evident from Table V, where the results are given for those infants with maternal antibody levels of 16 or less—levels which produced little or no interference with antibody response. Although the numbers are small, it appears that, in the case of types 1 and 3, the older the infant the better the response to vaccination, although in the older groups there was still a high proportion who did not respond, especially to type 1. With type 2, however, the age of the infant had no effect on the response, because in all groups all the infants except one responded well to this type.

Discussion

The chief points which emerge from this study are that the titres of maternal and cord blood neutralizing antibodies are strikingly similar for all three virus types; that the loss of placentally transmitted antibodies in the infant is of the same order for all three types, the level being halved approximately every 21 days; that the response of the infants to the vaccine varies with the level of transmitted antibodies, which interfere with the response to the homologous type; that this inhibiting effect is most easily overcome by the type 2 antigen; and that the age of the infant also plays a part in determining the ability to respond to types 1 and 3.

It is clear, therefore, that the earliest age at which infants can be successfully immunized against poliomyelitis depends on a number of different factors, but if, for practical purposes, it is assumed that the majority of infants are born with antibody levels of the order of those observed in the present investigation, it is unlikely that these will have disappeared, or fallen to non-inhibitory levels, until the infants are between 6 and 9 months old. This unfortunately precludes the use of poliomyelitis immunization as the first protection to be offered routinely to infants and leaves the problem of overcoming the risk of provoked paralysis still unsolved.

Early protection against pertussis is particularly desirable and can most conveniently and efficiently be combined with diphtheria and tetanus prophylaxis. To be effective in earliest infancy, this demands an alum-containing antigen (Feldman, 1957), which experience has shown to be the most dangerous in producing provoked paralysis. Some method must therefore be evolved whereby this triple antigen may be given with safety. One solution would be to boost the levels of placentally transmitted poliomyelitis antibodies by immunizing all pregnant women. This would ensure that the infant would have sufficiently high titres against poliomyelitis to last at least for the first four months of life and—under cover of this protection—immunization could be started as soon as possible after birth with three doses of triple antigen and thereafter followed with poliomyelitis vaccine. A study of such a procedure is already in progress, and will be the subject of a further communication.

Considered solely from the point of view of the protection of infants against poliomyelitis, the earliest age for successful immunization is still undetermined; for, although our evidence suggests that all infants would respond adequately to type 2 by the age of 6 to 9 months, it is not yet known whether this would hold true for type 3 and, more particularly, for type 1. This is at present being investigated, as also is the effect of a third inoculation given a month after the primary course, the usual practice for diphtheria, pertussis, and tetanus prophylaxis. It is possible that those infants who have shown no obvious response to their two primary injections of poliomyelitis vaccine may nevertheless have developed a sufficient degree of basal immunity to enable them to respond to the third injection.

Summary

The levels of poliomyelitis neutralizing antibodies in sera from the mother and from the umbilical cord are similar. The loss of maternal antibody in the infant is similar for all three types, the level being halved approximately every 21 days.

The response of infants to poliomyelitis vaccine depends partly on the age of the infant, but chiefly on the level of maternal antibodies, which inhibit the response to the homologous type. This inhibiting effect is overcome most easily by the type 2 antigen, not quite so easily by the type 3, and hardly at all by the type 1.

In order to avoid the inhibiting effect of the placentally transmitted antibody, immunization should at present be delayed until six to nine months after birth, although even at this age it is not yet known whether the responses to types 1 and 3 will be adequate. Studies are proceeding to determine the earliest age at which the response to all types will prove satisfactory.

Investigations are also in progress of alternative methods of immunization in early infancy.

Our thanks are due to Dr. G. V. Feldman, Dr. R. F. Jennison, and the nursing and laboratory staff at St. Mary's Maternity Hospital, Manchester, for their assistance, and to Miss K. South and Miss P. Tumber, of the Biological Standards Control Laboratory, London, for their help in titrating the sera. We also thank the Ministry of Health for the supply of poliomyelitis vaccine. This work was supported in part by a grant from the National Fund for Poliomyelitis Research to one of us (W. G.), for which we are most grateful.

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ORAL TREATMENT OF DIABETES TRIAL OF PHENETHYLDIGUANIDE (D.B.I.)

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In the treatment of diabetes insulin is irreplaceable: no satisfactory substitute has yet been discovered. However, the need for parenteral administration of insulin has stimulated the search for substances which will lower the blood sugar when given by mouth. Recently, certain sulphonylureas (notably carbutamide and tolbutamide) have been shown to do this. Unfortunately, sulphonylureas are effective only in mild diabetes, and this is in accord with the experimental finding that some functioning pancreatic islet tissue is necessary for them to exert full action (Levine, 1958).

