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PATENT SPECIFICATION

NO DRAWINGS

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The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act 1949, are SEYMOUR LESTER SHAPIRO of 160 High Street, Hastings-on-Hudson, State of New York, United States of America, and LOUIS FREEDMAN of 29 Lawrence Park Crescent, Bronxville, State of New York, United States of America, both citizens of the United States of America.

COMPLETE SPECIFICATION

Biguanide Compositions

We, U.S. VITAMIN CORPORATION, a corporation organized and existing under the laws of the State of Delaware, United States of America, located at 250 East 43rd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a composition of matter and a manner for utilization thereof. More particularly it pertains to a composition which contains as the essential constituent a biguanide derivative and indicates correlated improvements and discoveries whereby a composition is provided which has the property of lowering blood sugar.

For many years the appropriate treatment of the hyperglycemia associated with diabetes mellitus has been through the use of injectible insulin. This method has been most satisfactory and has indeed prolonged the lives and sustained the good health of hundreds of thousands of diabetics. The use of injectible insulin has associated with it, however, certain reservations. Since the diabetic condition is a chronic one, it requires constant and, ordinarily, daily injection of insulin. It has been the practice to permit the patient to make his own injections and thus introduce the hazards of improper measurements and non-aseptic injection techniques. Insulin as now available is subject to deterioration on standing, and unless properly refrigerated, will lose its potency. An additional hazard associated with the use of insulin is that in the achievement of desirably long-acting insulins, suspensions of active insulin (NPH insulin) are frequently utilized, and improper resuspension of these insulins results in more or less than the indicated dosage being administered and measured as a volumetric dose of a varying suspended insulin.

There is also associated with the use of insulin the factor that the physical and emotional stress of day to day existence will require additional quantities of insulin. This entails an estimate by the physician or the patient of his forthcoming stress, or additional injections. Additional factors associated with the use of insulin are that it involves difficulties concerned with the patient's economic, psychological and mental levels which make proper therapy difficult using insulin injection. Insulin therapy by injection is also associated with great inconvenience for those individuals who are not at home and are confronted with the problem of aseptic injections of an injectible requiring constant refrigeration.

These objections could be overcome by an oral therapy which would lower blood sugar levels, and which would be in the form of tablets containing a stated quantity of an active/stable ingredient.

It is the principal object of the invention to provide a hypoglycemic composition which obviates the above-mentioned disadvantages that attend the use of insulin.

It is an object of the invention to provide a composition which upon oral ingestion will rapidly and effectively lower blood sugar levels for sustained periods.

It is a further object of the invention to provide a composition which can be readily, effectively and economically prepared and accurately measured, and which can be ad-

[*Price 3s. 6d.*]

ministered in regulated oral doses affording rapid and effective lowering of blood sugar levels.

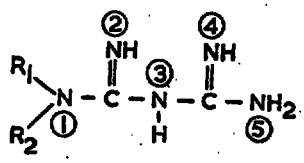
The biguanide compositions according to the invention have the property that their hypoglycemic effect can be rapidly reversed by the administration of glucose or other rapidly assimilable carbohydrate. It is well known that a hazard of insulin therapy is that of overdosage, which can lead to such a dangerous lowering of blood sugar levels that death results. The development of such a hypoglycemic response associated with insulin overdosage is correctable by administration of a carbohydrate. It is necessary also in oral therapy to have a similarly correctable pattern in the event of overdosage.

It is a particular object of the invention to provide hypoglycemic agents containing an organic material which is rapidly absorbed in effective amounts from the gastrointestinal tract, said organic material being an N^1-substituted biguanide.

The invention accordingly comprises a composition of matter possessing the characteristics, properties, and the relation of constituents which will be exemplified in the composition hereinafter described, and the scope of the invention will be indicated in the claims.

We have found that compositions containing certain biguanide derivatives and their salts are effective as oral hypoglycemic agents.

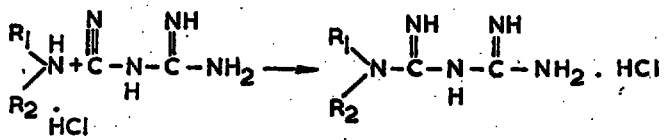
The substituted biguanides constituting the active ingredients of the compositions of the invention have the following general structure



in which R_1 is a straight chain saturated alkyl group containing 4 or 5 carbon atoms and R_2 is hydrogen (b) in which R_1 is phenyl-$(CH_2)_n$ where n is 1 or 2 and the phenyl radical group being substituted or unsubstituted, said may be substituted by one bromine, chlorine or methoxy and R_2 is hydrogen (c) in which R_1 is benzyl and R_2 is methyl or (d) in which R_1 plus R_2 constitutes a methylene chain joined at the nitrogen and containing 5 or 6 carbon atoms.

