neither by loss of control of the patients' diabetic state nor by the occurrence of hypoglycaemic attacks. Tolbutamide is less likely than insulin to produce a hypoglycaemic attack because its full effect takes place about four hours after administration, by which time the next meal is due.

Maintenance.—If satisfactory control is achieved the patient may be maintained indefinitely on up to 3 g. of tolbutamide daily. Such control should not be allowed to encourage any relaxation of the dietary restrictions.

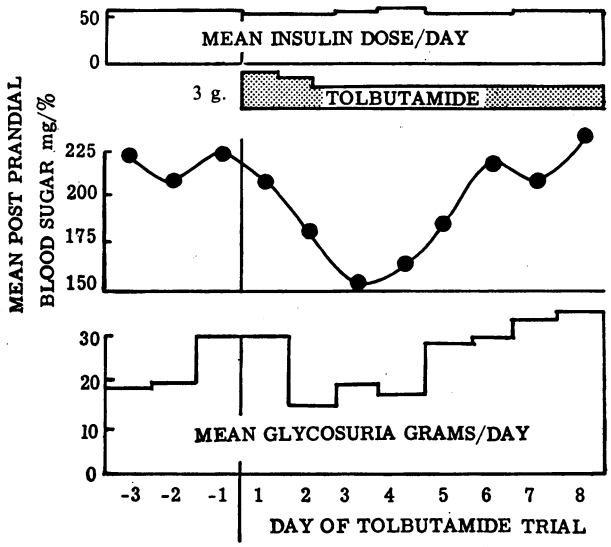

FIG. 2.—Mean results from 12 diabetics who showed a temporary response to tolbutamide but could not be maintained on it. Five of these patients had recently shown heavy acetonuria.

Side-effects.—In very few instances so far has tolbutamide had to be discontinued because of side-effects. Skin rashes appear to be the most common complication. They clear within a few days of discontinuing the drug, but antihistamine therapy may be indicated if the patient complains of much irritation. Early reports from the Continent suggested that a gain in weight was to be expected by patients maintained on the drug, but the average weight of our patients on tolbutamide has not increased during nine months or more. Blood dyscrasias, which were the major drawback to treatment with the sulphonamide carbutamide, are rarely seen with tolbutamide, which is not a sulphonamide. Renal damage has not been encountered, but it should be noted that tolbutamide is excreted in the urine as an oxidation compound which, under certain circumstances, gives a coarse flaky precipitate with sulphosalicylic acid and thus might be confused with albumin.

Long-term Treatment

Since clinical trials of tolbutamide were begun by the Hoechst Laboratories in Germany in August, 1955, some 150,000 patients have been treated with the drug in this country, in Germany, and in the U.S.A. for periods of up to two years. Though no one can be certain of the long-term effects of the drug, few other drugs can have had more extensive trials to ensure their safety.

We should guard against the mistake of believing that control of hyperglycaemia and glycosuria indicates cure of diabetes. The main therapeutic problem in the type of diabetes in which tolbutamide is successful is to prevent the progress of such complications as arterial disease, retinitis, neuritis, and renal disease. Insulin probably has some effect in preventing or reducing these complications, though it certainly has not eradicated them. It will be some years before we can assess the value of tolbutamide in the prevention of complications. So far it seems unlikely that it will be more effective than insulin. It will not prevent ketosis or the exacerbation of the diabetic state associated with infection or trauma. In one of our patients the rapid progress of retinitis and neuritis was not halted during a period of three months, during which time tolbutamide produced satisfactory control of the hyperglycaemia and glycosuria. It is necessary, therefore, to end on a note of uncertainty. Though tolbutamide may effectively control the hyperglycaemia of diabetes mellitus, we have yet to learn its effects on the progress of the underlying diabetic state and the development of diabetic complications.

Summary

Tolbutamide has proved an effective and apparently safe compound for controlling blood-sugar levels in some diabetics, especially the older stable type of patient, but there are no means of deciding which patients will respond satisfactorily short of an actual trial.

