POSSIBILITIES OF MODERN ORAL DIABETES THERAPY*

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The usefulness of oral antidiabetic therapy in the aged diabetic is well known, and this form of therapy is indispensable if difficulties exist in connection with insulin application; for example, due to defective vision, intellectual disturbances and manual clumsiness. This article deals with problems and possibilities of oral therapy, especially with the new sulphonylurea preparation glibenclamide (HB 419), and also with the combined therapy with biguanides in patients whose diabetes is refractory to treatment with either of the compounds alone. Bänder and colleagues[2] in 1966 described the hypoglycaemic effect of glibenclamide. We wish to point out the peculiarities in the mode of action and in the clinical effect of HB 419, as demonstrated by several investigators and by ourselves.

STUDIES ON THE SULPHONYLUREAS

The correlation between blood level of sulphonylurea and blood sugar decrease demonstrated earlier exists also for glibenclamide, as Schmidt and I[26] have shown. We determined blood levels and urinary excretion of ^{14}C-labelled HB 419 in healthy subjects after a single oral dose of different samples of the drug at various dose levels (Fig. 1). Blood glucose was determined at the same time. Accord-

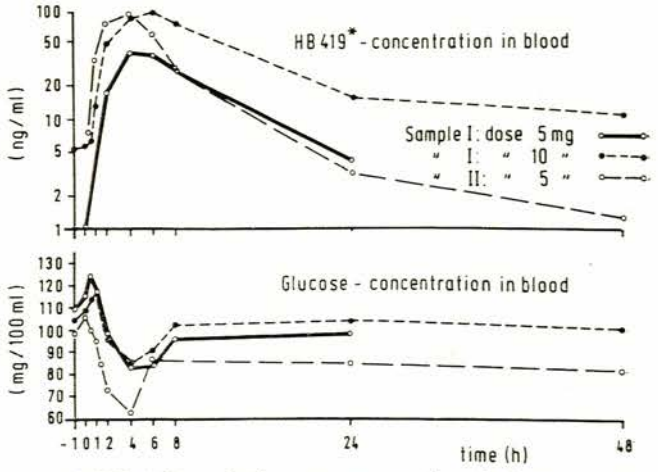

Fig. 1. HB 419* and glucose concentrations in blood after giving different doses and samples by mouth.[26]

ing to the amount of HB 419 administered, the maximum HB 419 concentration in the blood was reached after 4 or 6 hours, depending on the dose. The peak coincided with the minimum blood sugar concentration. The delayed blood sugar fall in our experiments by comparison with that found by other investigators is explained by

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the fact that we used the Gerritzen-method, giving two biscuits hourly from 7 a.m. to 4 p.m.

As in the treatment with carbutamide, tolbutamide and chlorpropamide, the mechanism of action is based on the influence on the β-cells of the islets of Langerhans with the release of stored pancreatic insulin. This is demonstrated by the increase of plasma insulin following administration of sulphonylureas (Fig. 2), and by typical morphological changes with pronounced degranulation of the cells. Bänder *et al.*[3] have recorded convincing light-optic-morphological pictures. These studies have recently been extended to ultramicroscopic investigations[14] (Fig. 3) and to studies on isolated islets.[21] In the rat,

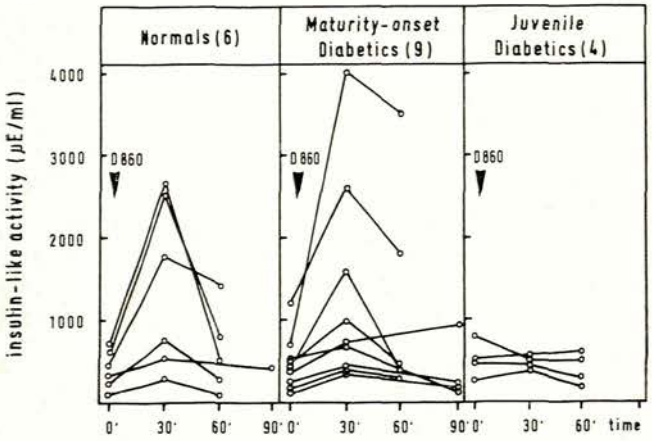

Fig. 2. Mean of insulin-like activity levels in different groups of human subjects after tolbutamide (Orinase) 25 mg/kg intravenously. (Pfeiffer *et al.*, 1959).

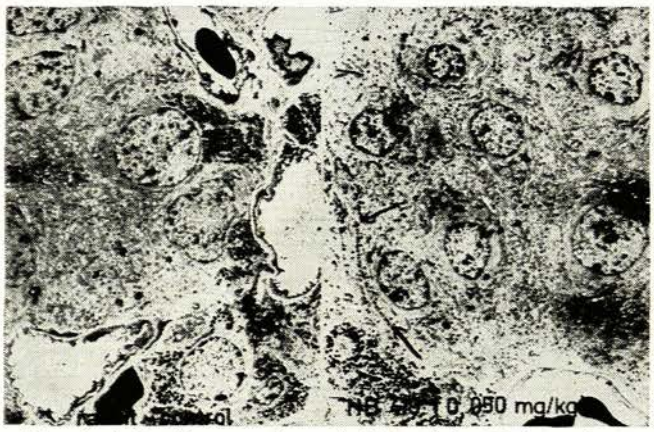

Fig. 3. Left: Survey view of islet of Langerhans in a normal rabbit. Alpha- and β-cells are in close relation to the capillaries.
Right: Degranulation of several β-cells in an islet of a rabbit treated with HB 419. Note the concentration of secretory granules along the plasma membrane (arrows) magnification 4375×.[14]

degranulation of β-cells and enlargement of Golgi complexes become apparent only after application of 10 or 20 times the minimal effective dose of HB 419. In the rabbit, the application of twice the minimal effective dose leads to significant degranulation, which becomes manifest after 24 and 48 hours. Fig. 3 shows degranulation of several β-cells with concentration of secretory granules along the plasma membrane. All these described alterations are morphological signs for release of insulin from β-cells.