The biguanides are relatively strong bases and form stable salts with inorganic and organic acids and hence the invention also provides for the use of the biguanides in the form of their salts. These biguanides can be obtained and utilized in the form of acid addition salts. The acids which can be used to prepare acid addition salts are suitably those which produce, when combined with the free base, salts whose anions are relatively innocuous to animal organisms in therapeutic doses thereof so that the beneficial physiological properties inherent in the free base are not vitiated by side effects ascribable to the anions. Appropriate acid addition salts are those derived from inorganic acids, such as hydrochloric, hydrobromic, nitric, phosphoric and sulfuric acids, and from organic acids such as acetic, citric, malic, tartaric, lactic, glycolic and beta-ethoxypropionic acids, and from acidic nitrogen compounds of the type which form salts with the biguanide bases such as theophylline, 8 - chlorotheophylline, saccharin, phthalimide, benzoxazine-2,4 - dione, and substituted benzoxazine-2,4 - diones, oxazolidine - 2,4 -dione, 5-substituted oxazolidine - 2,4 - diones, 1-butyl - 3 - *p* - methylbenzenesulfonylurea, succinimide, barbituric acid, and substituted barbituric acids.

The biguanides, as will subsequently be exemplified, may be prepared by suitable methods. Some of the compounds used as starting materials for the synthesis of the biguanides are known and commercially available, whereas others can be prepared by known methods. Thus the fusion of equivalent quantities of an amine hydrochloride and dicyandiamide for 0.5—3.0 hours at 120—200° C. affords the hydrochloride of the biguanide as illustrated by the following general formula:



wherein R_1 and R_2 have the same meanings as hereinabove.

Usually, the hydrochloride can be isolated from the fusion mixture by recrystallization. Where the hydrochloride is obtainable only with difficulty or in poor yield, the treatment of an aqueous solution of the fusion mixture with an excess of aqueous sodium nitrate causes precipitation of the less soluble substituted biguanide - nitric acid salt, which can be purified. Alternatively, basification and cooling of an aqueous solution of the fusion mixture with strong sodium hydroxide precipitates the biguanide as the free base which can be separated and purified by recrystallization, and converted to the salt desired by

reaction with stoichiometric amounts of acid.

The following examples are illustrative of the compounds of the invention and of the procedure for their preparation.

EXAMPLE 1.

N^1 - β - ~~Phenylethyl - biguanide~~ hydrochloride.

15.76 g. of β - phenylethylamine hydrochloride and 8.4 g. of dicyandiamide were ground and intimately mixed. The mixture was heated in an oil bath in a 3-neck flask fitted with a thermometer and stirrer, and the mixture began to melt at a bath temperature of 125° C. and was completely fluid at 130° C. Further heating at 145—150° C. initiated an exothermic reaction and the temperature of the fusion mixture (156° C.) exceeded the oil bath temperature (150° C.) by 6°. Heating was continued for one hour at bath temperature of 148—150° C. The reaction mixture was cooled, dissolved in about 100 cc. of methanol and filtered. The methanol filtrate was concentrated under reduced pressure, cooled, and the product (β - phenylethylbiguanide hydrochloride) filtered off and recrystallized from 95% isopropanol.

Analysis calculated for $C_{10}H_{16}N_5Cl$: C, 49.7; H, 6.7; N, 29.0.

Found: C, 49.7; H, 6.7; N, 29.4.

EXAMPLE 2.

~~N^{11}~~ - Hexamethylenebiguanide hydrochloride.

The hydrochloride of hexamethyleneimine was prepared by passing hydrogen chloride into an ethereal solution of the free base.

22 g. of hexamethyleneimine hydrochloride and 12.6 g. of dicyandiamide were mixed and fused. The mixture begins to melt at 97° C. (bath 127° C.) and fused completely at 120° C. (bath 132° C.). The bath temperature was raised gradually over a 1-hour period to about 170° C. and heating continued at a bath temperature of 170—179° C. for 50 minutes. The fusion mixture was cooled and dissolved in 130 cc. of hot ethanol, treated with carbon and filtered. The alcoholic filtrate was treated with 300 cc. of dry ether and 18.9 g. of precipitate was obtained which was dissolved in 180 cc. of hot isopropyl alcohol, treated with carbon and filtered. On cooling, the product was obtained.