Ungar *et al.* (1957) have investigated a series of compounds of different structure belonging to the diguanide group, and found that one of them, phenethyldiguanide, or N-beta-phenethylformamidinyl iminourrea (D.B.I.), was able to produce hypoglycaemia even in eviscerated or alloxan-diabetic animals. Later workers have confirmed that this substance can lower the blood sugar in the absence of insulin (Nielsen *et al.*, 1958). Clinical trials of D.B.I. have been carried out by Pomeranzen

(1957), and the results were held to be promising enough to warrant further investigation.

This paper records an attempt to assess the effectiveness of D.B.I. as a hypoglycaemic agent in diabetes of all grades of severity, to gauge its side-effects, and to compare its mode of action with that of insulin and tolbutamide.

Material and Methods

Forty diabetic patients were admitted to the ward for treatment with D.B.I. Their ages ranged from 18 to 78 years, average 57. The weights of 36 of them lay in the 5 to 95 centile range (Kemsley, 1952). Two males and two females were heavier than 95% of their compeers. Fourteen of the diabetics were newly diagnosed and had received no treatment; one was relapsing on dietary control, never having had insulin; and the remaining 25 had all at some time had insulin, in varying amounts, for periods ranging from 3 months to 21 years. Diabetics of all degrees of severity were included; five of them developed thirst, poly-

uria, and acidosis if insulin was withheld for more than 24 hours. Where feasible, the patients were managed for a week by dietary control alone before D.B.I. was administered. This enabled the exclusion from the trial of the mildest diabetics who became normoglycaemic after simple food restriction, and permitted estimation of control figures for the blood and urine sugar contents. The calorie value of the diets was arrived at by consideration of the patients' age, height, weight, sex, and activity, and was kept constant through the trial. Patients were also weighed before and during treatment with D.B.I.

On the first day of treatment 150 mg. of D.B.I. was given by mouth half an hour before breakfast, while on the second and subsequent days 50 mg. of D.B.I. was given orally three times daily before the main meals. The full course of treatment with D.B.I. lasted for six weeks. The total 24-hour urine output of glucose (method of Benedict (King, 1951)) was measured daily and venous blood sugars (method of Hagedorn and Jensen (1923)) were estimated each day at 12 noon before lunch. In addition, on the day before D.B.I. was given and on the first day of treatment with D.B.I. blood samples were taken at two-hourly intervals: at 6 a.m., 8 a.m., 10 a.m., 12 noon, 2 p.m., and 4 p.m. These samples were analysed for sugar, plasma inorganic phosphorus (method of Fiske and Subbarow, 1925), and plasma amino-acid nitrogen—method of Folin as modified by Danielson (1933) and Frame *et al.* (1943). From all patients, before and during treatment with D.B.I., blood was also collected for a haemoglobin estimation, for white cell count and blood-film examination, and for liver-function tests.

Results

Effect of Single Dose of 150 mg. of D.B.I. on Blood Sugar.—Fig. 1 shows the mean percentage falls in the blood sugars produced by a single 150-mg. dose in 24 diabetic patients, some of whom showed no hypoglycaemic response to D.B.I. The individual blood-sugar values on the first day of treatment are expressed as a percentage of the value obtained at the same time on the previous day. A hypoglycaemic response to D.B.I. begins to be apparent in four hours, is maximal at six hours, and ceases to be noticeable ten hours after the administration of D.B.I.

Effect of Protracted Treatment on Noon Blood Sugars.—Fig. 2 shows the percentage fall in blood sugars produced by several days' administration of D.B.I., 50 mg. t.d.s. For each patient the mean pre-treatment noon blood sugar was calculated, and each value before and after treatment was expressed as a percentage of this. There was no significant change in the blood sugars during the period of dietary restriction alone. Administration of D.B.I. led to a progressive fall in the mean blood sugars, the lowest level being attained by the sixth day of treatment. Two-hourly serial blood sugars measured a week after treatment in a few diabetic patients were all lower than those observed on the first day of treatment.

Effect of D.B.I. on Glycosuria.—The urinary output of sugar reflected the blood-sugar levels and there was no evidence of an altered renal threshold.

