken, in an initial dose of 300 mg., the dose being reduced to 200 or 100 mg. after a few days if a satisfactory hypoglycaemic response was obtained.

Liver-function tests, white blood count, haemoglobin estimation, and blood-film examination were done before treatment with metahexamide and six weeks later.

Results

In 20 patients the diabetes was well controlled by an initial dose of 300 mg. daily, later reduced to 50 to

200 mg. metahexamide daily. On this dose the blood-sugar levels remained within the normal range and the urine became virtually free of sugar. The hypoglycaemic effect on 10 patients was not sufficient to control their diabetes. Five of these were subsequently stabilized on insulin, one on chlorpropamide, three on phenethylguanide, one on a combination of chlorpropamide and phenethylguanide, and one on a combination of metahexamide and phenethylguanide.

Effect of Metahexamide on Blood-sugar Levels.—Fig. 1 shows the mean fall in noon blood-sugar levels produced by a week's administration of metahexamide to 24 patients, some of whom showed little or no

FIG. 1.—Effect of a week's treatment with metahexamide on noon blood-sugar levels (24 patients). Blood-sugar levels are expressed as a percentage of the mean pre-treatment level for each case. Each point is the mean value obtained from the number of diabetics shown above each point. The horizontal lines bracketing each point represent the standard error of each mean.

FIG. 2.—Mean blood-sugar levels at 8 a.m., noon, and 6 p.m. before and during treatment with metahexamide (16 patients). Each point on the upper curve is the mean of the week's pre-treatment blood-sugar levels. Each point on the lower curve is the mean of the blood-sugar levels on the seventh day after treatment with metahexamide was started. The horizontal lines bracketing each point represent the standard error of each mean.

hypoglycaemic response to the drug. The mean blood-sugar level tended to rise during the control period of dietary restriction. Administration of metahexamide led to a progressive fall in blood sugars. Fig. 2 shows the effect of metahexamide on the blood-sugar levels at 8 a.m., noon, and 6 p.m. in 16 patients. The blood-sugar levels during the week prior to treatment with metahexamide are compared with those after one week's treatment. Some of the patients included showed little or no response to the drug. It can be seen that metahexamide has greatly reduced the blood-sugar levels throughout the 24 hours.

Side-effects.—No rashes, gastro-intestinal upset, or evidence of blood dyscrasia were observed after treatment with metahexamide, and no patient complained of symptoms referable to hypoglycaemia. One patient, who was treated with metahexamide subsequent to this trial, developed jaundice.

The patient was a woman aged 67. Diabetes was diagnosed in 1955, since when she had been treated with 30 to 40 units of insulin daily. She was admitted to the ward for reassessment of diabetes and tried on metahexamide, 300 mg. daily. Response was only partly satisfactory and the drug was discontinued after 12 days on this dose. Insulin was then given with good response. Two days after discontinuation of metahexamide and while she was on insulin, mild jaundice was observed. Maximum serum bilirubin was 3.1 mg./100 ml., alkaline phosphate 24 units, thymol turbidity 4 units. Urine: bilirubin present, urobilinogen normal. Liver biopsy showed some cloudy swelling and trace of jaundice but no necrosis of parenchyma. Cholecystograms revealed normal gall-bladder, and no gall-stones were seen. Her general condition appeared unaffected by the jaundice, which faded after several days. Serum bilirubin fell to 0.7 mg./100 ml.

Chlorpropamide

Material and Methods

75 diabetic patients (49 female, 26 male) have been treated with chlorpropamide. Their ages ranged from 38 to 86 years, average 65. The weights of 69 lay in the 5–95 centile range (Kemsley, 1952). Six patients were heavier than 95% of their peers. 29 of the diabetics were newly diagnosed, 8 others had relapsed, having previously been well controlled on diet alone, and the remaining 38 had at some time been treated with either insulin or tolbutamide. Patients were selected as in the metahexamide trial. Those with mild diabetes who responded to dietary restriction were not included, nor were those with severe diabetes and a tendency to acetonuria. The patients were managed on dietary restriction alone for an initial period of at least two weeks, and chlorpropamide was introduced only when glycosuria and hyperglycaemia failed to diminish. Overweight patients were observed for a longer period and chlorpropamide was not used until they had lost weight. The diet was based on the patient's age, height, weight, sex, and activity as in the metahexamide trial.