Analysis Calculated for $C_8H_{16}N_5Cl$: C, 43.8; H, 8.3; N, 31.8.

Found: C, 43.5; H, 7.9; N, 32.0.

EXAMPLE 3.

N^1 - p - Chlorobenzylbiguanide (free base).

The hydrochloride of p - chlorobenzylamine was prepared from the free base as described in Example 2.

17.1 g. of p - chlorobenzylamine hydrochloride and 8.4 g. of dicyandiamide were mixed and fused as above. The mixture begins to melt and froth at 107° C. (bath 130° C.). The bath temperature was raised gradually to about 170° C. over a period of 30 minutes, whereupon an exothermic reaction was noted with internal temperature rising to 176° C. (bath 173° C.). The dark brown reaction mixture was heated for an additional 3 minutes. The fusion mixture was cooled and dissolved in 110 cc. of propanol, treated with carbon and filtered. On cooling, N^1 - p-chlorobenzylbiguanide hydrochloride is obtained on filtration, which was dissolved in 75 cc. of warm water, treated with carbon and filtered. The filtrate was cooled and stirred with 10 cc. of 40% sodium hydroxide, precipitating the free base which was permitted to crystallize at 5° C. Filtration afforded the impure base, which was dissolved in 60 cc. of warm water, treated with carbon, filtered and cooled. The precipitate of free base was filtered.

Analysis Calculated for $C_9H_{12}N_5Cl$: C, 48.0; H, 5.4.

Found: C, 48.0; H, 5.2.

EXAMPLE 4.

N^1 - Benzyl - N^1 - methylbiguanide acetic acid salt.

The hydrochloride of N - methylbenzylamine was prepared from the free base as described in Example 2.

62.8 g. of N - methylbenzylamine hydrochloride and 33.6 g. of dicyandiamide were mixed and fused as in Example 1. The mixture begins to melt at 80° C. and fuses completely at 126° C. (bath 139° C.). The bath temperature was gradually raised to 160° C. over a 25-minute period. Heating (bath 160—168° C.) was continued for an additional 2.25 hours. The cooled fusion product was dissolved in water, treated with carbon and filtered. The aqueous filtrate was treated with 80 cc. of 40% sodium hydroxide with cooling and stirring. A yellowish oil separated and congealed to a soft solid after standing at 5° C. The soft solid of the free base was separated and dissolved in 380 cc. of acetonitrile and filtered. The acetonitrile filtrate containing the free base was treated with 19 ml. of glacial acetic acid with stirring. A white precipitate separated which was filtered, rinsed with acetonitrile, filtered and dried yielding the product which was recrystallized from isopropyl alcohol.

Analysis Calculated for $C_{12}H_{19}N_5O_2$: C, 54.3; H, 7.2; N, 26.4.

Found: C, 54.1; H, 7.1; N, 26.0.

EXAMPLE 5.

N^1-m-Bromobenzylbiguanide nitric acid salt.

m-Bromobenzylamine was prepared by reaction of m - bromobenzoylchloride→m - bromobenzamide and reduction with lithium-aluminium hydride to m - bromobenzylamine which was converted to the hydrochloride.

12.7 g. of m - bromobenzylamine hydrochloride and 4.8 g. of dicyandiamide were mixed and fused as above. The mixture begins to melt at 125° C. (bath 139° C.) and fusion is complete at 153° C. Heating was continued at bath temperature of 150—160° C.

for one hour. The cooled fusion product was dissolved in 250 cc. of water, treated with carbon and filtered. The filtrate was concentrated to about 50 cc. by vacuum distillation and treated with a solution of 5 g. of sodium nitrate in 5 cc. of water, and after chilling at 5° C. the precipitate was collected and recrystallized from 90 cc. of acetonitrile. On concentrating the acetonitrile solution to 55 cc. and chilling at 5° C. the desired product was obtained.

Analysis Calculated for: $C_9H_{13}N_6BrO_3$: C, 32.5; H, 4.0; N, 25.2.

Found: C, 32.4; H, 3.9; N, 24.7.

EXAMPLE 6.

N^1-*p*-Methoxybenzylbiguanide free base.

