DISCUSSION

It is possibly unjustifiable to leap to conclusions from figures given by one individual, particularly in this series of obstetric cases which is probably only 1/50th of the total number of maternity cases in the Transkei over the same period, and is not a random selection in that all the patients had come into hospital, mainly in emergency. Nevertheless, this small representation of the total maternal and foetal mortality, and the accidents of labour, from one hospital, shows that there is vast room for improvements. These improvements must undoubtedly take the form of many more maternity beds, better antenatal facilities, and education in matters concerning childbirth and the care of the neonate. The maternity services of any given area must surely be as good as its antenatal services. The majority of the mission hospitals in the Transkei have good antenatal clinics, but these are a drop in the ocean. In the Umtata district only, there are antenatal clinics under the Department of Public Health, but there appears to be no collaboration with the hospitals.

One of the main problems appears to be the distribution of the population. It is felt that possible methods of improvement would be as follows: (1) Three or more large antenatal clinics should be provided at the bigger centres where there are hospitals that can deal with maternity cases. (2) Smaller clinics should be provided in all the smaller towns and villages in the Transkei. They should be established either by the provincial authorities or the central government and, besides giving antenatal services, should each have about 6 beds for immediate emergencies. These subsidiary clinics should be managed by one or two full-time midwives under the supervision of either the local district surgeon or other interested practitioner in the village concerned. (3) Flying squads should be established in conjunction with the provincial hospitals in the Transkei, independent of the usual ambulance services and staffed by trained midwives, who should be instructed in the technique of intravenous therapy for use while the patient is being transferred to hospital. Such flying squads have been established in rural areas of Rhodesia with some measure of success.

SUMMARY AND CONCLUSIONS

1. Some aspects of a survey of 8,701 non-booked obstetric cases are presented from a Transkei hospital, and some suggestions are made for improvements in the maternity services in the reserves.

2. The maternal and perinatal mortality is high and, in the main, preventable.

3. The incidence of multiple pregnancy (1 in 24 for twins, corrected) is high.

4. All the admissions being of an emergency nature, the incidence of obstetrical operations (Caesarean section, forceps delivery and destructive operations) is higher than in urban areas.

5. The incidence of eclampsia and pre-eclamptic toxaemia, notwithstanding the lack of antenatal care, appears to be lower than in the European, although the figures given are possibly not a true reflection for indicated reasons.

6. The incidence of abnormal presentations generally appears to be higher than in institutions where mainly booked cases are admitted. This applies, too, to the large number of cases of ruptured uterus (57) in the series. The foetal mortality from these complications is exceedingly high. Vesicovaginal fistula due to prolonged obstructed labour is commonly seen.

7. Suggestions are made for improvements in the maternity services in the reserves.

I should like to thank Dr. Hugh Reid, Medical Superintendent of Sir Henry Elliott Hospital, for permission to publish these figures. Also I am grateful to Dr. Dennis Lavery, of Baragwanath Hospital, Johannesburg, for his interest and figures supplied, and to Prof. James T. Louw for his encouragement.

REFERENCES


DBI (PHENETHYLDIGUANIDE) IN THE TREATMENT OF DIABETES MELLITUS

T. SCHNEIDER and S. LOPIS, Diabetic Clinic, General Hospital, Johannesburg, and
W. M. POLITZER, South African Institute for Medical Research, Johannesburg

The successful debut of the sulphonylureas, carbutamide and tolbutamide as oral hypoglycaemic agents was bound to act as a stimulus to the search for still more effective drugs in the treatment of diabetes mellitus.

In 1957 Ungar et al. were able to report on the effectiveness of N-β-phenethyl-formamidinyl-iminourea (also called phenethyldiguanide or DBI) as a blood-sugar-lowering agent. Further experimental confirmation of this finding was provided by Williams et al., and Tyberghien et al., and clinical reports of the successful use of DBI were soon presented by Pomeranze et al., and Krall et al. of the problems of maternity services in the reserves are discussed.

2. The maternal and perinatal mortality is high and, in the main, preventable.

3. The incidence of multiple pregnancy (1 in 24 for twins, corrected) is high.

4. All the admissions being of an emergency nature, the incidence of obstetrical operations (Caesarean section, forceps delivery and destructive operations) is higher than in urban areas.

5. The incidence of eclampsia and pre-eclamptic toxaemia, notwithstanding the lack of antenatal care, appears to be lower than in the European, although the figures given are possibly not a true reflection for indicated reasons.

6. The incidence of abnormal presentations generally appears to be higher than in institutions where mainly booked cases are admitted. This applies, too, to the large number of cases of ruptured uterus (57) in the series. The foetal mortality from these complications is exceedingly high. Vesicovaginal fistula due to prolonged obstructed labour is commonly seen.