Most of the patients received 500 mg. in one dose at 8 a.m. daily, reducing to 200 mg. daily if a satisfactory hypoglycaemic response was obtained. In the early part of the trial a few patients received 1 g. a day initially.

Venous blood-sugar levels were estimated regularly both during the period of observation on diet alone and while chlorpropamide was administered. Liver-function tests, haemoglobin estimation, white blood-cell count, and blood-film examination were done before treatment with chlorpropamide and again six weeks later.

More detailed investigation was undertaken on 18 of the patients admitted to the ward. Blood-sugar levels at noon (before lunch) and at 6 p.m. (before supper), and total 24-hour output of glucose in the urine, were estimated daily or on alternate days for the last five days of dietary treatment, and for the first seven days of treatment with chlorpropamide.

Results

Chlorpropamide was successful in controlling the diabetes of 50 patients. The blood sugar remained within normal limits while these patients were receiving the drug, and the urine became free from sugar for most of the day. In 20 patients the hypoglycaemic effect of chlorpropamide, though sometimes pronounced, was not sufficient to cause the blood-sugar level to fall to normal, and treatment with insulin or a diguanide was substituted. Chlorpropamide was discontinued in five cases before its effect on the diabetes could be determined with certainty because of intercurrent illness (three patients) or side-effects (in two patients, see below).

Effect of Chlorpropamide on Blood-sugar Levels and Glycosuria.—Fig. 3 shows the fall in 6 p.m. blood-sugar levels produced by several days' administration of chlorpropamide to 18 patients, some of whom showed little or no hypoglycaemic response. For each patient the mean pre-treatment 6 p.m. blood-sugar level was calculated and each value before and during treatment was expressed as a percentage of this. There was no significant change in the blood-sugar levels during the period of dietary restriction alone. Administration of chlorpropamide led to a progressive fall in the mean blood-sugar level. The noon blood-sugar levels similarly showed no change during the period of diet alone, and a progressive fall while chlorpropamide was given. The total 24-hour output of glucose in the urine reflected the blood-sugar levels; there was no evidence of altered renal threshold.

FIG. 3.—Effect of a week's treatment with chlorpropamide on 6 p.m. blood-sugar levels. Blood-sugar levels are expressed as a percentage of the mean pre-treatment level for each case. Each point is the mean value obtained from the number of diabetics shown above each point. The horizontal lines bracketing each point represent the standard error of each mean.

Side-effects.—In two cases a generalized rash suggestive of a sensitivity dermatitis developed during the first week of treatment on a dosage of 500 mg. daily. The rashes faded when the drug was discontinued. No evidence of blood dyscrasia or of disturbed liver function has been observed in any patient treated with chlorpropamide. No patient complained of any symptom attributable to hypoglycaemia.

Comparison of Chlorpropamide with Other Hypoglycaemic Agents.—Of the 20 patients who failed to respond adequately to chlorpropamide, 16 were stabilized on insulin, all requiring more than 20 units daily, and 11 requiring more than 30 units daily. Two patients were stabilized on a diguanide (one on dimethyldiguanide and one on phenethyldiguanide) and two on treatment with a sulphonylurea and phenethyldiguanide given together. Four patients who had previously failed to respond to tolbutamide responded readily to chlorpropamide, and four patients who had responded previously to tolbutamide, but had relapsed when it was withdrawn, also responded readily to chlorpropamide. One patient who failed to respond to 300 mg. of metahexamide daily responded to 500 mg. of chlorpropamide daily.

