PRELIMINARY OBSERVATIONS ON MANAGEMENT OF DIABETES WITH "STABINOL"

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The management of diabetes by oral preparations has now become commonplace in many countries throughout the world. The literature on this subject is voluminous and the drugs in use have been given to more than half a million diabetics. Of all the hypoglycaemic agents tolbutamide has been the most widely used, and to date has the smallest incidence of abnormal side-effects. Mehnert *et al.* (1958), in a recent review of the use of tolbutamide on a group of 1,030 patients for a period of 1 to 20 months, demonstrated that it produced good control on 52.6% and fair control on an additional 18.5%.

Krall and Camerini-Davalos (1958) have reported their results with DBI in a series of 121 patients. They found it to be an effective hypoglycaemic agent in 86%, but therapy had to be discontinued in 18% because of side-effects affecting mainly the gastro-intestinal tract.

The report of Baender (1959) on the comparative toxicology and pharmacology of tolbutamide, chlorpropamide, and metahexamide, showed that compounds with greater toxicity than tolbutamide are of no particular value in the management of diabetes. He pointed out that the price to be paid for lower drug dosage should never be greater toxicity.

Davis *et al.* (1959) have reported on the use of R.P. 2259, a sulphathiadiazole (2-sulphamido-*p*-aminobenzene-5-ter-butyl-1,3,4-thiadiazole; "glipisol"). This report showed R.P. 2259 to be a relatively toxic substance with a very large incidence of liver damage.

McColl (1960) presented his findings on the hypoglycaemic activity of a group of substituted thiadiazoles, synthesized by Chubb and Nissenbaum (1959), which, like tolbutamide, have no antibacterial properties.

One of the most potent of these substituted thiadiazoles, was made available for this study. This was the methoxy isobutyl derivative known as FWH 114, or "stabinol." This material produces hypoglycaemia after both oral and parenteral administration in fasted rats, rabbits, and dogs. In the rabbit, for example, significant hypoglycaemia occurs within an hour and reaches a maximum in five to six hours. Normal blood-glucose levels are reached within 24 hours.

Like tolbutamide, some functional pancreatic islet tissue appears necessary for hypoglycaemic response to stabinol. It also promotes the storage of glycogen in the liver of fasted rats. With normal hypoglycaemic doses in animals stabinol appears to possess no other important pharmacological activity. Hypoglycaemia may be reversed by the administration of glucose, Stabinol is devoid of any antibacterial action.

The acute oral LD₅₀ of stabinol in rats and mice is about 900 and 950 mg./kg. respectively. Chronic toxicity studies in Sprague-Dawley rats for period up to nine

months at doses of 150 and 300 mg./kg./day by the oral route revealed no significant toxicity.

Only one study with oral hypoglycaemic agents has been carried out in the Federated West Indies, and that was by Tulloch (1957) with carbutamide. The dosages given were large and side-effects were common. This drug was used very little in the Federated West Indies, but widely in the Dutch West Indies (Vinke, personal communication), with remarkably few side-effects. Tulloch also reported that the type II diabetic of Hugh-Jones is the predominant type in the West Indies; in fact, more than 70% of diabetics fall in this category. This is the mild type which one might expect to respond to adequate oral hypoglycaemic medication.

Formulae of Oral Hypoglycaemic Compounds

Procedure

In this study 33 diabetics were maintained as out-patients from the clinic at the Port of Spain General Hospital, and were selected on the basis of the insulin dosage being used, ranging from 12 to 52 units per day. In addition the patients were selected having regard to their regular attendance, their proximity of residence to the clinic, and the absence of complications. There

were no selections as regards insulin control. Two new patients were not on insulin and were being treated by diet alone with poor control. Three patients were lost to the study.

TABLE I.—Age Distribution

Age No. of patients	30-40 5	41-50 10	51-60 10	61-70 4	71-80 1
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TABLE II.—Duration of Diabetic Symptoms

Duration (years) No. of patients	<1 11	1 7	2 1	3 6	4 2	7 1	9 1	16 1
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The ages of the patients varied from 34 to 72, with the majority (20) from 41 to 60 years of age (Table I). Duration of illness was from a few months to 16 years, most (27) falling within the category of 0-4 years (Table II). All patients, regardless of insulin dosage, were started on four tablets of 250 mg. (1 g.) of stabinol (given in a single dose in the morning) after complete blood, urine, and liver-function studies had been carried out. They were seen every other day for the first week, twice weekly during the next two weeks, once a week for the following two weeks, and then monthly until the conclusion of the trial. All patients were advised of the possibility of side-effects and were instructed to report to the clinic in the event of any untoward reactions.