Criteria for selecting patients are given together with the details of a scheme which we have found useful in testing the patients' response to tolbutamide.

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TOLBUTAMIDE IN DIABETES

SOME CLINICAL AND BIOCHEMICAL STUDIES

BY

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Previous experience (Bertram *et al.*, 1955; Duncan *et al.*, 1956; Wolff *et al.*, 1956) has demonstrated that the sulphonylurea carbutamide (BZ 55) when given by mouth is capable of controlling the diabetic state in some patients. However, carbutamide was shown to have occasional toxic effects (Duncan *et al.*, 1956; Phemister, 1957), and in view of this fact another sulphonylurea, tolbutamide, is now being tried. Tolbutamide differs from carbutamide in that a methyl group replaces the *p*-amino group. Unlike carbutamide, it is therefore not a sulphonamide.

The present study has been undertaken with the following aims: (1) to assess the value of oral tolbutamide therapy in controlling diabetes, particularly in newly diagnosed cases; and in those patients successfully controlled by the drug, to see whether relapse occurred when this therapy was discontinued. (2) To determine whether tolbutamide behaved as insulin does in lowering plasma amino-acid nitrogen and inorganic phosphorus. (3) To correlate blood tolbutamide levels with the control of sugar in the blood and urine, with particular reference to the administration of tolbutamide as a single dose and in divided doses.

Method

Of 42 diabetic patients selected for trial with tolbutamide, 28 were newly diagnosed and had had no treatment prior to attendance at the diabetic clinic. Not all new diabetics were included; some refused to come into hospital, some had diabetes severe enough to need insulin immediately, while in many the diabetes was so mild that dietary restriction alone was sufficient. Of the diabetics previously diagnosed, two were on insulin but requested tablets, while the other 12 were relapsing or badly controlled on their current dietary regime without insulin.

All patients were admitted to the wards and during the first week were treated by dietary restriction alone. Diets were prepared in the diet kitchen under the supervision of the dietitian, and varied from 1,500 to 2,200 calories daily, containing from 150 to 220 g. of carbohydrate, depending on the patient's height, weight, age, and activity. Patients who showed steady diminution of urinary and blood sugars during this period were not treated with tolbutamide and were excluded from this trial. The remaining 42 diabetics, having shown persistent glycosuria and hyperglycaemia while on the diet, were started on tolbutamide on the eighth day. They were kept in hospital for at least another week and were then seen each week as out-patients. On discharge from hospital the importance of adherence to diet was stressed. Patients were maintained for a total of six weeks on tolbutamide and thereafter for a further six weeks on dummy tablets unless relapse occurred, in which case tolbutamide was reintroduced. After this period out-patient attendances were at fortnightly intervals, and no further tablets were prescribed if control was satisfactory.

The diagnosis of diabetes was confirmed in each new case by a standard glucose-tolerance curve. At each out-patient visit blood was collected from all patients for a haemoglobin estimation, white-cell count, platelet count, and blood-film examination.

The *dosage* was 3 g. on the first day and 2 g. daily thereafter. In the first 28 patients (referred to as group 1) the whole of the dose was given in the morning at 8 o'clock, whereas in the next 14 (group 2) the dose was divided into two equal portions and given at 8 a.m. and 12 noon.

Blood sugars were estimated by the method of Hagedorn and Jensen (1923). Venous blood was collected at 8 a.m., 12 noon, 2 p.m., and 6 p.m. on each alternate day while in the ward and once at each out-patient attendance.

Urine sugar was determined by Benedict's quantitative method (King, 1951). Daily 24-hour specimens were analysed in ward patients and at each visit in out-patients.

Plasma tolbutamide was estimated by the method of Forist *et al.* (1955, personal communication), and two to four samples for plasma blanks were taken from each of 19 patients before treatment was started. Eleven of these were on a single dose of tolbutamide and eight on a divided dose. Blood was collected at 8 a.m., 12 noon, 2 p.m., and 6 p.m.