Much work has been done in order to study insulin secretion following administration of tolbutamide and glibenclamide and glucose in diabetic and non-diabetic human subjects.[24] Fig. 4 shows the differences between blood sugar decrease and the rise in insulin serum after the administration of tolbutamide and glibenclamide. In contrast to the observations made with tolbutamide, HB 419, injected three times within 3 hours (Fig. 5), has no diminishing effect on the insulin secretion after the first two injections; after the third, the insulin secretion is reduced, but not significantly. The combined HB 419 - glucose injection leads to an enormous release of insulin.

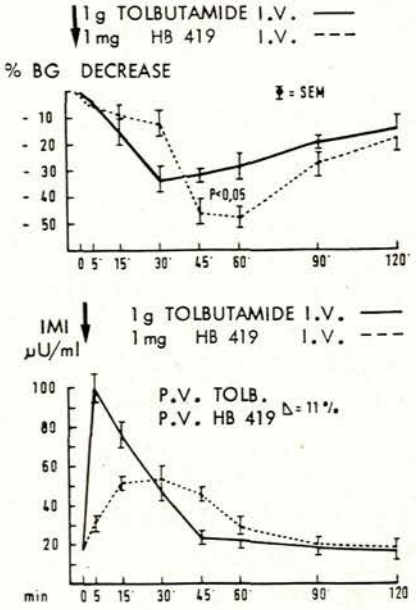

Fig. 4. Effect of intravenous tolbutamide and HB 419 on blood glucose (BG) and serum insulin (IMI) in normal subjects (n=15).[24]

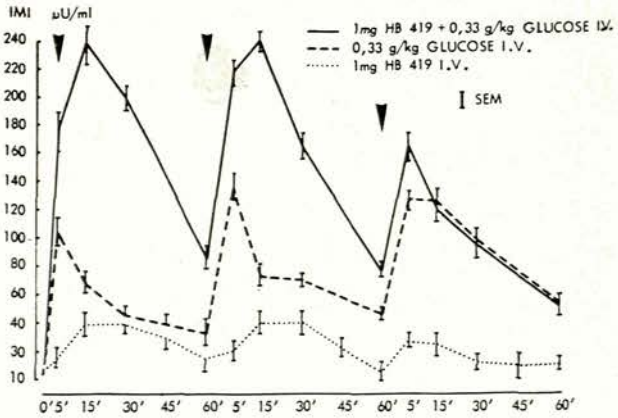

Fig. 5. Dynamics of insulin secretion after repeated intravenous doses of HB 419, glucose, and HB 419 + glucose in normal subjects (n=6).[24]

Three patients, in whom tolbutamide had practically no effect on the insulin or on blood sugar levels, showed with HB 419 a release of insulin and a decrease of blood sugar (Fig. 6). An additional dose of 50 g carbohydrate given orally ½-hour before the HB 419 injection intensifies the insulino-tropic effect. Finally, the repeated injection of tolbutamide at 4-hour intervals in diabetics (Fig. 7) causes only a very slight increase in insulin and practically no decrease in blood sugar, whereas an increase in insulin and decrease in blood sugar to the same extent as after the first injection was seen after HB 419. It is worth while mentioning that this new substance has also a marked effect in regard to the fat metabolism: we could demonstrate (Figs. 8 and 9) after HB 419 administration a significant reduction of free fatty acids and glycerol as signs of an antilipolytic insulin effect, while the cholesterol did not show any changes.[25]

The results on the dynamics of insulin secretion in diabetic and non-diabetic humans were extended by Fussgänger *et al.* of the Pfeiffer group.[9] These were also confirmed by comparative studies on the perfused isolated rat pancreas and the perfused isolated pieces and islets of rat pancreas (Fig. 10). Perfusion with low glucose concentration, to which sulphonylureas were added, responded to tolbutamide with a rapidly occurring peak in insulin secretion, subsiding despite addition of tolbutamide to the perfusion medium; HB 419, on the other hand, induced a more sluggish and lower but persisting and increasing enhancement of insulin liberation. These findings were interpreted as indicating a qualitatively rather than quantitatively different β-cytotropic action of tolbutamide and HB 419. They are similar to the diffe-

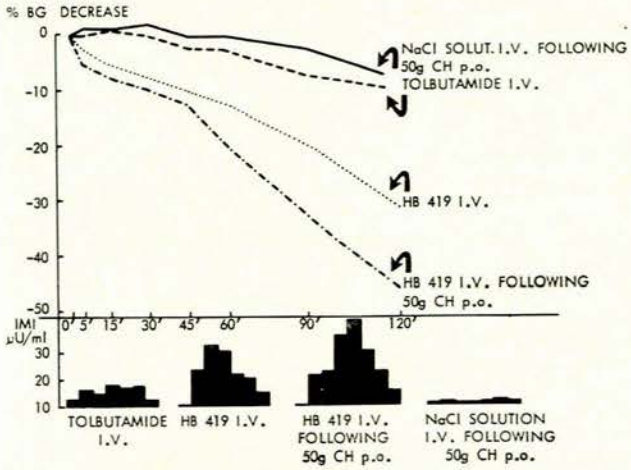

Fig. 6. Blood glucose (BG) and serum insulin (IMI) in adult-onset diabetics (n=3) after intravenous injection of tolbutamide, HB 419, and HB 419 preceded by oral intake of 50 g of carbohydrates.[24]