General Clinical Aspects

Table III as a brief summary of pertinent clinical aspects. At the beginning of the study all patients but two were on insulin. These latter were placed on oral therapy when diet alone gave poor results. The degree of control produced by previous insulin therapy varied from fair to very good. Of the 30 patients who com-

TABLE III.—General Clinical Aspects

Case No.	Sex and Age	Change in Wt. in lb.	Previous Insulin Dosage	Control	Oral Dosage (g.)	Control	Result*
1	F 58	+5	I.Z.S. 28	Poor	0.250	V. good	+
2	M 36	-1½	" 40	Good	0.125	"	+
3	M 34	-6	" 24	Fair	0.250	"	+
4	M 55	+5	" 12	Good	0.25	"	+
5	F 43	+23	Diet	Poor	0.500	"	+
6	M 44	+½	I.Z.S. 48	Fair	0.500	"	+
7	M 45	0	" 40	"	0.250	"	+
8	M 60	-2	" 36	"	0.375	"	+
9	F 48	-3½	" 24	V. good	0.250	"	0
10	M 52	0	" 20	Fair	0.125	Good	+
11	M 65	-3½	" 24	"	0.500	"	+
12	F 72	+1	Diet	Poor	0.750	"	+
13	F 46	-6	I.Z.S. 48	Fair	0.500	"	+
14	F 55	-7	" 40	"	0.250	"	+
15	F 54	+2	" 40	"	1.250	"	+
16	F 55	-1	" 24	"	0.500	"	+
17	F 69	+2	" 12	Good	0.425	"	0
18	M 40	-7	" 18	"	0.250	"	0
19	F 43	0	" 28	"	0.750	"	0
20	F 54	0	" 20	"	0.750	"	0
21	F 42	-3	" 48	Fair	1.500	Fair	0
22	F 43	+2	" 40	"	1.500	"	0
23	F 61	-2	" 20	Poor	1.500	Poor	0
24	F 61	0	{ Plain 20 P.Z.I. 20	"	1.750	"	0
25	F 50	+1	P.Z.I. 24	Fair	1.750	"	-
26	F 41	-6	I.Z.S. 40	"	1.750	"	-
27	F 54	+2	" 32	"	1.500	"	-
28	F 38	+2½	{ Plain 16 P.Z.I. 32	Good	1.750	"	-
29	F 52	+7	I.Z.S. 40	Fair	1.750	"	-
30	M 37	0	{ Plain 16 P.Z.I. 36	Good	1.500	"	-
31	F 42		Uncooperative } Discontinued Patient left Trinidad				
32	F 46						
33	F 46						

* Control with oral stabinol compared with previous control:
+ = Improved control. 0 = Unchanged. - = Not as well controlled.

pleted the trial, 15 (50%) showed improved control, 9 (30%) were unchanged, and 6 (20%) were not as well controlled. These results are not unlike those of McKendry *et al.* (1957) with tolbutamide therapy. By and large, the patients described themselves as feeling "much better," "more fit," and "stronger." All patients but one preferred the tablet form of therapy. This one patient appeared to be a case of primary failure.

Assessment of the degree of diabetic control was as follows:

Very Good.—Urine at all times "blue" (Benedict's test) or occasionally "green." Random blood-sugar not over 200 mg./100 ml.

Good.—As above, except for occasional "yellow" two or three times a month. Random blood-sugar occasionally over 200 mg./100 ml.

Fair.—Urine test mainly "blue"/"green" with "yellow" six to eight times a month. Random blood-sugar occasionally over 250 mg./100 ml.

Poor.—Urine tests occasionally "blue," usually "green"/"yellow" with "red" six to eight times a month. Random blood-sugar usually over 250 mg./100 ml.