Plasma amino-acid nitrogen was measured by Folin's method as modified by Danielson (1933) and Frame *et al.* (1943). Blood was taken from 13 group 1 in-patients at 8 a.m., 12 noon, and 6 p.m.

Plasma inorganic phosphorus was determined by the method of Fiske and Subbarow (1925) in 11 group 1 in-patients at 8 a.m., 12 noon, and 2 p.m.

Results

Of 42 patients treated with tolbutamide, 30 responded well, with a return to normoglycaemia, and a complete or almost complete disappearance of glycosuria. Twelve patients responded poorly or not at all. Of the newly diagnosed diabetics, 18 responded well while 10 failed to respond. The age, sex, and centile weights of these patients are set out in Fig. 1, and it can be seen that the majority of patients who responded were middle-aged or elderly, with centile weights lying in the 5–95 range, only three being considerably overweight. Examination of the urine by

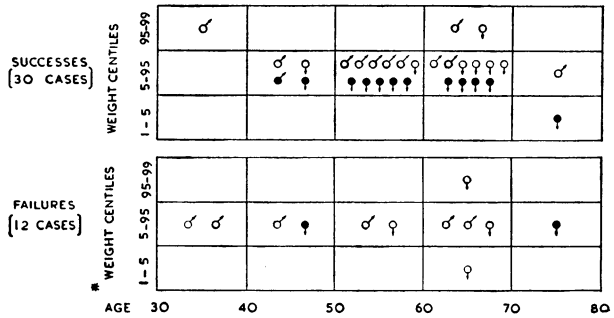

FIG. 1.—Age, sex, and centile weights of 42 diabetics treated with tolbutamide. New diabetics: male ♂, female ♀. Previously diagnosed diabetics: male ♂, female ♀. *Centile weights according to Kemsley (1951-2).

TABLE I.—*Blood- and Urine-sugar Levels for One Week Before and One Week After Beginning of Tolbutamide Treatment*

			Blood Sugar (mg./100 ml.)				Urine Sugar (g./24 Hours)
			8 a.m.	12 Noon	2 p.m.	6 p.m.	
Group 1: 19 "successes"	Control period	Mean	207	252	256	239	27·4
		Range	116–308	148–504	137–504	111–429	1·2–83·3
	Treatment ,,	Mean	172	152	167	176	10·5
		Range	93–345	79–320	82–291	88–274	0–40
	Reduction in sugar	Mean	35	100	89	63	16·9
		Range	106 to *−10	166 to 58	239 to 1	141 to 10	48 to −1·5
Group 2: 11 "successes"	Control period	Mean	242	289	279	269	24·4
		Range	146–352	132–419	106–449	145–414	4·1–73·3
	Treatment ,,	Mean	207	192	196	210	9·6
		Range	132–304	97–292	118–392	122–375	0–58
	Reduction in sugar	Mean	35	97	83	59	14·8
		Range	68 to −6	168 to 51	255–22	198 to 3	27·1 to −6·4
Group 1: 9 "failures"	Control period	Mean	251	314	332	281	50·0
		Range	178–340	202–457	189–461	191–451	3·8–160
	Treatment ,,	Mean	236	257	285	278	46·2
		Range	188–294	115–377	141–426	197–492	4·0–125
	Reduction in sugar	Mean	15	57	47	3	3·8
		Range	26 to −18	96 to −12	88 to −12	64 to −58	29·2 to −17·5
Group 2: 3 "failures"	Control period	Mean	250	287	361	355	37·5
		Range	159–33	240–355	188–544	268–566	9·1–106·6
	Treatment ,,	Mean	263	300	351	315	52·8
		Range	193–304	206–414	270–412	262–375	7·3–156·2
	Reduction in sugar	Mean	−13	−13	10	40	−15·3
		Range	6 to −95	30 to −57	143 to −89	163 to −33	0·2 to −45·6

* Increase in blood-sugar level.

Rothera's test during the control period revealed that all the patients who failed to respond had acetone in the urine.