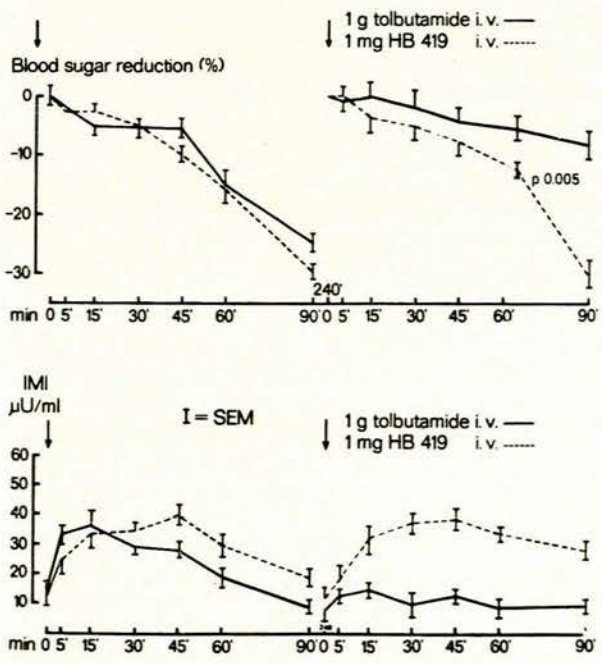

Fig. 7. Changes in blood sugar and serum insulin after two intravenous injections of tolbutamide or HB 419, 4 hours apart, given to 10 maturity-onset diabetics of normal body-weight.[24]

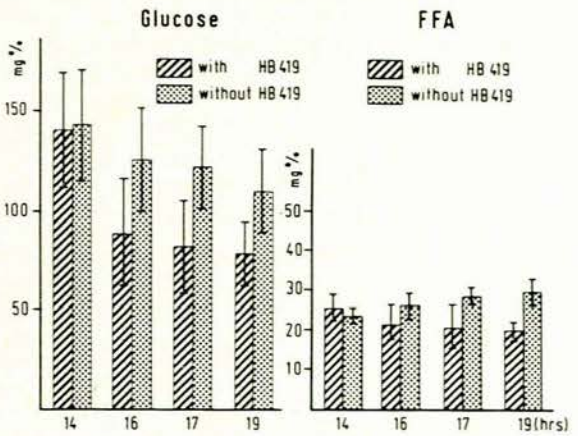

Fig. 8. Changes in the metabolites, glucose and free fatty acids, before and after administration of HB 419.[25]

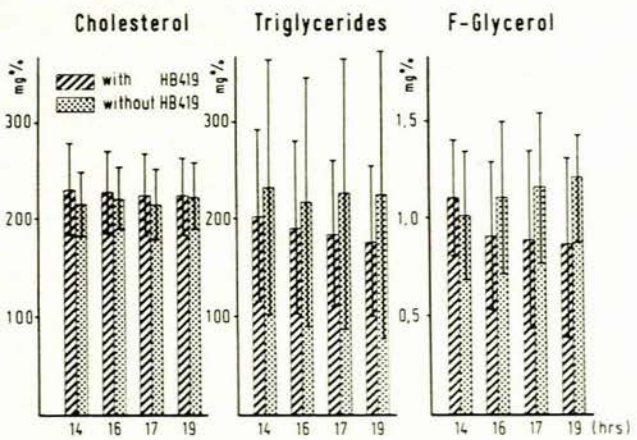

Fig. 9. Changes in cholesterol, triglycerides and glycerol before and after administration of HB 419.[25]

rences seen with the two sulphonylureas on both plasma insulin and blood glucose as mentioned before.

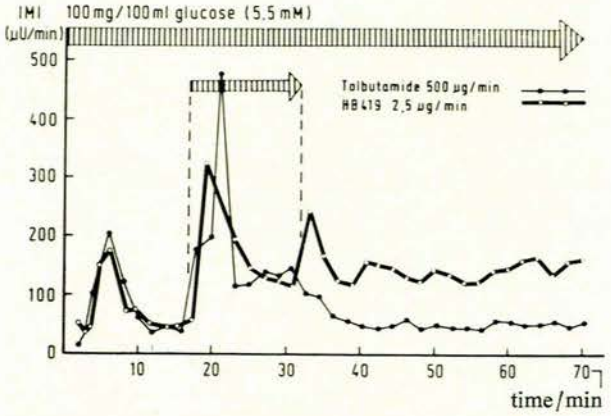

Fig. 10. Effect of tolbutamide 500 μg/min and HB 419 (glibenclamide) 2·5 μg/min on insulin secretion by the isolated perfused rat pancreas. Basal glucose concentration 100 mg/100 ml, 5·5 mM.[9]

Otto[21] has compared blood glucose and plasma insulin (IMI) levels in 10 healthy subjects after oral or intravenous administration of HB 419 and tolbutamide. In Fig. 11 the two values are shown after oral administration of HB 419 solution: the fall in blood sugar follows 10 - 20 minutes after the changes in insulin level. After intravenous injection of 2 mg HB 419 or 1 g tolbutamide the blood sugar fall is the same as before; only the action of glibenclamide is slower and more prolonged. The serum curves after intravenous application of 1 g tolbutamide and after 2 mg glibenclamide (Fig. 12) show striking

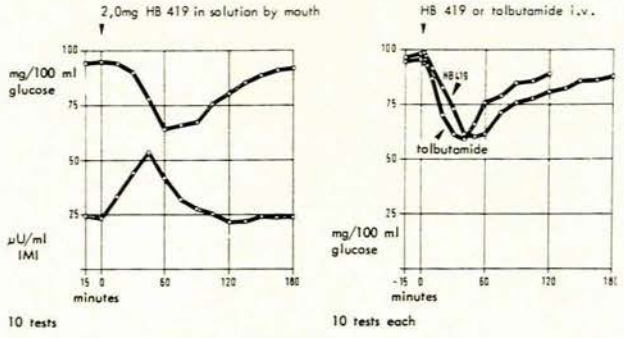

Fig. 11. Blood glucose and plasma insulin after oral and intravenous administration of tolbutamide or HB 419.[21]

differences between the substances: the peak rise in insulin concentration after tolbutamide is reached 1 minute after the end of the intravenous injection; after HB 419 the insulin discharge is slow, sustained and plateau-shaped, closely corresponding to the fall in blood sugar. Also, the two substances cause vigorous discharge of insulin from the pancreas, but there are clear-cut differences in the timing of the response.

