Brit. J. Pharmacol. (1947), **2**, 65.

THE ABSORPTION OF SOME SULPHAGUANIDINE DERIVATIVES IN MICE

BY

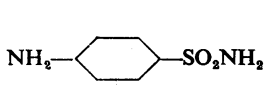
F. L. ROSE AND A. SPINKS

From the Research Laboratories, Imperial Chemical Industries, Ltd., Blackley, Manchester 9

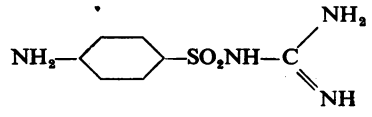
(Received October 17, 1946)

Sulphaguanidine (II) was independently prepared by Marshall, Bratton, White, and Litchfield and Roblin, Williams, Winnek, and English in 1940, and introduced for the treatment of bacillary dysentery on the basis of its poor absorption from the gut. It is now well established that orally administered sulphaguanidine attains only low concentrations in the blood of man (Marshall, Bratton, Edwards, and Walker, 1941 ; Anderson and Cruickshank, 1941 ; Beling and Abel, 1941 ; Frisk, 1941) and animals (Marshall, Bratton, White, and Litchfield, 1940 ; Roblin, Williams, Winnek, and English, 1940 ; Cameron and McOnie, 1941 ; Zozaya, 1941 ; Ambrose and Haag, 1942 ; Rose and Spinks, 1946), and that this is due partly to the absorption of only some 30–50 per cent of the administered drug and partly to a rather rapid rate of clearance by the kidney (Frisk, 1941 ; Zozaya, 1941 ; cf. Rose and Spinks, 1946 ; Fisher, Troast, Waterhouse, and Shannon, 1943). Little light has been thrown on the physical or chemical characteristics responsible for this poor absorption, which might be due either to a slow rate of diffusion across the intestinal membranes or to a partial availability of drug within the gut. Sulphaguanidine is relatively highly soluble compared with, for example, sulphapyridine and sulphathiazole, so that any such partial availability cannot be ascribed to low solubility over the intestinal pH range.

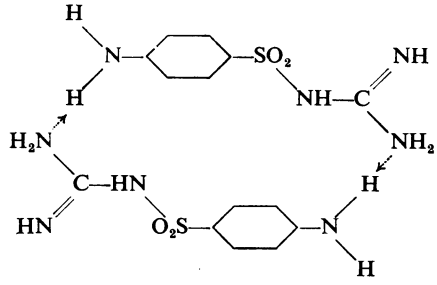
Whatever may be the cause of this phenomenon, it is not immediately apparent how such a striking effect could arise from the simple difference in chemical structure between the parent sulphanilamide, which is very well absorbed, and sulphaguanidine.



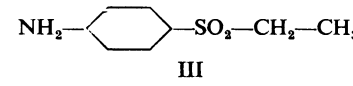
I



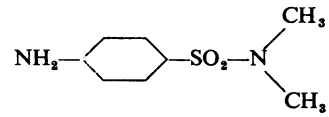
II



IIa



III



IIIa

Sulphanilamide (I) is derived from ammonia by replacement of a hydrogen atom of the latter by the sulphanilyl radicle. Although ammonia is a base, that is, in aqueous solution it acquires a proton to form the ammonium ion, the influence of the sulphonyl group is such that in sulphanilamide this tendency is reversed and the sulphonamide group exhibits feeble acidic properties, that is, it tends to liberate a proton. Guanidine is, however, a much stronger base than ammonia, and in combination with the sulphonyl group provides the sulphonylguanidine group, which is approximately electrochemically neutral; that is, it is neither markedly acidic nor basic. Krebs and Speakman (1946) have suggested as a corollary to their work on solubility and dissociation constants in the sulphanilamide series that poor absorption from the intestine is a result of this suppression of ionization. In our opinion, it is unlikely that this effect, which constitutes the main chemical difference between sulphanilamide and sulphaguanidine, can be the primary cause of their different pharmacological behaviour, otherwise compounds such as *p*-aminophenylethylsulphone (III) and sulphanildimethylamide (IIIa) which carry the non-ionizing sulphonylethane and sulphonyldimethylamide groups, respectively, might also be expected to resemble sulphaguanidine. As is shown below in Tables I and II, both of these compounds are relatively well absorbed, the former to the same extent as sulphanilamide.