Effect of D.B.I. on Ketosis.—The five patients whose life depended on insulin developed ketosis very rapidly when the insulin was discontinued. Administration of D.B.I. in these cases produced a small fall in the blood sugar, but the ketosis increased in severity. Of the remaining 35 cases, only occasional positive "acetests" were recorded before treatment. After D.B.I. was given, 11 of the 35 cases showed intermittent acetonuria, of greater frequency and concentration than before treatment, although normoglycaemia and aglycosuria had been produced. The acetonuria was

FIG. 1.—Effect of a single dose of D.B.I. on the blood-sugar level of 24 diabetics. Blood-sugar levels are expressed as a percentage of the value obtained at the same time the previous day. Each point on the graph is the mean of the figures 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.—Effect of protracted treatment with D.B.I. on noon blood-sugar levels. Blood-sugar levels are expressed as a percentage of the average pre-treatment level for each case. Each point is the mean value obtained from the number of diabetics shown above each point. Horizontal lines bracketing each point represent the standard error of each mean.

not due to starvation, as these patients had eaten well throughout. Acetonuria also developed in most patients who became nauseated, or who vomited while receiving D.B.I. In one case the paradoxical coexistence of ketonuria and aglycosuria was particularly marked.

An underweight male diabetic, aged 51, newly diagnosed, presented with thirst and polyuria. Heavy glycosuria and acetonuria were observed. The initial noon blood sugar was 391 mg./100 ml. D.B.I. was given after two days' observation, and the noon blood sugars fell to 80 mg./100 ml. after a week's treatment. Although no sugar was passed in the urine, the daily output of acetone exceeded 1 g. and the blood acetone was 10 mg./100 ml. The D.B.I. was discontinued, with immediate reappearance of glycosuria. After two days without the drug, acetone disappeared from the urine, although the sugar content exceeded 2%, and the blood sugar rose to 300 mg./100 ml. D.B.I. was again given and the blood sugar fell again to normal levels. Glycosuria disappeared, but acetone bodies reappeared in the urine, the acetest being positive at a dilution of 1:32. It was thought unwise to continue with D.B.I. and insulin was given. Although the blood-sugar levels were normal, two days elapsed before the ketonuria was eliminated. The patient, although making no spontaneous complaint while receiving D.B.I., immediately commented on a sense of improved health when insulin was given.

Effect of D.B.I. on Plasma Inorganic Phosphorus and Amino-acid Nitrogen.—Although 150 mg. of D.B.I. administered on the first day of treatment produced some reduction in the blood sugar in all the 11 patients studied, there was no increase in the postprandial fall of serum inorganic phosphorus (5.4% at 10 a.m. compared with 10% on the previous day at the same time). Similarly, no effect of D.B.I. on the plasma amino-acid nitrogen could be demonstrated.

Relation of Severity of Diabetes to Response to D.B.I.—Five patients had a severe, brittle type of diabetes and required more than 30 units of insulin daily. D.B.I. was substituted for insulin in dosage varying from 150 to 250 mg. per 24 hours, but failed to prevent severe ketosis, hyperglycaemia, thirst, and polyuria. Insulin had to be reintroduced in these cases. The remainder of the patients had a mild or moderately severe diabetes, and most of them showed a fall in the blood sugar in response to D.B.I. In 18 cases the noon blood sugar was reduced to below 180 mg./100 ml., and in seven of these to below 140 mg./100 ml.

Relation of Response to Duration of Diabetes.—Of the 14 newly diagnosed diabetics, 12 showed a good hypoglycaemic response to D.B.I., and five of these did not relapse when the D.B.I. was withdrawn. Of the cases with diabetes of long standing, 17 showed some hypoglycaemic response, but none could subsequently be managed by diet alone. The impression was obtained that the drug was more effective in cases of diabetes of recent onset.

Pejorative Effects of D.B.I.—No fewer than 26 out of the 40 patients developed gastro-intestinal disturbances while on the drug. Nausea, anorexia, abdominal discomfort, vomiting, and diarrhoea were variable in severity, but in most cases were persistent enough to necessitate cessation of treatment with the drug. Symptoms usually appeared three or four days after the beginning of therapy and were not related to hypoglycaemia. Discontinuation of the drug caused the symptoms to abate, usually within two or three days.

Effect of D.B.I. Compared with that of Tolbutamide.—In two patients in this series in whom tolbutamide had previously been employed with unsatisfactory fall in the blood sugar, D.B.I. was effective in lowering the blood sugar. Unfortunately, in each case nausea and vomiting precluded continuous use of D.B.I. In three other patients in whom D.B.I. had produced normoglycaemia and in whom treatment with the drug was stopped because of nausea and vomiting, tolbutamide was introduced, but was much slower and less effective in reducing blood sugar.