The effect of prolonged glibenclamide therapy on insu-

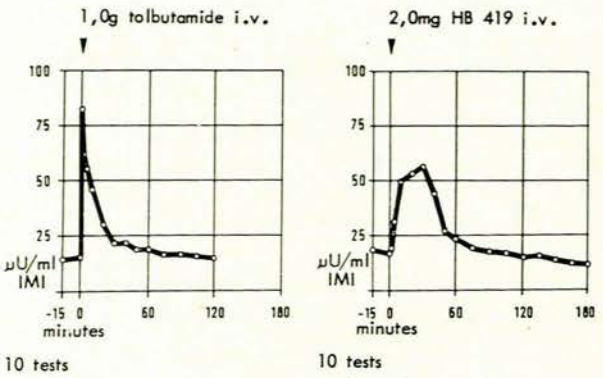

Fig. 12. Serum insulin curve after intravenous injection of 1 g tolbutamide and 2 mg HB 419.[21]

lin secretion following glucose loads was studied by Chandalia and co-workers[7] in 4 maturity-onset diabetics (Fig. 13). The 'lag phase' of insulin secretion was not corrected

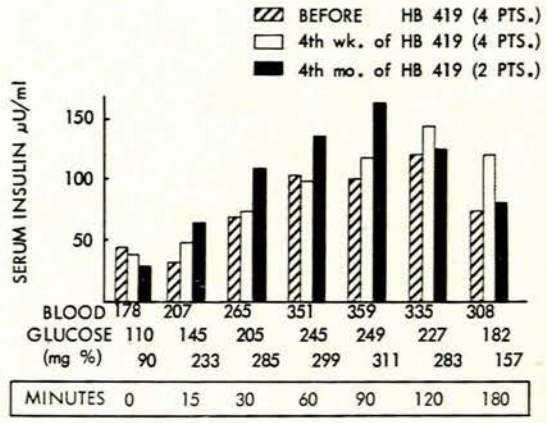

Fig. 13. Mean blood glucose and serum insulin levels during oral GTT before and after HB 419 therapy.[7]

following HB 419 therapy. The highest insulin levels were attained at 90 or 120 minutes during oral glucose-tolerance tests before as well as after HB 419 therapy. The glucose tolerance improved in all patients following therapy. The insulin levels after oral GTT increased during the fourth week and fourth month of therapy. Jackson[13] has shown similar results with chlorpropamide.

Indications

Having discussed this interesting new substance from the pharmacological and clinical point of view, we are now going to deal with some special therapeutic problems connected with sulphonylurea therapy. First of all the question arises, of course, under what circumstances the application of the new sulphonylurea substance is indicated. We feel that some failures and disappointments experienced initially were due to wrong indication and premature application. In view of our own experience of 1½ years and the general opinion held today, the diabetic who is in good control with the conventional sulphonylureas should be left for the time being on this

treatment. The decisive factor is that the criteria demanded for oral therapy—excellent or good control—are attained (Table I).[20]

TABLE I. CRITERIA FOR DEGREE OF CONTROL

Control	*Blood sugar (true glucose) (mg/100 ml)*	*Glucosuria/24 h*
Excellent		
Fasting	100	
1st hour postprandial	150	Neg.
2nd hour postprandial	130	
Good		
Fasting	130	
1st hour postprandial	180	Up to 5 g
2nd hour postprandial	150	
Fair		
Fasting	150	
1st hour postprandial	200	Up to 10 g
2nd hour postprandial	180	
Poor		
Fasting	220	
1st hour postprandial	280	Up to 30 g
2nd hour postprandial	250	

In view of what you have heard to date about the pharmacology of glibenclamide, it is justifiable, however, to carry out a therapeutic trial with this substance in all cases where the patients are no longer optimally controlled on the therapy currently applied. In such cases, one should start with a dose of 5 mg. The impression that has been gained is that more maturity-onset diabetics, whose management is the domain of the sulphonylureas, can be successfully treated with the new product than with earlier sulphonylureas. Generally, we prescribed up to 10 mg glibenclamide (2 tablets) to be taken in a single dose in the morning. Only if a dosage of 15 mg was necessary for the control and compensation of diabetes, was a third tablet administered in the evening.

Side-Effects

Let us now take a look at the problem of the side-effects of sulphonylurea therapy. We know that with the substances formerly used these amounted to between 2 and 3%, and consisted in the main of allergic skin reactions, and, less frequently, of intestinal complaints. Sometimes there may be considerable and prolonged hypoglycaemias, for instance in patients with renal insufficiency that results from delayed excretion and accumulation of the substance in the organism.[12] Also serious consuming processes with glycogen depletion of the liver, such as liver cirrhosis, adrenal insufficiency and postoperative stress, encourage the development of hypoglycaemia. Moreover, alcohol can have the effect of promoting hypoglycaemia if sulphonylureas are taken at the same time, which, in connection with traffic accidents, for instance, may be of great significance.