Dimethyldiguanide

Material and Methods

Eight diabetic in-patients (seven female, one male) have been treated with dimethyldiguanide. Their ages ranged from 47 to 75 years, average 65. The weights of all lay in the 5–95 centile range (Kemsley, 1952). Two of the patients were newly diagnosed, one had relapsed while on diet, and the other five had had insulin, tolbutamide, or chlorpropamide previously. As before, patients were observed for a preliminary period on diet alone, and dimethyldiguanide was introduced only when glycosuria and hyperglycaemia failed to diminish. One patient had more severe diabetes with ketonuria on admission, and was treated after only two days of diet.

As in the metahexamide and chlorpropamide trials the calorie value of the diet was individually prescribed for each patient and was kept constant throughout the dietary control period and the period of treatment with the drug. Preprandial venous blood-sugar levels were estimated at noon daily, and the urine was tested every four hours during the day for glucose concentration and acetone. Liver-function tests, haemoglobin estimation, white blood-cell count, blood-film examination, and blood-urea estimation were carried out in each patient before treatment and after six weeks.

Dimethyldiguanide was given in a single dose of 3 g. daily after breakfast, the dose being reduced to 2 g. or 1 g. daily if a satisfactory hypoglycaemic response was obtained.

Results

Seven of the eight patients had a satisfactory hypoglycaemic response to dimethyldiguanide. The blood-sugar levels became normal and glycosuria minimal on a dose of 1–3 g. daily. One patient had a hypoglycaemic response to the drug, but this was not sufficient for stabilization and phenethyldiguanide was substituted with good response.

Side-effects.—Five of the eight patients complained of nausea, vomiting, or diarrhoea while they were taking the drug. These symptoms necessitated stopping the administration of the drug to three patients though the diabetes was satisfactorily controlled. Mild nausea

and diarrhoea in two patients stopped when the dose was reduced. No rashes, evidence of blood dyscrasia, or disturbance of liver function has been observed in any patient, and no patient complained of any symptom attributable to hypoglycaemia.

Biochemical Studies with Metahexamide

Serum Metahexamide Levels.—The serum metahexamide levels (method of Bratton and Marshall (1939) for sulphonamides) of normal individuals and of diabetic patients after the administration of 300 mg. of metahexamide are shown in Table I. The drug is rapidly absorbed and peak levels are reached between two and four hours after ingestion.

Half-life Studies.—The half-life of metahexamide—that is, the time taken for any given blood level to fall by 50%—ranged from 5 to 16 hours, with a mean of 10 hours in eight normal individuals; and from 21 to 28 hours, with a mean of 26 hours, in six diabetic patients. The half-life for each individual was calculated by plotting the serum metahexamide concentrations against

TABLE I.—Serum Metahexamide Levels After 300 mg. of Metahexamide by Mouth in Normal Individuals and in Diabetic Patients

Hours after 300 mg. Metahexamide By Mouth	Mean Serum Metahexamide (mg./100 ml.) (Range given in Parentheses after the Mean)	
	Normal Individuals (8 Subjects)	Diabetic Patients (6 Subjects)
2	3.6 (1.0-4.6)	2.8 (2.5-3.2)
4	3.1 (2.1-3.8)	3.3 (2.2-3.9)
8	2.4 (2.0-3.2)	
10	2.1 (1.2-2.9)	2.9 (1.7-3.8)
12	1.8 (1.4-2.6)	
24	0.8 (0.2-1.6)	2.0 (1.1-2.5)
Mean half-life in hours	10 (5-16)	26 (21-28)

time on a semi-log scale. In Fig. 4 the concentrations are expressed as percentages of the initial blood level in order to compare the half-lives of metahexamide in normal individuals and in diabetic patients.