Biochemical Aspects

Five liver-function studies were performed before starting oral therapy, as well as at the conclusion. These were "bromsulphalein" retention, bilirubin, thymol turbidity, zinc sulphate turbidity, and colloid gold flocculation. The results of these tests, both before and after, were essentially negative. Blood of each patient was analysed before and after for the following constituents: urea, total protein, albumin, globulin, and haemoglobin. These were essentially normal. The cellular elements in the blood were examined before and after the trial and no abnormalities were detected. The urine of each patient was examined before, during, and after the trial, and no abnormalities attributable to the drug were found. The urine was examined regularly by means of "clinitix," and the use of this method of glucose determination proved very satisfactory. Throughout the trial selected specimens of urine were also checked with Benedict's reagent and there was satisfactory correlation between both tests.

Discussion

Since the advent of the use of sulphonylurea compounds in the management of diabetes, most diabetics have been grouped either as the juvenile or the maturity onset type. This is obviously unsatisfactory as a scientific method of classification, since it gives no indication of the severity of the individual's disease. However, most workers have found that the diabetic whose disease became apparent late in life was most likely to respond to oral therapy. This was considered when patients were chosen for this study. As we expected, the majority did respond and were as well controlled as on insulin, and in some cases control was better. Many workers have shown that there is no direct correlation between insulin dosage and that of various forms of oral therapy. This holds true in this study, as is shown in Table III.

There are, of course, obvious advantages to the management of diabetes with oral preparations in countries such as the British West Indies, where the use of sterile parenteral equipment becomes a major problem. Most of the patients are afraid or unable to give themselves insulin, and most relatives or neighbours are not prepared to learn. Because of these factors at this clinic,

most of the patients on insulin attend daily for their injection. The cost of transport, tropical rain, and any mild intercurrent illness resulted in irregular attendance. In the long run, therefore, management with oral preparations would probably be cheaper for the patients.

While not all diabetics will respond to oral therapy, this study shows that a large number of selected patients will respond satisfactorily to this particular drug. In view of its safety, as evidenced by liver-function, blood, and urine studies, stabinol appears to be a worth-while addition to the therapy of diabetes.

Summary

The antidiabetic effect of stabinol has been evaluated on a group of 33 patients with diabetes of the maturity onset type. Of this group three were lost to the study.

Of the remaining 30 patients, 15 (50%) were better controlled with the oral agent than they had previously been on insulin therapy, 9 (30%) were controlled equally well on either regimen, and 6 (20%) were not as well controlled on oral therapy as they were on insulin therapy.

Liver-function studies and blood and urine findings remained normal throughout the study.

There were no side-effects or abnormal reactions.

We wish to thank Frank W. Horner Ltd. for supplies of stabinol used in this study, and for a grant to one of us (M. F. H.); Ames Company for supplies of clintix; Dr. J. Ray MacDougall, medical director, Frank W. Horner Ltd., for advice and help; and the patients who volunteered for the trial. We are grateful to the Minister of Health, Water and Sanitation, and the Director of Medical Services for permission to publish these findings.

ADDENDUM.—Since the completion of this trial in April, 1959, 16 of these patients have been maintained on stabinol with very good or good control for a further eight months. They have been on the drug for over one year.

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Medical Memoranda

Callosities with Horny Plugs

Patients are often sent to dermatological departments with the diagnosis of plantar wart, when the lesion consists of a callosity in the centre of which is a little horny plug (Fig. 1). The callosity usually lies under the heads of the second and third metatarsals and may be associated with some degree of hammer-toe in the second digit. The condition is described in some orthopaedic books, where it is thought to be a form of callosity, but often it is diagnosed by general practitioners as a plantar wart; some dermatologists

believe this is correct. The treatment of these two conditions is so different—a wart being removed whilst a callosity requires an orthopaedic adjustment—that I have investigated a number of these lesions to see if it is possible to decide their true nature.

The histology of a plantar wart is characteristic, with ballooning of the cells and fragmentation of the nuclei spreading right up into the horny layer and giving a very bizarre appearance. In contrast to this the horny plug (Fig. 2) under discussion shows perfectly regular parakeratosis with uniform non-fragmented nuclei and a well-formed horny layer without any ballooning of cells or vacuolization. The column of parakeratosis

FIG. 1.—Callosity with little horny plug in centre.

FIG. 2.—Photomicrograph of section of horny plug.

ends more or less abruptly and passes into the hyperkeratotic horny layer of the surrounding callosity.

It seems clear, therefore, that these lesions are not plantar warts and that such treatments as radiotherapy or even curettage are unlikely to produce a permanent cure. They should be dealt with along the usual orthopaedic lines for a callosity.

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