One extremely important factor is to be found in the fact that serious hypoglycaemias during sulphonylurea therapy may occur as a result of other medicaments being administered simultaneously. These in turn have a hypoglycaemia-promoting action due to the fact that they considerably prolong the half-life time of the sulphonylureas (Tables II and III). These tables list a number of such substances and demonstrate a prolongation of

TABLE II. DRUGS PROLONGING HALF-LIFE OF TOLBUTAMIDE[1]

Half-life before drug (hours)	*Drug combined with tolbutamide*	*Half-life prolonged to (hours)*	*References*
8	Sulphaphenazole 1 g/day	24	Dubach *et al.*
5-6	Sulphaphenazole 2 g/day	24	
4	Sulphadimethoxine 2 g/day	4	
7	Sulfisoxazole 2 g/day	7	
4	Sulphaphenazole 2 g/day	17	Christensen
6½	Dicoumarol (plasma level 1·2 µg/ml)	18	Christensen & Mølholm Hansen
4½	Dicoumarol (plasma level 1·2 µg/ml)	10	
3·3	Dicoumarol (plasma level 1·2 µg/ml)	10	
4½	Dicoumarol (plasma level 1·2 µg/ml)	17	
5	Dicoumarol (plasma level 10·8 µg/ml)	24	
6½	Dicoumarol (plasma level 10·8 µg/ml)	25	
2·8	Dicoumarol (plasma level 10·8 µg/ml)	17·6	
11·6	Dicoumarol 50 mg/day	?	Solomon
6·5	Dicoumarol 50 mg/day	14·6	
4	Phenyramidol 400 mg 3 × day	15	
8	Phenyramidol 400 mg 3 × day	17	
9	Phenyramidol 400 mg 3 × day	22	

TABLE III. TOLBUTAMIDE HALF-LIFE IN BLOOD BEFORE AND AFTER TREATMENT WITH DIFFERENT DRUGS[25]

Drug tested	*No. of persons tested*	*Half-life of tolbutamide (hours)*	
		Before treatment	*During treatment*
Sulphaphenazole	4	3¾	22
Methylsulphaphenazole	5	4¾	37½
Ethylsulphaphenazole	5	4¾	32¾
Phenylbutazone	6	4½	10½
Oxyphenylbutazone	5	4¾	12
Sulphadiazine	4	3½	5½
Sulphadimethoxine	5	5	2¾
Phenazone	3	4¾	5
Aminophenazone	2	4¼	5¼
Dicoumarol	8	5	17½
Phenindione	3	5½	6

the half-life times, which is in part quite considerable when tolbutamide is used.

Shock symptoms do not differ from those arising from the use of long-acting insulin, but the hypoglycaemic effect is considerably longer in duration and can vary from hours to several days. Hence a condition of shock may occur even after sulphonylurea treatment has been withdrawn and patients must be kept under careful observation for several days after the first shock event. The hypoglycaemic reaction is very frequently associated with neurological focal symptoms, sometimes arising as a transient hemiparesis which at first resembles that of a cerebrovascular attack, and causes delay in the initiation of correct therapy.

For the study of the side-effects following glibenclamide administration, Retiene *et al.*[25] from the Schöffling clinic carried out extensive investigations based on blood picture controls, etc., effected during an 18-month period. None of the patients developed incompatibility or toxic side-effects due to the drug (Fig. 14).

Secondary Failures

The principal reason for their occurrence is, as is known, that the insulin content of the pancreas diminishes in the course of life, and hence also the possibility of stimulating the secretion of insulin by means of the sulphonylureas. In connection with this, Balodimos *et al.*[4] have made an interesting contribution (Fig. 15). On the basis of a 9-year study with tolbutamide, they found that the proportion of secondary failures averaged 19·6%, and, from the second year on, accounted for approximately

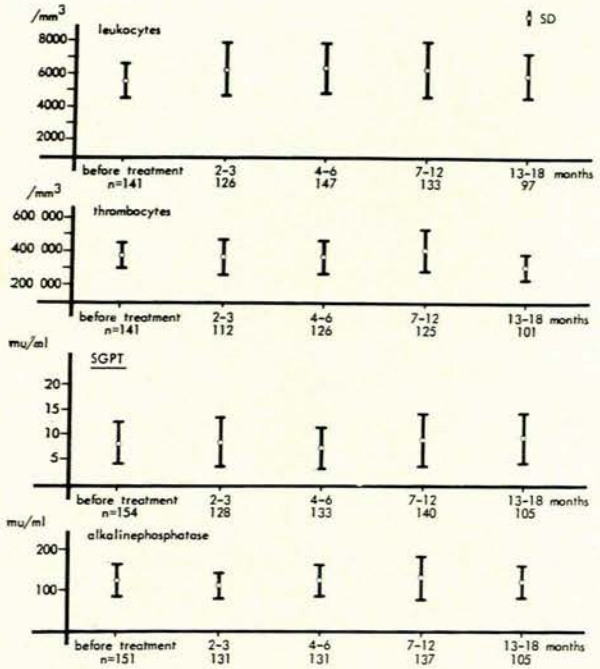

Fig. 14. Mean values of leucocytes, thrombocytes, alkaline phosphatase and SGPT throughout an 18-month clinical study with glibenclamide.[25]

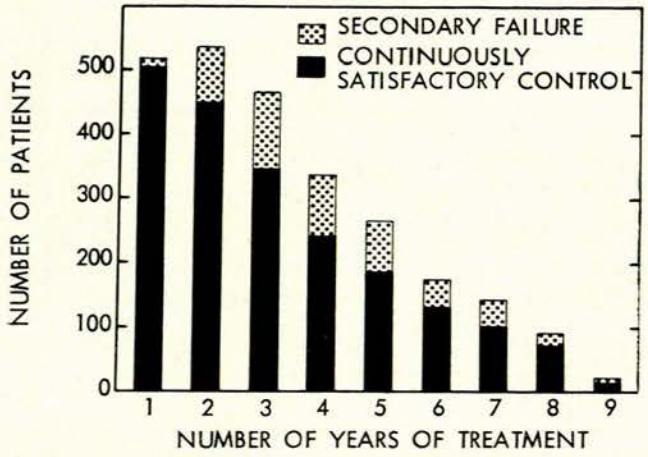

Fig. 15. Number of patients with continuously satisfactory control and secondary failure in each year of tolbutamide therapy.[4]

one-quarter of all patients treated. The statistics furthermore very clearly show the progressive decline in the number of optimally controlled diabetics in the course of the years.