The hydrochloride of *p* - methoxybenzylamine was prepared from the free base as above.

17.3 g. of *p* - methoxybenzylamine hydrochloride and 8.4 of dicyandiamide were mixed and fused as in Example 1. The mixture begins to melt at 143° C. (bath 158° C.) and fuses completely at 167° C. with abrupt rise of internal temperature to 170° C. (bath 164° C.). Heating (bath 164—169° C.) was maintained for 1.3 hours. The cooled fusion product was dissolved in 200 cc. of water, treated with carbon and filtered. The filtrate was concentrated to 125 cc. by vacuum distillation and there was added, with cooling and stirring 10 cc. of 40% sodium hydroxide and the reaction mixture was stored at 5° C. Filtration and drying gave the product which was dissolved in 30 cc. of acetonitrile, treated with carbon, filtered and cooled.

Analysis Calculated for $C_{10}H_{15}N_5O$: C, 54.3; H, 6.8; N, 31.7.

Found: C, 54.2; H, 6.7; N, 32.0.

EXAMPLE 7.

N^1-*n*-Amylbiguanidine hydrochloride.

The hydrochloride of *n* - amylamine was prepared by passing dry hydrogen chloride into an ethereal solution of the amine. The insoluble hydrochloride was filtered and dried.

52.9 g. of *n* - amylamine hydrochloride and 36.2 g. of dicyandiamide were ground and intimately mixed. The mixture was heated gradually with stirring on an oil bath over a one hour period to 158° C. and maintained at this temperature for four hours. The fusion mixture was cooled, dissolved in 229 ml. of isopropanol, treated with carbon and filtered. Upon cooling there was obtained 24.1 g. of product, m.p. 174—176° C.

Analysis Calculated for $C_7H_{18}N_5Cl$: C, 40.5; H, 8.8; N, 33.7.

Found: C, 40.7; H, 8.8; N, 33.8.

EXAMPLE 8.

N^1-*n*-Butylbiguanide nitric acid salt.

105.6 g. of *n* - butylamine hydrochloride and 79.3 g. of dicyandiamide were ground intimately and mixed. The mixture was heated by means of an oil bath, gradually with stirring, and after thirty minutes when the internal temperature had reached 150° C., an exothermic reaction ensued with internal temperature rising to 178° C. The reaction mixture was removed from the oil bath until the internal temperature had fallen to 150° C. and then heating was resumed at 150° C. for one hour. The cooled fusion mixture was dissolved in 3 liters of acetonitrile, and on cooling 51.3 g. of *n* - butylbiguanide hydrochloride precipitated. This was dissolved in 70 ml. of hot water and 30 ml. of a solution containing 26 g. of sodium nitrate, and the reaction mixture stored at 10° C. for 18 hours. The crystalline product was separated, dried and recrystallized from 55 ml. of acetonitrile, there being obtained 22.4 g. of product, m.p. 125—126° C.

Analysis Calculated for $C_6H_{16}N_6O_3$: N, 38.2.

Found: N, 38.0.

THERAPEUTIC COMPOSITION.

Although the compounds made as described herein are effective as hypoglycemic agents in small dosages, the exact amount required will vary with the severity of the condition, the weight of the individual and the response to the compound.

The active compounds are compounds with a solid excipient, which must be non-toxic and chemically inert to the substituted biguanide or biguanide salt. The proportion of the excipient should be at least sufficient to separate the particles of the hypoglycemic agent from each other, and to cause quick solution or dispersion of the hypoglycemic composition when contacted with the gastric juice of the stomach. The amount thereof may be from about 0.3 to about 4 parts for 1 part of the active ingredient.

As solid excipients utilization may be made of lactose, sucrose, starch, pre-gelatinized starch, gum arabic, gum tragacanth and mixtures of these. Suitably, the solid excipient may contain also admixed magnesium stearate, talc, cornstarch, or two or more of these additives to promote separation of the composition from the plunger and mould used in shaping the composition into tablets for use orally.

HYPOGLYCEMIC TABLET

	Weight in Mgs.	Approximate Percentage
N^1-β-Phenylethylbiguanide hydrochloride	100.0	62.0
Sucrose	25.9	16.0
Starch	22.1	13.5
Acacia	7.8	4.5
Talc	3.1	2.0
Magnesium Stearate	1.5	1.0
Stearic acid	1.6	1.0

PATENT OFFICE

Acid

It will be understood that the biguanide derivative mentioned in the above composition may be substituted by any of the other derivatives described herein on an equal weight basis.