Distribution of Metahexamide in the Body.—By extrapolating the line representing the rate of decrease of serum metahexamide to zero time the theoretical initial concentration of metahexamide was obtained. From this figure the volume of fluid in which the dose of metahexamide was diluted was calculated and expressed as a percentage of the body weight. Values of from 9 to 24.5% body weight were obtained (mean

FIG. 4.—Rate of disappearance of metahexamide from plasma of normal individuals and diabetic patients.

from 14 subjects=12.7%). These values correspond approximately to the percentage of body weight occupied by extracellular fluid. The amount of metahexamide present in red cells was calculated from estimations of whole-blood and plasma metahexamide and the haematocrit estimation. No metahexamide was found in the red cells in blood taken at two and four hours after metahexamide was given (five patients). At eight hours after, amounts varying from 0.07 to 0.2 mg./100 ml. were found, and at 12 hours from 0 to 0.08 mg./100 ml. These results would appear to indicate that metahexamide is restricted to the extracellular fluid.

Investigation of Possible Cumulative Effect.—Because of the long half-life of the drug in diabetic patients, daily fasting levels of serum metahexamide were estimated in eight patients to see whether the drug accumulates in the blood after prolonged administration. Fig. 5 shows that when daily doses are given there is a

FIG. 5.—Mean fasting serum-metahexamide levels during the first week of treatment with the drug, and concurrent blood-sugar levels (eight patients).

rise in serum metahexamide for the first four days, and thereafter the level becomes stabilized. Concurrent fasting blood-sugar estimations show a progressive fall in the blood-sugar level.

Relapse Rate After Discontinuation of Chlorpropamide

Patients who responded to chlorpropamide were maintained on this treatment for six weeks and were thereafter observed in diet alone. All patients were seen each week by the same observer at a special clinic and the blood sugar was estimated at each visit. They usually tested their own urine for sugar three times daily, the specimens examined being those passed before their main meals. Constant stress was placed on adherence to diet both while the patient was on chlorpropamide and thereafter. The dietitian was in regular attendance. Relapse was soon manifest by the appearance of glycosuria, and blood sugars were elevated to more than 200 mg. per 100 ml., the blood being taken an hour or two after a main meal.

Of 44 patients observed for more than one month after a six-weeks course of chlorpropamide, 19 have so far relapsed while on diet alone, and chlorpropamide has been successfully reintroduced. So far, the remaining 25 are well controlled, either on the same or on a higher calorie diet than had previously been demonstrably ineffective in controlling their diabetes before the introduction of chlorpropamide.

Fig. 6 shows the proportion of 44 patients who relapsed within one, two, three, six, and nine months after completing the six-weeks course of chlorpropamide.

Twelve out of 20 (60%) of patients who had previously had insulin relapsed within nine months, compared with only seven out of 24 (28%) of patients who were newly diagnosed or to whom insulin had never been given. This difference in relapse rate after discontinuation of treatment is not peculiar to chlorpropamide. Fig. 7 displays comparable experience with 80 patients treated with oral hypoglycaemic drugs other than chlorpropamide. Here, too, the relapse rate was less in new patients than in those previously treated with insulin, though the follow-up has extended to two years. The upper line in Fig. 7 refers to the group of 40 patients who had been treated with insulin before the oral hypoglycaemic drug was introduced. Thirty-one patients in this group received tolbutamide, seven phenethylidiguamide, and two dimethyldiguamide. The lower line refers to the 40 patients who were newly diagnosed or who had never received insulin before oral drug therapy. Thirty-four patients in this group received tolbutamide, four phenethylidiguamide, and two dimethyldiguamide.

Glucose-tolerance tests before and after a six-weeks course of chlorpropamide were done on 11 patients taken at random. In all cases the second glucose-tolerance test was performed while the patients were well controlled by dietary restriction, at times varying from a few weeks to several months after the course of chlorpropamide. Fig. 8 shows that all the blood-sugar levels of the glucose-tolerance test have fallen after chlorpropamide, but that the curve is still abnormal.