The combination of sulphonylureas with insulin should be restricted to individual cases. Additional doses of sulphonylureas may undoubtedly give rise to an increased endogenous release of insulin, also in the case of diabetics treated with insulin, so that the exogenous administration of insulin can be reduced. The combined therapy of sulphonylureas and biguanides will be discussed later.

BIGUANIDES

Biguanides differ completely in their mode of action from sulphonylureas and certainly represent a true extension to the scope of diabetes therapy (Fig. 16). Beckmann[5] has

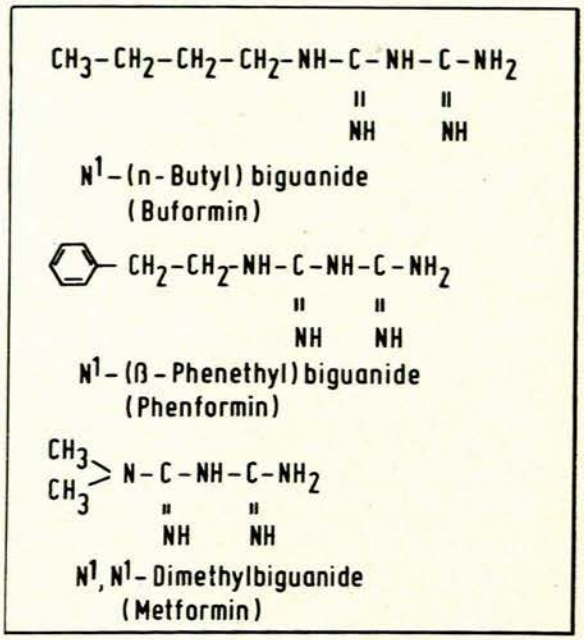

Fig. 16. The formulae of buformin, phenformin and metformin.

shown that the effective dose of buformin is 2 mg/kg, that of phenformin is 1 mg/kg and that of metformin is 20 mg/kg. He also demonstrated that the hypoglycaemic action of these substances differs widely between different animals and that the dose that reduces the blood sugar by 50% in animals is almost identical with the LD_{50}. Suicide attempts have indicated that humans can, in contrast with animals, tolerate more than 20 times the therapeutic dose and this is yet another instance where the results of animal trials do not correlate well with results achieved in man.

The essential difference between the metabolically healthy subject and the diabetic is set out in an article by Madison and Unger,[26] in which the effect of phenformin on the glucose concentration in the arterial and venous blood of diabetics and healthy persons is compared and no effect is seen in healthy persons (Fig. 17). It is of particular interest that biguanides improve glucose utilization, i.e. increase sensitivity to insulin, despite a reduced plasma insulin concentration; this is in direct contrast with sulphonylureas. Evidence of this is given in the next two illustrations. In Fig. 18 Grodsky and co-workers[10] have demonstrated the effect of phenformin on the blood glucose level and immuno-reactive insulin in 4 obese maturity-onset diabetics after an oral glucose load of 50 g. Before the second load the patients received 10 times 50 mg phenformin-retard at 8-hourly intervals; the blood glucose and the IRI declined during biguanide therapy. In a subject with a strong family history of diabetes (Fig. 19) levels of circulating insulin were noted after

administration of glucose by mouth, despite the presence of a normal glucose-tolerance curve. After treatment with phenformin, levels of serum insulin subsequent to oral glucose administration were all lowered.

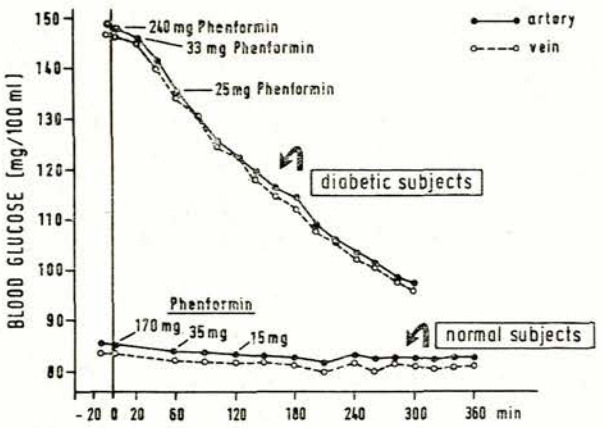

Fig. 17. Effect of phenformin on the glucose concentration in arterial and venous blood of 7 diabetic and 5 healthy subjects.[16]

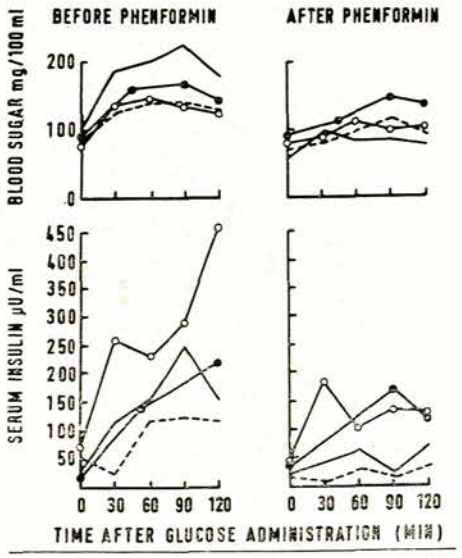

Fig. 18. The effect of phenformin on levels of serum insulin and blood glucose after oral administration of 50 g glucose to 4 obese maturity-onset diabetic subjects.[10]