Only one of the successfully treated patients had persistent acetonuria, although some others showed acetone on occasion. The mean blood-sugar and urine-sugar levels were lower in patients who later responded than in those who failed, but there was a wide and overlapping range. The mean reduction of blood and urine sugars in the successful group is contrasted with that in the failures in Table I.

Thirty patients who had been successfully controlled by tolbutamide while in the ward were maintained on this treatment as out-patients for a total of six weeks. Dummy tablets were substituted for a further period before discontinuation of all tablets. Fig 2 shows that seven patients

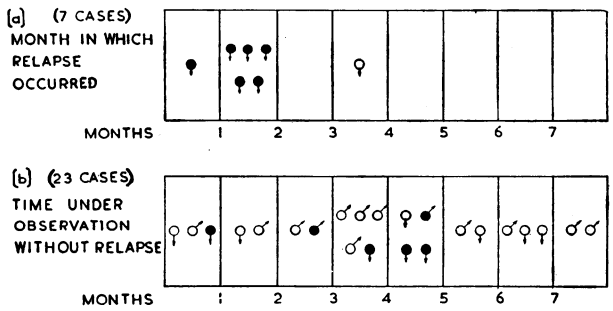

FIG. 2.—Follow-up of 30 cases after discontinuance of tolbutamide. New diabetics: male ♂, female ♀. Previously diagnosed diabetics: male ♂, female ♀.

relapsed when tolbutamide was stopped, six within the first two months. All but one of the seven had had previous treatment for diabetes. Two had been treated with insulin immediately before the trial and four had had insulin in the past. The one new patient had responded slowly to tolbutamide but had become normoglycaemic and sugar-free. She began to relapse three months after discontinuation of tolbutamide. Twenty-three patients remain well controlled on dietary regime alone after six weeks on tolbutamide, and Fig. 2 shows how long they have so far been observed after the discontinuation of tolbutamide without evidence of relapse. These 23 patients include all but one of the 18 newly diagnosed diabetics. Three of this group were above the 5 to 95 centile weight range while all the others lay within it.

Of the seven patients who relapsed when tolbutamide was discontinued, six responded well to its reintroduction and are now again satisfactorily controlled on 2 g. daily. One patient developed sepsis of a toe, and this was assumed to be responsible for the relapse in her diabetic state. Although the sepsis was controlled with penicillin, she failed to respond to a second course of tolbutamide. Despite coaxing, she refused insulin. Carbutamide was therefore substituted for tolbutamide in the same dosage (2 g. daily) and led to a return to normoglycaemia.

Biochemical Findings

Plasma Tolbutamide

Twenty-eight patients (group 1) were treated with a single dose of tolbutamide given at 8 a.m.—3 g. on the first day and 2 g. thereafter. The next 14 patients (group 2) were given the same amount of tolbutamide, but this was split into two equal doses, one given at 8 a.m. and the other at 12 noon. In the patients responding to tolbutamide in the ward, the mean reduction in mean blood-sugar levels throughout the day and in the 24-hour urine sugar was the same whether the patients had been treated with a single or divided dose (Table I). The mean levels of plasma tolbutamide for the first day of treatment and the mean levels from the third to the seventh day inclusive are shown in Tables II and III.

In group 1 patients, peak levels were reached in from four to six hours after the administration of tolbutamide

TABLE II.—*Tolbutamide Given as a Single Daily Dose at 8 a.m. (11 Patients). Plasma Tolbutamide Levels (mg./100 ml.)*

	1st Day of Treatment			3rd–7th Day of Treatment			
	12 Noon	2 p.m.	6 p.m.	8 a.m.	12 Noon	2 p.m.	6 p.m.
Mean	12·8	13·5	7·8	0	11·1	9·2	5·6
Range	4·5–22·0	7·8–18·5	One estimation only		1·8–30·7	0·7–22	0–16·6

TABLE III.—*Tolbutamide Given in Two Doses at 8 a.m. and 12 Noon (8 Patients). Plasma Tolbutamide Levels (mg./100 ml.)*