Clinical Effects.—It was originally intended to administer D.B.I. for six weeks in all cases. In 25 out of the 40 patients this was not possible because of unpleasant side-effects or because an adequate fall of blood sugar had not been obtained, 20 of these cases now receiving insulin and five

tolbutamide. Of the remaining 15, six are still receiving D.B.I. (50 mg. t.d.s.) and are satisfactorily controlled. When the drug was discontinued in the rest after six weeks' treatment, in four the diabetes relapsed, necessitating treatment with insulin in two and with tolbutamide in two. In five dietary control seemed adequate to control the diabetes. Where D.B.I. was effective in lowering the blood sugar without causing gastro-intestinal symptoms, adequate relief of diabetic symptoms such as thirst or polyuria was afforded. Of the 15 patients who received a prolonged course of D.B.I., five complained of a sensation of lassitude and epigastric fullness after meals. One patient to whom a second course of D.B.I. was given after relapse of her diabetes mentioned that she felt much better "in herself" while receiving the tablets.

No skin rashes, blood dyscrasia, or toxic effects on the liver were observed in this series.

Discussion

D.B.I. has been demonstrated to be an effective hypoglycaemic agent in mild and moderate diabetes. At a dosage of 50 mg. three times a day it has been shown to reduce the blood sugar to normal levels, in some cases even in the presence of ketonuria and in some patients who have failed to respond to tolbutamide. Unfortunately, its administration was accompanied by gastro-intestinal disorders in no less than two-thirds of the diabetics in whom it was used. Nausea, abdominal discomfort, vomiting, and diarrhoea were severe enough to necessitate withdrawal of the drug in these patients. Symptoms usually quickly subsided on cessation of treatment, but vomiting is a particularly unwelcome symptom in diabetics. No toxic effects were observed in the blood or in the liver of patients so far treated, but the period of observation has not extended for more than a few months. While this paper was in preparation, Williams *et al.* (1958) recorded their experiences with the drug. They found a similar proportion of gastro-intestinal disturbances in patients on diguanides, but observed no permanent ill effect of any type. Pomeranze (1957) has stated that labile diabetics can be better controlled with supplementary use of the drug, but we have not investigated this aspect of its use.

Experimental evidence (Williams *et al.*, 1957) suggests that the drug has two main modes of action; firstly, it decreases the output of glucose from the liver by depressing gluconeogenesis, and, secondly, it increases glucose utilization by the tissues. Lundbæk *et al.* (1958) have also shown that D.B.I. has a strong effect on the uptake of glucose by the tissues. As, however, the amount of glycogen in muscle was decreased by D.B.I. (Williams *et al.*, 1957; Rafaelsen, 1958) the effect of D.B.I. on the carbohydrate metabolism of muscle differs from that of insulin, and Williams *et al.* (1957) have suggested that the increased glucose uptake is due to increased anaerobic glycolysis. Our results support the view that D.B.I. does not act like insulin. In contrast to insulin, D.B.I. was quite unable to relieve acidosis in severe diabetics, and normoglycaemia could be attained in only about a third of diabetics to whom the drug was given.

Further, the appearance of ketone bodies *pari passu* with the development of normoglycaemia in certain cases makes it likely that carbohydrate oxidation is not completely rectified even when the drug has returned the blood sugar level to normal. The lack of a fall in a plasma inorganic phosphate may be due to the milder effect of D.B.I. on glucose uptake. Lotspeich (1949) found that insulin promoted the synthesis of proteins from amino-acids. The resultant lowering of the plasma amino-acid nitrogen could be seen in normal individuals (Luck *et al.*, 1928) as well as in diabetic patients. The lack of effect of D.B.I. on the amino-acid nitrogen levels in the present trial indicates again that D.B.I. does not act like insulin. On the other hand, the impression was obtained that D.B.I. was more potent as a hypoglycaemic agent than the sulphonylureas. As with tolbutamide, however, several days of treatment must elapse before maximal effect is demonstrated, and

D.B.I., like the sulphonylureas, proves more effective in patients whose diabetes is of short duration.

The ultimate value of maintaining normoglycaemia in diabetics by substances whose mode of action differs from that of insulin remains undecided. There is evidence that hyperglycaemia *per se* is harmful if allowed to persist and can be responsible for the degenerative changes that occur in diabetics (Duncan *et al.*, 1958). The search for an effective non-toxic hypoglycaemic agent is justifiable on these grounds. D.B.I., although its range of action is probably wider than that of tolbutamide, is unsuitable for general use because of the high incidence of unwanted side-effects.