Combined Treatment

In nine patients whose treatment with chlorpropamide or metahexamide failed to lead to a useful hypoglycaemic response, phenethylidiguamide was tried at a starting dose

FIG. 6.—Relapse rate after completion of a six-weeks course of chlorpropamide. The upper line refers to 20 patients who, prior to treatment with chlorpropamide, had had insulin at some time. Each point on it represents the percentage of patients who had relapsed up to the time indicated. The lower line refers to 24 patients who had been treated unsuccessfully by diet only before treatment with chlorpropamide. Each point on it represents the percentage of patients who had relapsed up to the time indicated.

FIG. 7.—Relapse rate after completion of a six-weeks course of an oral hypoglycaemic agent other than chlorpropamide (see text).

of 150 mg. daily. Three of these patients responded to this drug on its own. In the remaining six a combination of chlorpropamide or metahexamide with phenethylidiguamide was then tried. Three of these responded to such a combination, having failed to respond adequately to either drug of the combination when given separately. The following case is illustrative.

The patient was a woman aged 49. Diabetes was diagnosed in August, 1952, since when she has been

FIG. 8.—Glucose-tolerance tests before and after a six-weeks course of chlorpropamide. Each point is the mean from 11 patients.

FIG. 9.—Effect of oral hypoglycaemic agents on midday blood-sugar levels of a woman aged 49.

treated with 20 units of insulin daily and a 1,800-calorie diet. She was well controlled until January, 1959, when heavy glycosuria and acetonuria developed. She was admitted to the ward for stabilization, and was there controlled by approximately 60 units of insulin daily in divided doses. Fig. 9 shows the midday blood-sugar levels throughout her stay in hospital. Insulin was stopped on the ninth day. The effect, in turn, of metahexamide 300 mg. daily, of chlorpropamide 500 mg. daily, and of phenethyldiguanide 150 mg. daily was tried. She failed to show a satisfactory hypoglycaemic response until a combination of metahexamide 300 mg. and phenethyldiguanide 150 mg. daily was given. She was discharged home taking metahexamide 150 mg. daily and phenethyldiguanide 100 mg. daily, and her diabetes remained well controlled. Weekly mid-afternoon blood-sugar levels were satisfactory (102, 222, 141, and 150 mg./100 ml). At this time she ran out of tablets for five days and the blood sugar was 355 mg. at her next attendance. Her urine contained acetone and more than 2% sugar. A week after recommencing treatment with metahexamide and phenethyldiguanide the blood-sugar level had fallen to 150 mg./100 ml. and the urine was free from sugar and acetone.

Discussion

Metahexamide appears to be a well-tolerated and effective hypoglycaemic agent when given by mouth to patients with mild diabetes. As with tolbutamide, it will not control diabetes in young patients or severe cases, and its use is best confined to the maturity-onset diabetic who is not controlled by simple dietary restriction and whose insulin requirements are not more than about 30 units daily. In conjunction with diet the starting dose of 300 mg. daily can be reduced to 200 or 100 mg. daily. One patient developed transient jaundice of the obstructive type, and, though no other toxic effects were observed in this short-term trial, clearly long and much wider experience will be necessary before its safety can be vouchsafed. The only apparent advantage over tolbutamide is that it has a longer-sustained action and offers effective control in susceptible patients when given once daily. The mean half-life of metahexamide in diabetics has been shown to be approximately 26 hours, whereas that of tolbutamide is only 3.5 hours (range 2 to 5 hours) as calculated from previous results on seven patients (Crowley *et al.*, 1957). Effective blood levels have been obtained with 200 mg. of metahexamide as against 2 g. of tolbutamide.

In estimating half-life values for metahexamide an unexpected finding was that the drug disappeared more rapidly from the plasma of normal individuals than from the plasma of diabetic subjects. This could be due to a difference in the metabolism of the drug in the body or in its excretion by the kidney. No significant impairment of kidney function in the diabetics could be demonstrated by the usual methods, but this would not preclude changes in the renal transport mechanism. Stowers *et al.* (1958) demonstrated that probenecid, which affects tubular transport mechanisms, slowed the rate of disappearance of tolbutamide from the blood, and that salicylates had a similar effect on chlorpropamide blood levels (Stowers *et al.*, 1959). There appears to be no difference in the half-life of tolbutamide in normal and diabetic subjects, the mean value of 3.5 hours being identical with that obtained by Stowers (1958) in six normal individuals. Knauff *et al.* (1959) found no difference in the half-life of chlorpropamide between two diabetic and two normal subjects.