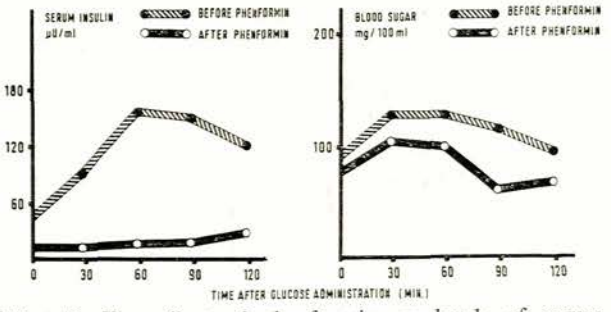

Fig. 19. The effect of phenformin on levels of serum insulin and blood glucose after oral administration of 50 g glucose to a non-obese, non-diabetic 'normal' male with a strong family history of diabetes mellitus.[10]

Berger *et al.*[6] showed that 11 patients who had received a 7-day preliminary treatment with phenformin performed better in a glucose-tolerance test after a 100-g glucose load despite a lower plasma insulin concentration. Thus biguanides improve glucose utilization through increased sensitivity to insulin. Other explanations of the mode of action of the biguanides are an impairment of intestinal glucose absorption[8] and inhibition of gluconeogenesis by the liver.

The importance of biguanides in monotherapy and combined therapy is largely due to the work of Mehnert.[17,18] Monotherapy with biguanides can occasionally bring good metabolic control in overweight maturity-onset diabetics. Additional biguanide therapy should, however, certainly be attempted particularly for those patients in whom sulphonylureas are no longer achieving adequate metabolic compensation. Biguanides extend the scope of therapy quite considerably, and have spared many patients temporarily or permanently from the necessity of insulin therapy. This has been recognized by the various pharmaceutical manufacturers who have developed drugs containing fixed combinations of both active substances. We ourselves are now working with a combination of both glibenclamide and phenformin as was described in 1969 by Schneider at the International Tegernsee Conference.[27] The great disadvantage of earlier biguanide preparations —their poor intestinal compatibility—has been largely removed through the development of long-acting preparations and reduction of the single dose.

Fig. 20 from the work of Mehnert and Krall[19] demonstrates the value of combination therapy in patients for whom diet or tolbutamide or Silubin alone were unsuccessful, the optimal result being only achieved with a combination of these three. Finally, two other opportunities to use biguanides are worthy of note: in insulin resistance and labile diabetes, especially in young diabetics. Fig. 21 shows a case history of a patient receiving twice 60 units insulin per day and who had a urinary excretion of glucose of over 100 g/day and a blood sugar between

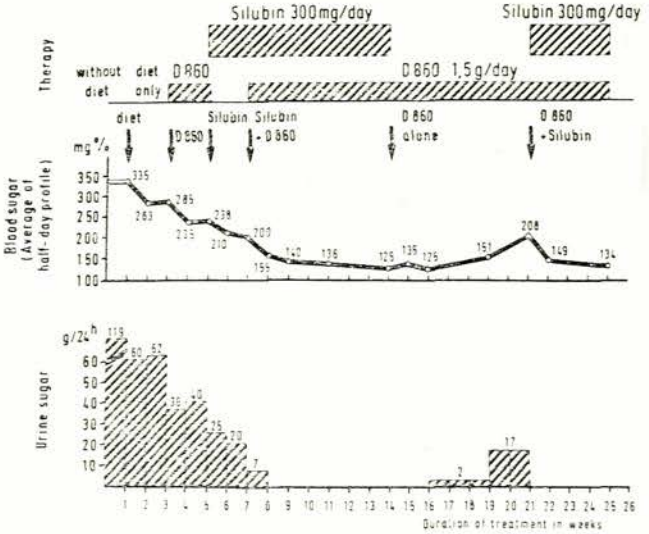

Fig. 20. Typical metabolism diagram of a patient on combined therapy with tolbutamide and biguanide.[19]

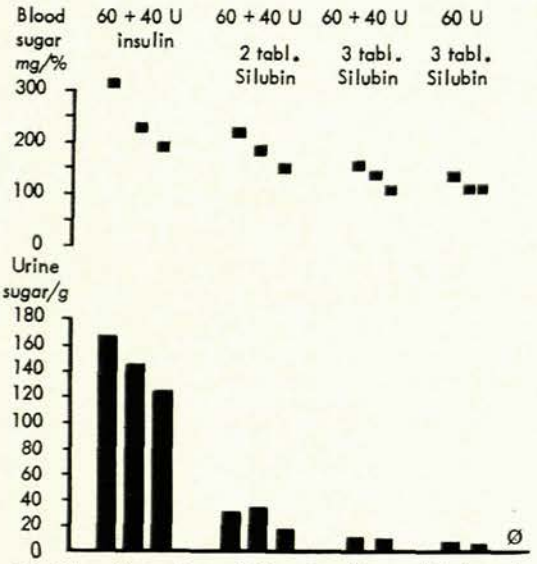

Fig. 21. The effect of combining insulin and buformin in insulin-resistant patients.[29]

200 and 300 mg/100 ml. The additional administration of Silubin then normalized the metabolic condition, and the insulin requirement fell back to 60 units per day.[29]

Opinions are divided regarding the management of labile diabetics, but the smoothing effect of biguanides on the fluctuating blood sugar of such patients is very frequently observed, particularly in the early stages of treatment.[22,23]

SUMMARY

The new sulphonylurea substance glibenclamide (HB 419) exhibits differences in its mode of action and its clinical effect in comparison with the conventional sulphonylureas. A stimulation of the insulin secretion is even possible in healthy subjects and diabetics in whom tolbutamide was found to have a significantly diminished effect on blood sugar decrease and plasma insulin. Studies on perfused isolated pancreas and islets in the rat, stimulated by tolbutamide or glibenclamide, showed different insulin release, and must be interpreted as indicating a qualitatively rather than quantitatively different β-cytotropic action of these substances.