	1st Day of Treatment		3rd–7th Day of Treatment			
	12 Noon	2 p.m.	8 a.m.	12 Noon	2 p.m.	6 p.m.
Mean ..	4·3	7·2	2·1	11·3	12·0	8·9
Range ..	2·0–8·4	1·6–13·7	0–8·8	1·4–26·6	3·8–17·0	5·7–12·5

and some was still present after 10 hours (mean level 5.6 mg./100 ml., range 0 to 16.6 mg./100 ml.). No tolbutamide was detected after 24 hours. In group 2 patients higher tolbutamide levels were found at 6 p.m. (mean levels 8.9 mg./100 ml., range 5.7 to 12.5 mg./100 ml.), and some tolbutamide was occasionally found the next day. The mean levels at 2 p.m. (12.0 mg./100 ml., range 3.8 to 17.0 mg./100 ml.) were somewhat higher than in group 1 patients (9.2 mg./100 ml., range 0.7 to 22 mg./100 ml.) at the same time. There were three failures among the group 1 patients and one failure in group 2 on whom plasma tolbutamide was determined. Plasma tolbutamide levels similar to those of the successes were found in these four failures.

Plasma Amino-acid Nitrogen

Out of a total of 207 amino-acid nitrogen estimations, only six were above the upper limit of normal (taken as 7.8 mg./100 ml.); the raised values being 7.9, 8.0, 8.1, 8.1, 8.3, and 8.7 mg One value of 8.1 mg./100 ml. was found during the period of treatment with tolbutamide. The other raised values were seen in four patients during the control period, but the levels had returned to normal before the beginning of treatment. Tolbutamide produced some reduction in blood sugar in all the 13 patients concerned, and in nine patients ("successes") the blood sugars were substantially reduced. However, it will be seen from Tables IV and V that no effect of tolbutamide on the plasma amino-acid nitrogen can be demonstrated.

TABLE IV.—*Plasma Amino-acid Nitrogen Levels (mg./100 ml.) on First Day of Tolbutamide Treatment. 3 g. Tolbutamide Given at 8 a.m.*

Patient	8 a.m.	12 Noon	2 p.m.	6 p.m.
A. C. ..	7·8	7·0	7·6	
H. B. ..	6·9	6·7	7·3	
A. Q. ..	3·5	3·8	3·7	
E. Y. ..	3·5	4·1	3·5	3·8
G. R. ..	4·3	4·0	3·9	4·5
L. Z. ..	6·0	5·3	6·1	6·0
E. M. ..	5·6	5·3	4·6	
G. D. ..	5·3	5·3	5·5	
Mean ..	5·4	5·2	5·3	
Range ..	3·5–7·8	3·8–7·0	3·5–7·6	

TABLE V.—*Plasma Amino-acid Nitrogen Levels (mg./100 ml.) During the Control Period and First Week of Treatment with Tolbutamide*

Time		"Successes" (9)		"Failures" (4)	
		Mean	Range	Mean	Range
8 a.m. ..	Control period	5·7	3·7–8·7	4·3	2·9–6·1
	Treatment ,,	5·8	3·8–8·1	4·0	2·3–5·3
12 noon ..	Control ,,	5·5	3·3–8·3	4·7	3·3–6·4
	Treatment ,,	5·5	3·3–7·6	4·2	2·7–5·6
2 p.m. ..	Control ,,	5·5	3·6–8·0	4·6	3·6–6·1
	Treatment ,,	5·6	3·8–7·6	4·8	3·5–6·5
6 ,, ..	Control ,,	4·7	4·1–5·0	5·0	3·9–6·6
	Treatment ,,	5·6	4·2–7·1	4·9	3·3–6·8
Average daily level	Control ,,	5·5	3·3–8·7	4·6	2·9–6·6
	Treatment ,,	5·6	3·3–8·1	4·4	2·3–6·8

Plasma Inorganic Phosphorus

Although tolbutamide produced some reduction in blood sugar in all the patients studied and in eight patients (" successes ") the blood sugars were substantially reduced, it will be seen from Tables VI and VII that no effect on the plasma inorganic phosphorus has been demonstrated.