Chlorpropamide is another effective hypoglycaemic agent that is well tolerated when given by mouth. Five hundred mg. appears to be a suitable initial dose, and this can be reduced to a maintenance level of 200 mg. daily. As with metahexamide, its action is sufficiently prolonged to enable it to be given once a day, its half-life being 34.5 hours (Stowers *et al.*, 1959). At the dose levels stated chlorpropamide has a wider range of action than tolbutamide and probably metahexamide. Chlorpropamide was effective in four patients in whom tolbutamide had been ineffective, and in one in whom metahexamide had been unsuccessfully given. Chlorpropamide appears to be a more potent hypoglycaemic agent than tolbutamide (West and McCampbell, 1958; Stowers *et al.*, 1959; Tornow *et al.*, 1959) and may give rise to sweating, palpitations, and mental confusion due to hypoglycaemia (Tornow *et al.*, 1959). To offset this advantage of greater effectiveness, drug rashes were recorded in two patients in this series following chlorpropamide. Obstructive jaundice similar to that seen with chlorpromazine (Andersson, 1958; Hadley, *et al.*, 1959), gastro-intestinal disturbances (Sugar *et al.*, 1958), and vertigo (Walker, 1958) have also been reported, but in many of these cases the dose has been more than 500 mg. daily, and the reactions have subsided when chlorpropamide has been discontinued. No toxic effects on liver or blood have been observed in this series, either in in-patients or in out-patients. Chlorpropamide has now been used quite widely (Murray *et al.*, 1958; Drury, 1958; O'Driscoll, 1958; Smith and Dube, 1958; Andersson, 1958; Tornow *et al.*, 1959) and no serious toxic effects have been so far reported.

Dimethyldiguanide was administered at an initial dose of 3 g. daily, reducing to 2 or 1 g. in responsive diabetics. As with phenethyldiguanide, it appeared to be a more effective hypoglycaemic agent than the sulphonylureas (Hall *et al.*, 1958), but unhappily is not well tolerated, giving rise to nausea, vomiting, or diarrhoea at the dosage stated. This clearly limits its value when given on its own, and it seems to offer no advantage over phenethyldiguanide.

Table II outlines the clinical use of chlorpropamide, metahexamide, and dimethyldiguanide, and compares them with carbutamide, tolbutamide, and phenethyldiguanide.

Though the mode of action of the oral hypoglycaemic agents is still uncertain there appears to be a difference between the action of the diguanides and that of the sulphonylureas. In contrast to the sulphonylureas the diguanides will reduce the blood sugar of alloxan-diabetic animals (Ungar *et al.*, 1957), possibly by

TABLE II.—*Oral Hypoglycaemic Agents*

Drug	Initial Daily Dose (g.)	Maintenance Daily Dose (g.)	Frequency of Dose	Tolerance	Toxic Effects
Carbutamide (Wolff <i>et al.</i> , 1956)	2	1	Daily	Good	Blood dyscrasias (Duncan <i>et al.</i> , 1956). Skin sensitivity
Tolbutamide (Crowley <i>et al.</i> , 1957)	2	1-1.5	Twice daily	"	Nil
Chlorpropamide	0.5	0.2-0.25	Daily	"	Skin sensitivity.
Metahexamide	0.3	0.05-0.1	"	"	Jaundice
Phenethyldiguanide (Hall <i>et al.</i> , 1958)	0.15	0.05-0.1	Twice daily	Nausea. Vomiting. Diarrhoea	Nil
Dimethyldiguanide	3	1-3	Daily	"	Nil so far

promoting anaerobic glycolysis (Williams *et al.*, 1957). Hence there would seem to be reason in trying a combination of a sulphonylurea and a diguanide in patients who have failed to respond to the drugs when given singly. In fact, three patients in the present series responded to such a combination, having failed to respond adequately to either drug of the combination when given separately.