7. Suggestions are made for improvements in the maternity services in the reserves.

I should like to thank Dr. Hugh Reid, Medical Superintendent of Sir Henry Elliott Hospital, for permission to publish these figures. Also I am grateful to Dr. Dennis Lavery, of Baragwanath Hospital, Johannesburg, for his interest and figures supplied, and to Prof. James T. Louw for his encouragement.

REFERENCES

for periods of up to 1 year. They consisted of 25 females and 4 males whose ages varied from 39 to 75 years with an average of 56.3 years. The duration of diabetes varied between 2 and 24 years with an average of 9.8 years.

All the cases were proved diabetics and had been treated previously for varying periods of time with one or more regimens of treatment. Thus 9 cases had been on diet only, 18 on diet plus insulin, and 8 on diet plus tolbutamide.

The initial dosage of the drug was 25 mg. twice daily. This was increased by 25 mg. at weekly intervals or less until effective control was obtained or until side-effects precluded further increase. The maximum dosage administered was 250 mg., but usually no more than 150 mg. daily was given, because gastric irritation became marked above this amount. Insulin, where administered, was decreased slowly once the hypoglycaemic action of DBI had become manifest. It was found that administration during meals was better tolerated than either before or after, and in the later cases this method of administration was adhered to. The drug was always given in divided doses.

Fasting venous blood sugars (method of King and Garner) were initially estimated at least at weekly intervals and at two-weekly intervals after the first month. Complete blood counts and erythrocyte-sedimentation rates were performed at fortnightly intervals and a battery of 12 liver-function tests every 3 months.

Our clinical results have been evaluated as good, fair, or poor according to our previous criteria.10

RESULTS

The hypoglycaemic action of DBI is shown in Fig. 1. In this case 50 mg. of DBI was administered 3 times daily during meals. During the first 24 hours no real hypoglycaemic effect was noted, but the patient became aglycaemic from the fourth day onwards and frequent blood-sugar estimations showed a good hypoglycaemic effect on the tenth day.

Diet-only Group

Nine cases (2 males and 7 females) had previously been on a diet-only regimen. Five were obese and 4 medium in build. They had been known diabetics for periods of 2-13 years and their ages varied from 46 to 75 years. One was under good control, 3 under fair control and 5 under poor control.

The good-control diabetic was included in the hope that the blood sugar could be reduced to entirely normal levels. No such effect was noted, the blood sugars remaining at their previous levels.

Six cases improved to the good category, 4 having previously been under poor control and 2 under fair control. Of one of these cases, which had previously graduated from the poor to good category, has again deteriorated to the poor group after 10 months. One case improved from the poor to fair category on treatment with tolbutamide, 0.5 g. thrice daily plus 25 mg. of DBI 3 times daily. This case is of interest because neither diet only, nor diet plus tolbutamide, nor diet plus DBI were able to improve diabetic control, and only combined treatment was able to effect some improvement.

The remaining 'fair-control' case was unaffected by treatment.

Insulin Group

Eighteen cases (2 males and 16 females) had previously been treated with insulin. Of these 11 were obese and 7 medium in build. They had been known diabetics for periods ranging from 5 to 24 years and their ages varied between 39 and 69 years. Control was good in 1, fair in 5 and poor in 12 cases. The dosage of insulin varied between 15 and 90 units daily. In one case DBI replaced the 15 units of protamine zinc insulin previously required to keep the diabetes under good control, while in another improved control (from fair to good) occurred while replacing the whole dosage of 10 units protamine zinc insulin. In 2 further cases improvement from poor to good control was achieved on DBI together with insulin, the latter being reduced by 10 units (Lente insulin 30-20 units and 35-25 units). Three cases improved from poor to fair control on DBI plus insulin, the daily dosage of the latter being 7-10 units less than previously (NPH 27-20 units, Lente 30-20 units, NPH 20-10 units). The remaining cases stayed in the poor category, but in 2 of these it was possible to reduce insulin by 20 and 30 units (70 to 50 and 90 to 60 units of Lente insulin) without producing any increase in blood sugar. Withdrawal of DBI was a signal for the return of insulin requirement to its previous level.

In 3 cases the side-effects were so severe as to necessitate abandonment of DBI treatment. One case which had failed on a regime of 40 units of Lente insulin plus 50 mg. of DBI thrice daily, improved to fair control when tolbutamide was substituted for both these drugs. The patient, a female aged 60 years, had been diabetic for 10 years and had been poorly controlled on either tolbutamide or chlorpropamide, improved to the fair category on 25 units of Lente plus 75 mg. of DBI daily. Four poor-category cases were labile diabetics who had experienced both hypo- and hyperglycaemic coma. Administration of DBI did not in any way alter their liability, and they remained poorly controlled.