In making the tablet the biguanide is mixed with the sucrose and gum acacia, and then with the starch made previously into a paste with a small amount of distilled water. This mixture is dried at low heat and put through a granulator which converts it into a granular powder. This mix is then blended with the talc, magnesium stearate and the stearic acid which act as mould lubricants. The whole is now mixed in a pony mixer or other suitable powder mixing equipment, and then is ready for tabletting on any type of tabletting machine or for filling into hard gelatin capsules.

The following specific examples present illustrative data demonstrating the effectiveness of the novel compositions as oral hypoglycemic agents.

After hypoglycemic activity had been established by subcutaneous route the biguanides were evaluated by the oral route in terms of their capacity to lower blood sugar levels of test animals. The routine procedure was to establish the minimum lethal dose (MLD) in the laboratory animals and then to assess the hypoglycemic activity of the biguanide at a level approximately one third of that of the established MLD. As will be seen from data that follow on alloxan treated animals, the MLD as routinely established here does not reflect the true toxicity of the compounds but rather the level at which they cause a hypoglycemic death.

The following results were obtained in guinea pigs and are expressed as a function of time in terms of the percentage reduction in blood sugar from that found for the normal animal. Thus a normal level of 80 mg.% reduced to 20% is represented as a 75% reduction.

Guinea pigs were used as the test animal and the findings are indicated in Table I.

The minimum lethal dose (MLD) was established by intraperitoneal injection in mice. With these active hypoglycemic agents the lethal dose as established in the absence of supportive glucose is essentially a measure of toxic hypoglycemia and animals receiving such dosage levels show blood sugar levels as low as 5 and 10 mg.%.

In the instance of the control compounds, Synthalin (decamethylenediguanidine dihydrochloride) shows extreme toxicity and latent hypoglycemia with the effect being noted only after 24 hours; whereas with N - *p* - methylbenzenesulfonyl - N^1 - *n* - butyl urea high dosages are required and its overall hypoglycemic effect is such that blood sugar levels cannot be depressed to the point of hypoglycemic death.

TABLE I

Hypoglycemia in Guinea Pigs on Oral Administration

Compound		M.L.D. Mg/kg	Oral Dosage	% Reduction in Glucose in Hours		
R_1	R_2			3	5	24
Ph—CH_2—	H	150	50	51	73	0
Ph—CH_2—	CH_3	500	150	20	44	0
p—Cl—Ph—CH_2—	H	100	33	22	40	23
m—Br—Ph—CH_2—	H	200	70	19	43	0
p—CH_3O—Ph—CH_2—	H	150	50	15	34	15
Ph—CH_2—CH_2—	H	100	33	69	70	0
Control Compounds						
Synthalin		10	20	0	0	41
N-*p*-Methylbenzenesulfonyl-N¹-*n*-butyl urea		>1000	150	35	38	0

It was noted that the hypoglycemic effect is reversible, with the level of blood sugar approaching the normal glucose levels with time, generally in 24 hours. It was also observed that animals receiving glucose during the test period survived doses of the compound which produced fatal hypoglycemia in control animals.

The next series of experiments was to establish the capacity of the compounds to reduce the blood sugar levels of alloxan-diabetic animals. While alloxan-diabetes does not completely parallel human diabetes mellitus, it serves as a convenient laboratory method for the study of diabetes in animals.

Rats were given 300—400 mg/kg of alloxan intraperitoneally and their blood glucose level rose to 200—450 mg.%. Owing to the severity of the diabetes, the doses of the test compound required to depress the blood sugar to normal levels varied considerably. Consistent values were, however obtained when the dose necessary to lower blood glucose by 100 mg.% was determined. These values are given in Table II as averages of four animals in each group.

TABLE II

Reduction in Blood Sugar in Alloxan Rats

Compound		Oral Dosage mg/kg Dose Causing Reduction of 100 mg. % Glucose
R_1	R_2	
Ph—CH_2—CH_2—	H	400
Ph—CH_2—	H	100
p—Cl—Ph—CH_2—	H	70
—$(CH_2)_6$—		300
Synthalin (a)		50 (not reversible, animals died)

Footnote (a) — A compound which has been used in diabetes, Decamethylene diguanidine dihydrochloride.