As in trials with tolbutamide (Crowley *et al.*, 1957), chlorpropamide was administered only to diabetics who had failed to respond to dietary restriction alone, and in responsive patients the drug was given for six weeks and then discontinued. In newly diagnosed cases in particular, relapse did not often occur when therapy was withdrawn, the patients remaining well controlled on simple dietary restrictions for the periods under observation. Similar observations have been made in some new diabetics treated with insulin (Bloom, 1959). The advantage of a short-term course of tablets followed by observation is that patients are not kept unnecessarily on the drug and more stress can be placed on the importance of diet. Patients who relapse when oral therapy is discontinued remain responsive to it when it is reintroduced (Crowley *et al.*, 1957).

Glucose-tolerance tests done at various times after discontinuation of chlorpropamide showed a marked fall at all points on the curve as compared with those before chlorpropamide. The fall in the blood-sugar level from the peak at one hour to that at two and a half hours after ingestion of 100 g. of glucose suggests an insulin effect (Fraser *et al.*, 1941). This fall is much more pronounced after treatment with chlorpropamide, and it is possible, therefore, that the clinical remission was a result of an improved supply of endogenous insulin.

Finally, it should be stressed that oral hypoglycaemic therapy should be considered only in diabetic patients who have failed to respond to a reasonable diabetic diet.

Summary

Metahexamide is a well-tolerated hypoglycaemic agent, effective in mild diabetics with onset at maturity. Its action is more sustained than that of tolbutamide, so it can be administered once daily. Jaundice was observed in one patient after treatment with the drug.

Chlorpropamide is a more effective oral hypoglycaemic agent than tolbutamide, and need be given only once a day. It is well tolerated, but occasionally gives rise to sensitivity reactions.

Dimethyldiguanide is an effective hypoglycaemic agent but is not well tolerated by mouth.

Half-life studies on metahexamide show that the drug disappears from the plasma more rapidly in normal individuals than in diabetic patients.

Many diabetics, particularly new ones, remain controlled by simple dietary restriction alone after a six-weeks course of oral therapy, though the length of remission is variable.

Three diabetic patients who failed to respond either to a sulphonylurea derivative or to phenethylidiguanide when administered separately were stabilized on a combination of the two.

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The success in the metropolitan hospital world of the King Edward's Hospital Fund for London has been due at least in part, as the Fund's Annual Report for 1958 points out, to "its financial capacity for sustained effort." This desirable state of affairs is reflected in the steady increase in the volume of direct and indirect assistance it has given, assistance which accounted for £427,534 out of the year's income of £430,127. Many of its grants are major ones, and devoted to such well-known and long-term projects as the Emergency Bed Service, the Hospital Personal Aid Service for the Elderly, the Division of Hospital Facilities, the Division of Nursing with its staff colleges, the Hospital Administrative Staff College, and Hospital Catering services. The Fund, however, gives many small sums to hospitals, which attract little attention, but may yet make a considerable difference to the day-to-day life of both patients and staff. Anyone who has tried to lift a 17-stone patient, for example, will appreciate the value of the £575 which has been spent on buying six lifting devices for the handling of heavy inert patients. The equipment has been loaned to various hospitals, who will report on it after a year's trial, a sufficiently long period of time, the Fund feels, for difficulties to become known, so that "reports shall not be tinctured with the first enthusiasm for a new toy." A further experimental grant has been made to the "Dread-nought" Seamen's Hospital to enable it to set up and study a system it has devised itself for dealing with that hospital bugbear, foul linen. In making such grants, as in its major contributions, the King's Fund continues to show an awareness of contemporary hospital needs that is both sensitive and practical.