Tolbutamide Group

Eight cases (all females) had previously been treated unsuccessfully with tolbutamide. Their ages ranged from 41 to 69 years and the duration of diabetes from 2 to 19 years. Three were obese and 5 were medium in build. Transfer to DBI alone was sufficient to improve control to good in 1 case and fair in another. A further case improved to fair when DBI 75 mg. daily, was added to tolbutamide, 0.5 g., 3 times daily.

Two cases improved to the fair category on DBI plus insulin (20 and 10 units respectively), but showed no improvement on DBI alone.

The remaining 3 cases showed no alteration in control when switched to DBI therapy.

Side-effects

Twenty-one cases experienced side-effects. These were so severe in 6 cases as to necessitate discontinuation of treatment.

The side-effects noted were as follows: Dry mouth in 3 cases, bitter taste in 4 cases, abdominal discomfort and cramp in 3 cases, abdominal distension in 2 cases, nausea.
in 7 cases, vomiting in 4 cases, hiccup in 1 case, diarrhoea in 4 cases, faintness and dizziness (not related to hypoglycaemia) in 8 cases, malaise in 4 cases, headaches in 3 cases, and loss of weight in 1 case.

In 6 cases the side-effects gradually disappeared despite a constant dosage. In 4 other cases reduction in dosage alleviated the side-effects, and in 1 other case these disappeared when dosage was reduced and did not recur when DBI was increased to its original dosage after a period of 1 month. The remainder were able to continue treatment in spite of side-effects.

Laboratory Investigations
Blood counts, erythrocyte-sedimentation rates and liver-function tests did not show any significant changes during the period of this trial.

DISCUSSION
DBI has a definite hypoglycaemic action which was found to occur after the administration of the first dose in some cases, but only after continued administration over a period of several days in others. This delayed type of reaction is shown in Fig. 1. Single doses of the drug have shown a hypoglycaemic response in 4 hours, maximal at 6 hours, and almost disappeared in 10 hours.11

Experimental studies have suggested that DBI lowers blood-sugar levels by promoting anaerobic glycolysis with increased glucose utilization by the tissue, and by causing decreased gluconeogenesis with decreased output of glucose from the liver. In contradistinction to insulin, DBI leads to a decreased muscle glycogen concentration.12,13 While it produces a definite hypoglycaemia in depancreatized and in alloxanized animals, it has a much greater effect in those in which the pancreas is present.13

The clinical studies reported here show that DBI has a mild blood-sugar lowering effect. Six out of 9 cases previously on a 'diet only' regime graduated to the good category while on DBI. Insulin-treated cases did not respond so well. In only 2 of these was it possible for DBI to replace the total 10 and 15 units of insulin which were required to control the diabetes effectively. Partial replacement of insulin by DBI was possible in a further 7 cases. Thus, 2 cases improved from poor to good and 3 from poor to fair while insulin requirement was reduced by not more than 10 units. Eight cases remained under poor control, but insulin requirement was 20 and 30 units less, while the blood sugar remained constant.

Thus, the maximum amount of insulin replaced, in this series, was 30 units. The effect of DBI must, therefore, be considered to be mild and owing to side-effects it was found impossible to continue treatment with dosages larger than 150 mg. daily; with this dosage no marked hypoglycaemic symptoms were noted.

Twenty-one of the 29 cases experienced side-effects—a high incidence for a drug which must be used over a prolonged period. In 6 cases these effects were so severe as to warrant discontinuation of treatment. The side-effects were mainly gastro-intestinal, but patients often felt depressed and 'miserable' as a result.

While reduction in dosage or the passage of time were sufficient to allow these symptoms to disappear in 10 cases, the frequent side-effects suggested that the drug could have only a limited use. On the other hand no haematologic, hepatic or renal complications were found in any patient in this group of cases treated for periods up to 1 year. Ketonuria has been reported coincidentally with the elimination of glycosuria, but this was not noted in our series. This
type of ketonuria has been referred to as 'starvation ketonuria' and can be eliminated by reduction in DBI dosage
or by a liberal intake of carbohydrate. Hall et al. 11 have suggested that carbohydrate oxidation is not completely
rectified even when the drug has reduced the blood-sugar level to normal.

It has been suggested that one of the uses of the drug is
control of the labile diabetic by means of DBI and insulin. 8
In the 4 cases studied no such stabilizing effect was noted,
the lability being uninfluenced.

In 1 of 8 cases where tolbutamide had failed, DBI was
able to improve control to such an extent that the case could
be placed in the good category. DBI plus insulin was able
to take over effective control in several other cases, but a
slightly larger dose of insulin alone could have done this.