After cessation of treatment with the compounds, the blood sugar levels rose again due to the alloxan-diabetes. In particular, the results of this table demonstrate the essential lack of toxicity of the compounds of this invention when their capacity to induce death by hypoglycemia is overcome, by the use of animals having pathologically high sugar levels. In the case of the control compound, Synthalin, dosage of 50 mg/kg resulted in substantial falls of blood sugar but at this level of Synthalin a progressive fall in the blood sugar ensued and the animals ultimately died.

Recently, two urea derivatives, N - sulfanilyl - N^1 - *n* - butyl urea and N - *p* - methylbenzenesulfonyl - N^1 - *n* - butyl urea, have been offered as oral therapeutics in diabetes and these drugs are reported not to lower the blood sugar in the alloxan-diabetic animal.

Additional work with alloxan was conducted in rabbits with the compound β-phenylethylbiguanide hydrochloride. Rabbits were rendered diabetic by intravenous injection of 200 mg/kg of alloxan. Three rabbits developed substantially elevated blood sugar levels of about 200 mg.% and one rose to 400 mg.%. Upon oral administration of 80 mg/kg of the test compound the blood sugar levels of the first three rabbits fell to normal levels and could be so maintained as long as the treatment was continued. The rabbit with severe diabetes required 200 mg/kg of the test compound to reduce the blood sugar level by half. After a period of 4 to 5 days with cessation of treatment the blood glucose rose again in all the animals.

The overall effectiveness as oral hypoglycemic agents having been demonstrated, and with the manifestation of their essential lack of toxicity divorced from the hypoglycemic effect being evident from the alloxan work, it remained to demonstrate that a dosage level approximately 1/25 to 1/50 of that proven essentially non-toxic would operate effectively as a hypoglycemic agent. For this work the rhesus monkey was selected as the test animal using the compound β - phenylethylbiguanide hydrochloride and the observations are given in Table III.

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TABLE III

"Hypoglycemic Effects in Monkey"

Dose Level Mg/Kg	Monkey	Control Level	Blood Glucose — Mg % Hours 2	5	24	48
0	A	63.6				
2			60	56	59	
5			64	50	43	59
10			43	43	48	71
0	B	71				
2			68	65	53	
5			54	49	57	68
10			43	43	43	60

Definite hypoglycemic effects are manifest at dosage levels of 1/200 to 1/80 of that readily tolerated by the alloxan-diabetic rat.

While the mode of action of the compounds of this invention is not as yet completely understood, and although it is not our purpose to offer a mechanism, nevertheless it is instructive to offer additional data reflecting the fact that these compounds have an insulin-like action.

It is well known that insulin added to an *in vitro* preparation of rat diaphragm will accelerate the uptake of glucose by the muscle. Rat hemidiaphragms were suspended in Warburg flasks in oxygen-saturated Ringer solution containing 1 mg/ml of glucose. After one hour the muscle was removed and the glucose determined in the surrounding solution. Taking into account the spontaneous oxidation of glucose, the amount which disappeared from the solution was assumed to be taken up by the muscle. The results are contained in Table IV.

TABLE IV

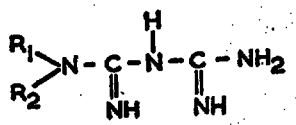
Test Compound R_1	Test Compound R_2	Mg of Compound Used	Increase in Glucose Uptake Mg/g. Muscle/Hour
Ph—CH_2—CH_2—	H	6	1.6
		12	2.6
		24	5.1
—$(CH_2)_5$—		6	2.7
		12	3.3
		24	4.1
Control Compounds			
Synthalin		6	0.8
		20	2.0
N-*p*-Methylbenzenesulfonyl-N^1-*n*-butyl urea		10	0.9
		100	0.9
Insulin		0.05 units	1.2
		0.07 units	1.8
		0.10 units	2.1

The insulin-like character of the biguanides is thus manifest by the increasing capacity to afford increased glucose uptake by the rat muscle with increasing dose of the compound.

It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained and, since certain changes may be made in the above composition of matter without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT WE CLAIM IS:—

1. A composition of matter for treating diabetes mellitus by oral administration containing as the active ingredient a biguanide having the following free base formula:



which is within one of the groups (a) in which R_1 is a straight chain saturated C_4 or C_5 alkyl and R_2 is hydrogen (b) in which R_1 is phenyl-$(CH_2)_n$ where n is 1 or 2 and the phenyl radical may be substituted by one chlorine, bromine or methoxy, and R_2 is hydrogen (c) in which R_1 is benzyl and R_2 is methyl, and (d) in which R_1 plus R_2 is pentamethylene or hexamethylene, or a salt of such a biguanide, together with one or more innocuous solid substances chemically inert to the active ingredient.