We were therefore led to consider the possibility that a physical difference between sulphaguanidine and sulphanilamide other than that suggested by Krebs and Speakman might account for their observed physiological behaviour.

The work of Hunter (1941) has drawn attention to the capacity of amidine and guanidine groups to take part in hydrogen bond formation, and we tentatively supposed that similar effects involving both the sulphonylguanidine group and the primary amino group in the *para* position of the benzene ring might account for the poor absorption of sulphaguanidine through union with some substrate or substrates to be found in the gut contents. A further factor might be the formation of dimeric molecules of type (IIa) in which, it is suggested, hydrogen bonds again play a part. It is presupposed that in either event, the sulphonylguanidine and *p*-amino groups operate simultaneously, the former as a hydrogen

acceptor and the latter as a hydrogen donor. Any charge displacement resulting from the acceptance of a hydrogen atom in one part of the molecule would then be balanced by an opposite and approximately equal displacement in another.

Union with a substrate would necessarily reduce the amount of drug available for absorption, while the increased molecular weight resulting from dimer formation would probably lead to slower absorption. In the latter connection, sulphanilamide derivatives of molecular weight comparable to that of the hypothetical dimer, which have been studied in these laboratories, for example some sulphanilamidoquinolines, have attained only low concentrations in the blood of mice, and it must be emphasized that what is to be explained is not a complete failure of absorption, but partial absorption to a degree not much less, in some species, than that shown by, say, sulphapyridine.

The first hypothesis, that of union with a substrate, cannot easily be tested by direct experimentation. The second should be capable of proof or disproof by molecular weight determinations in aqueous solution. So far, however, it has not been possible to obtain unequivocal results by such determinations. Indirect evidence for an effect involving two point hydrogen bonding has been sought by examining the absorption in mice of a number of sulphaguanidine derivatives. In these the molecule has been modified so that the possibility of association through hydrogen bonding is either left unchanged or is reduced or wholly eliminated. The several chemical types were selected on the following basis:

Type I. Compounds carrying substituents in the guanidine residue

A twofold influence was anticipated in this instance. The introduction of one or more alkyl groups on the terminal nitrogen atom would enhance the electronegativity of the latter and might therefore be expected to strengthen hydrogen bond formation. Against that, the steric effect of the substituents, depending upon their sizes, should inhibit the necessary close approach to a second molecule, and would probably be the more important factor.

Type II. Compounds in which double hydrogen-bonding is not possible

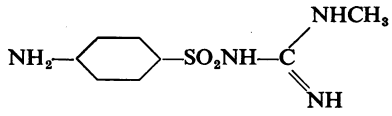
The substitution of nitro for the primary amino group (XI) or the transference of the latter to the *meta* position (XII) would effectively modify the formation of the double hydrogen-bond systems ; in the first compound because the nitro group is devoid of the necessary hydrogen atom, and in the second because of the markedly different relative positions of the significant groups in the drug molecule, rendering impossible, for example, the achievement of a structure such as (IIa). A further compound (XIII) was also included under this heading, in which it was anticipated that the presence of a methyl in the *ortho*

position to the primary amino group might inhibit to some extent the participation of the latter in hydrogen bond formation. The correspondingly substituted sulphanilamide (XIIIa) was examined as a control substance.

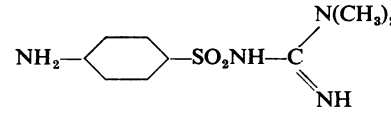
In addition to compounds classified under the above two headings, we included in this investigation several miscellaneous substances such as the two acetyl derivatives of sulphaguanidine (XIV) and (XV), and the sulphonyl acetamidine (XVI) which closely resembled sulphaguanidine chemically, and which could be involved in hydrogen bond formation in the same manner as the latter drug.

The substances employed in this investigation are listed below. For the preparation of some of them we are indebted to our colleagues, Dr. F. H. Slinger and Dr. G. Swain. Details of the chemical work will be described in the *Journal of the Chemical Society*.