TABLE VI.—*Plasma Inorganic Phosphorus Levels (mg./100 ml.) on First Day of Tolbutamide Treatment. 3 g. Tolbutamide Given at 8 a.m.*

Patient	8 a.m.	12 Noon	2 p.m.
A. C. ..	3·5	3·5	4·0
H. B. ..	3·7	3·4	4·1
E. Y. ..	3·4	4·0	4·0
L. Z. ..	2·8	3·2	3·0
E. M. ..	3·3	3·0	2·9
G. D. ..	3·0	2·9	3·3
E. S. ..	4·4	4·3	4·4
K. B. ..	4·3	4·4	4·3
Mean ..	3·6	3·6	3·8
Range ..	2·8–4·4	2·9–4·4	2·9–4·4

TABLE VII.—*Plasma Inorganic Phosphorus Levels (mg./100 ml.) During Control Period and First Week of Treatment with Tolbutamide*

Time		"Successes" (8)		"Failures" (3)	
		Mean	Range	Mean	Range
8 a.m. ..	Control period	3·4	2·3–4·6	3·5	3·0–4·2
	Treatment ,,	3·5	3·1–4·1		
12 noon ..	Control ,,	3·5	2·3–4·4	3,3	3·2–3·5
	Treatment ,,	3·4	2·7–4·4	3·3	2·9–4·0
2 p.m. ..	Control ,,	3·4	2·5–4·1	3·9	3·0–4·5
	Treatment ,,	3·5	2·9–4·1	3·6	3·3–4·0
Average daily level	Control ,,	3·46	2·3–4·6	3·5	3·0–4·5
	Treatment ,,	3·46	2·7–4·4	3·6	2·9–4·4

Other Findings

No toxic effects were recorded in any patients during this trial. There were no skin rashes and no changes in the blood picture, in the white-cell count, or in the platelet count.

Weight recordings failed to reveal any particular trend. The majority showed no weight change while on tolbutamide. When the tolbutamide was discontinued there was a mean reduction of 3 lb. (1.36 kg.) in weight in patients observed over the next two months.

Discussion

Forty-two diabetic patients presenting with mild symptoms of the disease were admitted to the ward and treated with tolbutamide when dietary restriction alone had failed to reduce hyperglycaemia and glycosuria. As with carbutamide, it soon became apparent that tolbutamide could not control the diabetes in all the diabetics to whom it was administered. Young diabetics were not included in this trial, nor were patients presenting with severe acidosis and provocative symptoms of the disease. Even so, of 42 patients treated with tolbutamide 12 failed to respond. Although none of these could be described as severe diabetics they all showed acetone in the urine and tended to have higher blood and urinary sugars than those who responded. However, there was no reliable method of predicting which patient would respond, since one of those who did respond showed acetone in the urine while some who responded showed higher blood sugars than others who failed.

Patients whose diabetes was controlled successfully by tolbutamide in the ward were maintained on this treatment for a total of six weeks and the drug was then discontinued. It is a striking fact that of 18 diabetics newly diagnosed only one has so far relapsed after discontinuation of tolbutamide. While it is true that more may relapse in time, it seems unjustifiable on this evidence to treat new diabetics who respond to tolbutamide for indefinite periods with these tablets. The mode of action of the sulphonylureas is unknown, as are their long-term effects, and these are good reasons for not prescribing these drugs unnecessarily. It seems preferable to treat responsive diabetics with a six-weeks course of tolbutamide, especially as the drug can be given again to patients who relapse. There seems to be nothing to lose by adopting this plan, for, excepting one patient whose relapse was due to sepsis, all the other patients who relapsed when tolbutamide was discontinued responded equally well when it was reintroduced.