Summary

A new oral hypoglycaemic substance, phenethyl-diguamide (D.B.I.), was administered to 40 diabetic patients, of all grades of severity.

A significant fall of blood sugar occurred in about two-thirds of cases.

Ketosis was not rectified, and occasionally developed, in patients on D.B.I.

In five cases in which tolbutamide proved ineffective, D.B.I. produced a fall in blood sugar.

Ill effects (usually nausea, vomiting, or diarrhoea) appeared in 25 of the 40 cases, precluding the general use of D.B.I. in diabetes.

We thank the Medical Research Committee of the North-west Metropolitan Regional Hospital Board for a grant to pursue these studies, and also Dr. Simpson, of Duncan Flockhart and Co., for supplies of D.B.I. We are grateful to Dr. J. McSorley for haematological investigations, to Miss J. Savage for laboratory assistance, to Mrs. Collins for diet supervision, and to the ward sisters and nursing staff for their most helpful co-operation.

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The annual meeting of the Medical Sickness Annuity and Life Assurance Society, Ltd., was held in London on June 24, under the chairmanship of Mr. R. J. MCNEILL LOVE, F.R.C.S. There had been an unprecedented increase in both sickness and life business, he said, arising from the excellent results of the 1956 valuation and the reduction in premiums for sickness and accident insurance. The sickness insurance fund now stood at over £2,700,000, the annual premium income exceeding £360,000, while the life assurance and annuity fund exceeded £5m., with a premium income of over £500,000. The net new life business at practically £2½m. was nearly 40% better than the previous year. New business under the scheme to cover the risk of death under the Medical Sickness Finance Corporation's hire purchase agreements amounted to £661,000. This subsidiary, which financed the hire purchase of cars and medical and dental equipment, charged rates little more than half those current among the ordinary finance companies. The society had formed a new subsidiary company, the Permanent Sickness Insurance Co., Ltd., whose non-cancellable sickness and accident policies would be issued to those in other than the medical and dental professions and, it was hoped, also to nurses, physiotherapists, and others in the ancillary medical services.

A NEW ORALLY EFFECTIVE LONG-ACTING GANGLION-BLOCKING AGENT FOR HYPERTENSION (189c56)

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The substance 189c56, as can be seen from the formula, is a derivative of the group of ganglion-blocking sub-

stances originally described by Adamson, Billingham, Green, and Locket (1956). Careful and prolonged clinico-pharmacological investigation of these agents over a period of years has shown that systematic variations in certain chemical groupings could produce corresponding systematic and progressive alterations in pharmacological properties (Locket, 1956b; Green, 1956; Billingham, 1956). 189c56 is one of the compounds developed as a result of this investigation. Chemically it is related to pentacynium methylsulphate ("presidal"), a ganglion-blocking agent used in the treatment of hypertension (Locket, 1956a; McKendrick and Jones, 1958).

Clinico-pharmacological Studies of 189c56

Compared with pentacynium methylsulphate, about twice the dose of the active cation of 189c56 by subcutaneous or intravenous injection produced the same fall in blood pressure. Initial studies demonstrated that 189c56 produced hydrodynamic changes and effects on renal function comparable to those of pentacynium.

It was possible to identify 189c56 in human urine many days after the last therapeutic dose had been injected. For this identification special biological techniques using mice were developed (A. F. Green and N. B. Ward, 1957, personal communication). Prolonged excretion could mean prolonged action with appropriate dosage, and this might be of great advantage because of longer control of the hypertension.

The hypotensive effect of 189c56 begins about two minutes after intravenous injection, but may require up to three hours before reaching its lowest level. The subcutaneous dose is two to four times larger than that necessary to produce a comparable fall in blood pressure by intravenous injection. A local reaction due to the cation may occur at the site of the subcutaneous injection, and this may be immediately apparent. The fall in blood pressure begins half an hour after subcutaneous injection, but on occasion this interval may be two hours.

Administration by Mouth

The observations of the action of the drug by mouth extend over a period of more than a year and are based on many more patients than the few "long-term" cases here reported. The small supply of drug necessitated as wide a coverage as was practicable, on a short-term basis, of severely ill hypertensive patients.

The clinical results are better than with any other member of this series so far used therapeutically, and in many ways better than those obtained in comparative trials with the other ganglion-blocking agents available for clinical use by oral administration (see Cases 2, 4, 5, 7, and 9). Within the dose range of 200* to 1,250 mg. daily by

*All dosages in this communication refer to the salt bis-methylsulphate trihydrate unless specifically stated otherwise.