The mode of application is discussed and reference made to side-effects, and, in particular, to factors that promote hypoglycaemia; the significance of drugs which influence and prolong the half-life times of sulphonylureas is also mentioned.

The biguanides have a completely different mode of action to that of the sulphonylureas, and certainly represent a true extension to the scope of diabetes therapy. The biguanides improve the glucose utilization and increase sensitivity to insulin, despite a reduced plasma insulin concentration. Other explanations of the mode of action are an impairment of intestinal glucose absorption and inhibition of gluconeogenesis by the liver. The combined therapy of biguanides with sulphonylureas extends the possibilities of oral diabetes therapy.

REFERENCES

1. Ariens, E. J. (1969): Acta diabet. lat., **6**, suppl. 1, 143.
2. Aumüller, V. W., Bänder, A., Heerdt, R., Muth, K., Pfaff, W., Schmidt, F. H., Weber, H. and Weyer, R. (1966): Arzneimittel-Forsch., **12**, 1640.
3. Bänder, A., Pfaff, W. and Schesmer, G. (1969): *Ibid.*, **19**, 1448.
4. Balodimos, M. C., Camerini-Davalos, R. A. and Marble, A. (1966): Metabolism, **15**, 957.
5. Beckmann, R. (1968): *Proceedings of the 2nd International Biguanide Symposium*, pp. 3 - 12. Stuttgart: Georg Thieme.
6. Berger, S., Downey, J. L. and Traisman, H. S. (1968): Ann. N.Y. Acad. Sci., **148**, 859.
7. Chandalia, H. B., Hollobaugh, S. L., Pennington, L. F. and Bosheli, B. R. (1969): Horm. Metab. Res., **1**, suppl., 73.
8. Czyzyk, A. (1969): Acta diabet. lat., **6**, suppl. 1, 636.
9. Fussgänger, R. D., Goberna, R., Hinz, M., Jaros, P., Karsten, C., Pfeiffer, E. F. and Raptis, S. (1969): Horm. Metab. Res., **1**, suppl., 34.
10. Grodsky, G. M., Karam, J. H., Pavlatos, F. C. and Forsham, P. H. (1963): Metabolism, **12**, 278.
11. Hellman, B. and Hellerström, C. *in* Pfeiffer, E. F. (1969): *Handbook of Diabetes Mellitus*, vol. I, pp. 89 - 118. Munich: J. F. Lehmanns Verlag.
12. Jackson, W. P. U. (1964): *On Diabetes Mellitus*. Springfield, Ill.: Charles C. Thomas.
13. Jackson, W. P. U. *in* Campbell, G. D. (1969): *Oral Hypoglycaemic Agents: Pharmacology and Therapeutics*. London: Academic Press.
14. Kern, H. F., Kern, D., Schmidt, F. H. and Stork, H. (1969): Horm. Metab. Res., **1**, suppl., 11.
15. Kristensen, M. and Christensen, L. K. (1969): Acta diabet. lat., **6**, suppl. 1, 116.
16. Madison, L. L. and Unger, R. H. (1960): Diabetes, **9**, 202.
17. Mehnert, H. (1963): 'Experimentelle und klinische Untersuchungen zum Wirkungsmechanismus und Indikationsbereich blutzuckersenkender Biguanidderivate', Habilitationsschrift, München.
18. *Idem* (1968): *Proceedings of the 2nd International Biguanide Symposium*, pp. 173 - 180. Stuttgart: Georg Thieme.
19. Mehnert, H. and Krall, L. P. (1960): Dtsch. med. Wschr., **85**, 577.
20. Müller, R., Bauer, G., Schröder, R. and Sato, S. (1969): Horm. Metab. Res., **1**, suppl., 88.
21. Otto, H. (1969): In *Tegernsee-Konferenz über das neue orale Antidiabetikum HB 419*. Frankfurt. Farbwerke Hoechst AG and Boehringer Mannheim GMBH.
22. Petrides, P. (1966): Dtsch. med. Wschr., **91**, 689.
23. *Idem* (1969): *Diabetes Mellitus*, pp. 229 - 232. Vienna: Verlag der Wiener Medizinischen Akademie.
24. Raptis, S., Rau, R. M., Schröder, K. E., Faulhaber, J. D. and Pfeiffer, E. F. (1969): Horm. Metab. Res., **1**, suppl. 65.
25. Retiene, K., Petzoldt, R., Althoff-Zucker, C., Beyer, J. and Schöffling, K. (1969): *Ibid.*, **1**, suppl., 55.
26. Schmidt, H. A. E. and Petrides, P. (1969): In *Tegernsee-Konferenz über das neue orale Antidiabetikum HB 419*. Frankfurt: Farbwerke Hoechst AG and Boehringer Mannheim GMBH.
27. Schneider, T. (1969): *Ibid.*
28. Schräpler, P., Petrides, P. and Yazdanfar, A. (1969): Med. u. Ernähr., **10**, 120.
29. Schricker, K. T. (1964): Med. Bild., **6**, 187.