The purpose of treating diabetics for a limited period with tolbutamide is to reduce hyperglycaemia and hence to enable the patients by simple dietary restrictions to remain controlled by their endogenous insulin. Dohan and Lukens (1947) have shown experimentally in cats that the insulin-secreting cells of the pancreas can become exhausted in an attempt to control a sustained hyperglycaemia, and that reducing the blood sugar may break a vicious circle and allow the beta cells to recover. It has been commonly observed that many diabetics started on insulin because of persistent hyperglycaemia show a steadily diminishing need for it, and the insulin can be safely discontinued after a time without relapse. It is precisely in this type of diabetic that tolbutamide may offer a simple and apparently safe alternative to insulin.

As to the question of dosage, although patients on the divided daily dose showed a higher blood level of tolbutamide at 2 p.m., 6 p.m., and 8 a.m. the following day than patients on the single dose, the mean reduction in blood and urinary sugar was the same in both groups where the drug was successful. This suggests that the level of blood tolbutamide is not the determining factor in the fall in blood and urine sugar. The fact that similar levels of tolbutamide were found in both successes and failures would lead to the same conclusion.

If tolbutamide acts by stimulating the release of insulin from the pancreas (Loubatières, 1955), or by inhibiting the breakdown of insulin by insulinase (Mirsky *et al.*, 1956a, 1956b), the general physiological effects of tolbutamide should be those of insulin. Insulin increases glucose uptake and the fall in plasma inorganic phosphorus which takes place is associated entirely with the peripheral utilization of glucose (Nichols, 1955). The fact that in the present series the plasma inorganic phosphorus did not fall during tolbutamide therapy is in accordance with the findings of Renold *et al.* (1956) and Purnell *et al.* (1956) and indicates that tolbutamide does not increase glucose uptake. If this is so, it can be assumed that tolbutamide does not itself act by stimulating the secretion or preventing the destruction of insulin.

Lotspiech (1949) found that insulin promoted the synthesis of proteins from amino-acids. The resultant lowering of the plasma amino-acid nitrogen level could be seen in normal individuals (Luck *et al.*, 1928) as well as in diabetic patients. The lack of effect of tolbutamide on the amino-acid nitrogen levels in the present trial indicates again that tolbutamide does not act in the same way as insulin.

Summary

Tolbutamide was used in the treatment of 42 patients on standard diets whose diabetes was neither so mild as to be controlled by diet alone nor so severe as to need insulin immediately.

All 12 patients who failed to respond showed acetonuria with a tendency to higher blood- and urine-sugar levels than those treated successfully.

Thirty patients responded to tolbutamide and were maintained on this therapy for six weeks. In 23 of these relapse has not occurred so far on discontinuation of treatment.

Seven patients relapsed following discontinuation of tolbutamide. The drug was successfully reintroduced in six of these.

When tolbutamide treatment was given in the form of 1 g. twice daily the concentration of the drug in the

blood differed from that found when treatment was by a single dose of 2 g. However, the effect on the blood and urine sugars was the same in both cases.

Analyses of plasma amino-acid nitrogen and inorganic phosphorus indicate that tolbutamide has a mode of action different from that of insulin.

No toxic effects due to tolbutamide were observed.

We express our thanks to the Medical Research Committee of the North-west Metropolitan Regional Hospital Board for a grant to pursue these studies, and also to the Wellcome Foundation for supplies of tolbutamide and placebos. We are grateful to Dr. J. McSorley for blood estimations, to Mrs. Collins for diet supervision, and to Miss J. Savage for laboratory assistance.

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HALOTHANE: ITS USE IN CLOSED CIRCUIT

BY

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This paper describes experience of the use of halothane ("fluothane") in a closed circuit. Others (Johnstone, 1956; Bryce-Smith and O'Brien, 1956) have reported on its open and semi-open administration. Halothane was given from a standard Marrett apparatus to over 1,550 cases during a period of nine months.

Preliminary Trial

Halothane was placed in the large ether jar of a standard Marrett machine. The flow of gas was usually 400–500 ml. of oxygen per minute. The level of liquid in the jar was not kept constant, but this made no noticeable difference to the control setting until the level fell below 2 fl. oz. (57 ml.).