2. A composition as claimed in claim 1 in which R_1 is β - phenethyl, and R_2 is hydrogen.

3. A composition as claimed in claim 1 in which R_1 is *n* - amyl and R_2 is hydrogen.

4. A composition as claimed in claim 1 in which R_1 is *n* - butyl and R_2 is hydrogen.

5. A composition as claimed in claim 1 in which R_1 is *m* - bromobenzyl and R_2 is hydrogen.

6. A composition as claimed in claim 1 in

TABLE IV

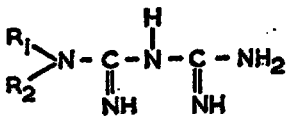
Test Compound R_1	Test Compound R_2	Mg of Compound Used	Increase in Glucose Uptake Mg/g. Muscle/Hour
Ph—CH_2—CH_2—	H	6	1.6
		12	2.6
		24	5.1
—$(CH_2)_5$—		6	2.7
		12	3.3
		24	4.1
Control Compounds			
Synthalin		6	0.8
		20	2.0
N-*p*-Methylbenzenesulfonyl-N^1-*n*-butyl urea		10	0.9
		100	0.9
Insulin		0.05 units	1.2
		0.07 units	1.8
		0.10 units	2.1

The insulin-like character of the biguanides is thus manifest by the increasing capacity to afford increased glucose uptake by the rat muscle with increasing dose of the compound.

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WHAT WE CLAIM IS:—

1. A composition of matter for treating diabetes mellitus by oral administration containing as the active ingredient a biguanide having the following free base formula:



which is within one of the groups (a) in which R_1 is a straight chain saturated C_4 or C_5 alkyl and R_2 is hydrogen (b) in which R_1 is phenyl-$(CH_2)_n$ where *n* is 1 or 2 and the phenyl radical may be substituted by one chlorine, bromine or methoxy, and R_2 is hydrogen (c) in which R_1 is benzyl and R_2 is methyl, and (d) in which R_1 plus R_2 is pentamethylene or hexamethylene, or a salt of such a biguanide, together with one or more innocuous solid substances chemically inert to the active ingredient.

2. A composition as claimed in claim 1 in which R_1 is β - phenethyl, and R_2 is hydrogen.

3. A composition as claimed in claim 1 in which R_1 is *n* - amyl and R_2 is hydrogen.

4. A composition as claimed in claim 1 in which R_1 is *n* - butyl and R_2 is hydrogen.

5. A composition as claimed in claim 1 in which R_1 is *m* - bromobenzyl and R_2 is hydrogen.

6. A composition as claimed in claim 1 in

* C L M S *

which R_1 is *p* - chlorobenzyl and R_2 is hydrogen.

7. A composition as claimed in claim 1 in which R_1 is *p* - methoxybenzyl and R_2 is hydrogen.

MARKS & CLERK.

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CORRECTION OF CLERICAL ERROR

SPECIFICATION NO. 852,584

The following correction is in accordance with the Decision of the Assistant Comptroller acting for the Comptroller-General, dated the twentyeighth day of June, 1961.

Page 1, line 1, *after* "We," *insert* "U.S. Vitamin & Pharmaceutical Corporation, formerly known as"

THE PATENT OFFICE,
17th July, 1961.

DS 94624/1(3)/R.153 200 7/61 PL

ERRATA

SPECIFICATION No. 852,584

Page 1, line 15, *for* "indicates" *read* "includes"
Page 1, line 29, *for* "injection" *read* "injections"
Page 1, line 65, *delete* hyphen *after* "active" and *insert* comma
Page 2, line 39, *before* "in" *insert* "and are within one of the four groups (a)"
Page 3, line 31, *for* "N^{11}" *read* "N^1,N^1"
Page 3, line 38, *for* "fused" *read* "fuses"
Page 4, line 10, *for* "55° C" *read* "55 cc."
Page 4, line 41, *for* "Amylbiguanidine" *read* "Amylbiguanide"
Page 5, Tablet: 1st column, *for* "acid" *read* "Acid"
Page 6, line 26, *for* "Table II" *read* "Table III"

THE PATENT OFFICE
2nd November 1964