Where tolbutamide alone was ineffective, a combination of
DBI with tolbutamide improved control to the fair category
in 1 case. This is one use of DBI which merits further
investigation in the patient who would prefer oral diabetic
therapy.

CONCLUSIONS

Our experience in a middle-old-age group of diabetics points
to DBI being a mild hypoglycaemic agent which is prone to
give rise to side-effects, mainly gastro-intestinal in type.
While reduction of blood sugar to normal limits is possible
in mild cases, DBI alone is unable to control the severe
diabetic. In the latter type a combination of DBI and
insulin can allow of smaller doses of insulin being adminis-
tered, but in most cases this would have no advantage over
giving larger doses of insulin alone. We have been unable
to substantiate the claim that DBI is useful in stabilizing
labile diabetes. The possibility, however, exists that a com-
bination of tolbutamide or chlorpropamide with DBI may
improve control in some stable cases, and particularly
where control deteriorates after initial successful stabilization
with tolbutamide. It is apparent that DBI has only a
limited use in the treatment of diabetes.

SUMMARY

1. Twenty-nine diabetics in the middle-old-age group were
treated with phenethyldiguanide (DBI) for periods up to
1 year.
2. Side-effects, mainly gastro-intestinal, were noted in
21 cases. In 6 cases these side-effects necessitated discon-
tinuation of treatment.
3. DBI was able to replace a maximum of 30 units of
insulin.
4. DBI alone was unable to control severe diabetes
although reduction in insulin dosage was possible by means
of combined therapy.
5. In 4 cases of labile diabetes DBI did not exert any
stabilizing effect.
6. The suggestion is made that combined therapy with
other oral anti-diabetic drugs may prove useful.
7. DBI has only a limited use in the treatment of diabetes
mellitus.

We wish to thank the U.S. Vitamin and Pharmaceutical
Corporation for generous supplies of DBI, and Sister D. E. Maxwell.
Dr. S. Kramer and the Photographic Department of the
Department of Medicine, University of the Witwatersrand, for their
kind cooperation.

REFERENCES

(N.Y.), 95, 190.
2. Williams, R. H., Tyberghein, J. M., Hyde, P. M. and Nielsen, R. L. (1957):
Metabolism, 6, 311.
95, 29.
95, 345.

UNIVERSITY NEWS : UNIVERSITEITSNUS

UNIVERSITEIT VAN PRETORIA

By die Promosiepleegteilig op 18 en 19 Maart 1960 is die volgende grade en medailles toegeken:

Graad van Baccalaureus in Geneeskunde en Strykunde

Bedford, Michael Charles
Booysen, Frederik Jacobus Zacharias
Botha, Cyril Vincent
Botha, Johan
Bouwer, Ernest Louwrens
Brody, Hubrecht van Dalsen
Buitendag, Gert Stephanus
Christ, Helmut Horst
Cloete, Adéo (met loot in Kindergenees-
kunde)
De Beer, Marius Gerard
De Kock, Michiel Johannes
De Muileneme, Luc Georges Alice Gustave
Ruith
De Villiers, Theodore Heinrich
Erlink, Johann Duncker
Ferreira, Augusto Franciso
Fichardt, John Barry (met loot in Obstetrie
en Ginekologie)
Finestone, Abe
Griesel, Petrus Johannes Casparus
Grobbeelaar, Johannes Jacobus
Groenevald, Johannes Hendrik
Groenevald, Johannes Wilhelmus
Hack, Maureen (met loot in Kindergenees-
kunde)
Hattingh, Colombé Madeleine
Heuer, George Klee
Hills, Edwin Hennemann
Hugo, Paulina Maria
Jacobs, Christina Johanna
Jooste, Jacobus Andries
Joubert, Petrus Gerhardus (met loot in
Radiologie)
Kotze, Johannes van Zyl
Kriel, Johannes Nicolaas
Le Roux, Daniel Bartholomeus Hugo
Lindeque, Petrus Johannes
Louw, Jacobus Adriaan
Lups, Anna Hindrika Jacoba
Malan, Petrus Jacobus
Myburgh, Dirk Petrus
Nell, John Hay
Ockerse, Albert Bekker
Pio, Abraham Hendrik Ludolf
Pretorius, Francois Johannes
Roussouw, Alewyn Petrus
Saayman, John Henry Moodie
Scholtz, Hermanus Berhardus
Secie, Rosemarie Ruth Cathrina Clara
Smitt, Bérend Jakobus
Snyman, Philipus Johannes Nicolaas Horn
Steyn, Philipus Johannes (met loot in Interne
Geneeskunde, Obstetrie en Ginekologie
en Kindergeneeskunde)
Stronkorst, Johannes Hendrikus
Theron, David Francois