The ether control on the Marrett apparatus is divided into four divisions. During the travel of the control knob (see Diagram) from "off" to "¼ on" (the first two divisions on the scale) only the patient's breath passes into the jar. The gases from the flowmeters are delivered direct to the inlet unidirectional valve. This range of the control is equivalent to the full range of closed-circuit vaporizers on most other machines.

To ascertain the relative strength of halothane, a personal trial was undertaken. With half a litre of oxygen a minute and the control set at three-fourths of the first division (see Diagram), no irritant effect was noticed; nor the buzzing in the head so characteristic of nitrous oxide and other inhalation anaesthetics. Loss of consciousness, accompanied by marked jaw relaxation and loss of corneal reflex, took three minutes, and recovery was complete in five minutes, with no subsequent headache or nausea. With the control set at the second division (full on for the closed circuit) the vapour produced coughing, but was soon tolerated, and loss of consciousness took one minute, with 10 minutes for recovery and again no headache or nausea. It was therefore clear that the concentration was safe and that halothane was likely to be most useful for inductions, particularly if an intravenous anaesthetic was contraindicated as in the very old or emergencies; it would probably also be useful for resistant dental cases, provided only a few breaths were given to allow the third stage to be established. It remained, however, to find out if there was any accumulation in the body after a long administration in closed circuit, or if there was any "build up" of concentration in the breathing circuit.

Induction and Maintenance

Although premedication causes respiratory depression, for the patient's comfort the premedication usual at this hospital was continued—that is, "omnopon," ¼ gr. (22 mg.), and scopolamine, 1/150 gr. (0.43 mg.), for the healthy adult up to 56; morphine, ⅙ gr. (10 mg.), and atropine, 1/100 gr. (0.65 mg). were used for the elderly, and atropine, 1/100 gr. (0.65 mg.), for the bad risk and those over 70.

As halothane itself is known to depress respiration, for induction a dose of thiopentone varying from 0.15 to 0.25 g. was used in healthy adults instead of the usual 0.5 g. The mask was then placed on the face with the halothane control at three-fourths of the first division and an oxygen flow of half a litre a minute. Sometimes the respiratory depression from the thiopentone persisted when the halothane was added, though normal respirations would return immediately after a painful stimulus or pulling on the chin. At this stage a tough individual might become restless, but if the control was put to the second division (full on) he would quieten after three or four breaths, although he might cough. With a strong vapour patients might cough, but laryngeal spasm was never encountered, nor was it possible to produce one purposely—a most useful attribute.

For a major abdominal operation the control was then slowly advanced until the abdomen relaxed. At this stage depth of respiration was normal for the closed circuit, and blind or direct intubation could be performed early owing to the complete relaxation of the jaw and larynx. After this all cases were conducted on the principle of physiological breathing, full relaxation for all abdominal operations always being obtainable. At the start of the series D-tubocurarine was used in doses of 5–10 mg. for abdominal operations, but with further experience this proved unnecessary; also, apnoea often occurred and the systolic pressure might fall as low as 45 mm. Hg, although this would rise quickly after an injection of atropine, 1/100 gr. (0.65 mg.).

The maintenance of anaesthesia was usually with the control set at three-fourths of the first division 2% halothane. and at the first division 2.4% for abdominals. A setting beyond the first division was always too much. The margin between light and deep anaesthesia was narrow, so if the patient became too "light" a few breaths of a slightly stronger concentration would soon settle him; but unless this concentration was very soon reduced apnoea developed. If from overdose respiration became too shallow recovery occurred quickly on cutting down or turning off the halothane. On closure of the peritoneum the halothane and soda lime were switched off, and nitrous oxide, oxygen, and air substituted for the remainder of the operation.

The patients all recovered quietly, with a remarkable lack of post-operative vomiting and nausea, and were quite obviously little affected by their operation when seen the following day. There was never the slightest suggestion of