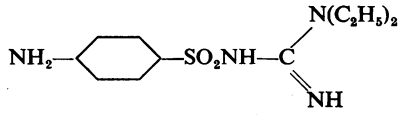
Type I



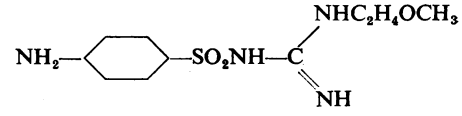
IV



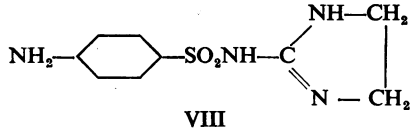
V



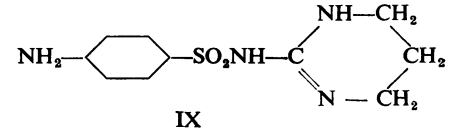
VI



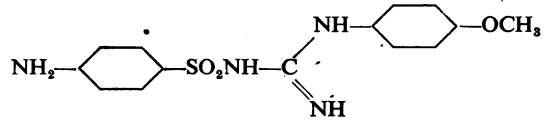
VII



VIII

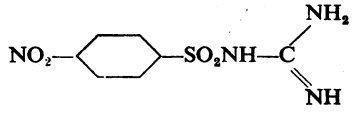


IX

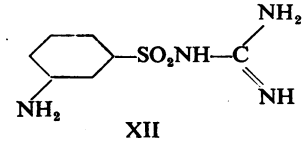


X

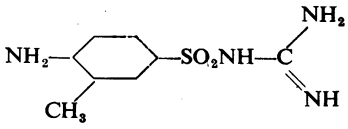
Type II



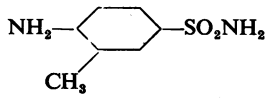
XI



XII

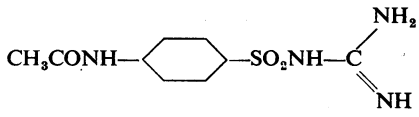


XIII

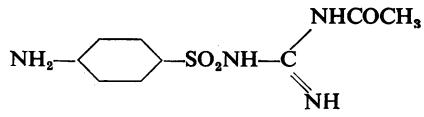


XIIIa

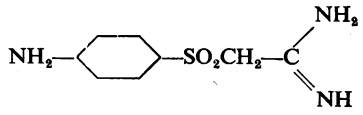
Miscellaneous



XIV



XV



XVI

A few compounds of Type I have been described by Winnek, Anderson, Marson, Faith, and Roblin (1942), who also recorded the maximum blood concentrations attained following the oral administration to mice of single doses of 0.5 g./kg. They concluded from experiments with the ethyl, propyl, and butyl homologues of (IV) that the presence of the alkyl groups led to an increased absorption, the increase being particularly marked in the case of the propyl derivative.

EXPERIMENTAL

1. Analytical methods

With two exceptions (XI and XIV) each compound was determined by the micro method of Rose and Bevan (1944). The advantages of this method have recently been summarized elsewhere (Spinks and Tottey, 1946). Adequate recoveries (±10 per cent) of each compound were established by trial analyses of known amounts added to blood.

p-Nitrobenzenesulphonylguanidine was determined by the following method based on that of Eckert (1943) for *p*-nitrobenzoic acid. 0.02–0.04 ml. blood was measured and pipetted into 0.4 ml. water in a test tube (18×100 mm.), and 0.2 ml. trichloroacetic acid added. After centrifugation, the clear supernatant fluid was decanted into a similar tube graduated at 2 ml., the protein residue being washed with 0.2 ml. water: one drop of Eckert's tartaric acid mixture was then added, followed by 1 drop of *N*/20 titanous sulphate, and the tube was heated for 10 min. at 100° C. On cooling, 0.2 ml. 0.10 per cent sodium nitrate was added, and, 20 min. later, 0.4 ml. of 1 per cent N-β-sulphatoethyl-*m*-toluidine (Rose and Bevan, 1944). Thirty min. were allowed for coupling and the volume was then made up to the mark with distilled water. Immediately before a reading in the colorimeter each tube was centrifuged, since some turbidity was usually evident. This procedure was found to give only 70–80 per cent recoveries of *p*-nitrobenzenesulphonylguanidine from

blood. Eckert obtained similar results with *p*-nitrobenzoic acid. Instead of using a conversion factor, unknown samples were read against standards (0, 0.01, 0.03, 0.05, 0.07, and 0.10 ml. volumes of a 10 mg./100 ml. aqueous solution of *p*-nitrobenzenesulphonylguanidine), to which blood (0.04 ml.) had been added. In spite of the centrifugation immediately before colorimetry individual blood concentration-time curves obtained for *p*-nitrobenzene-

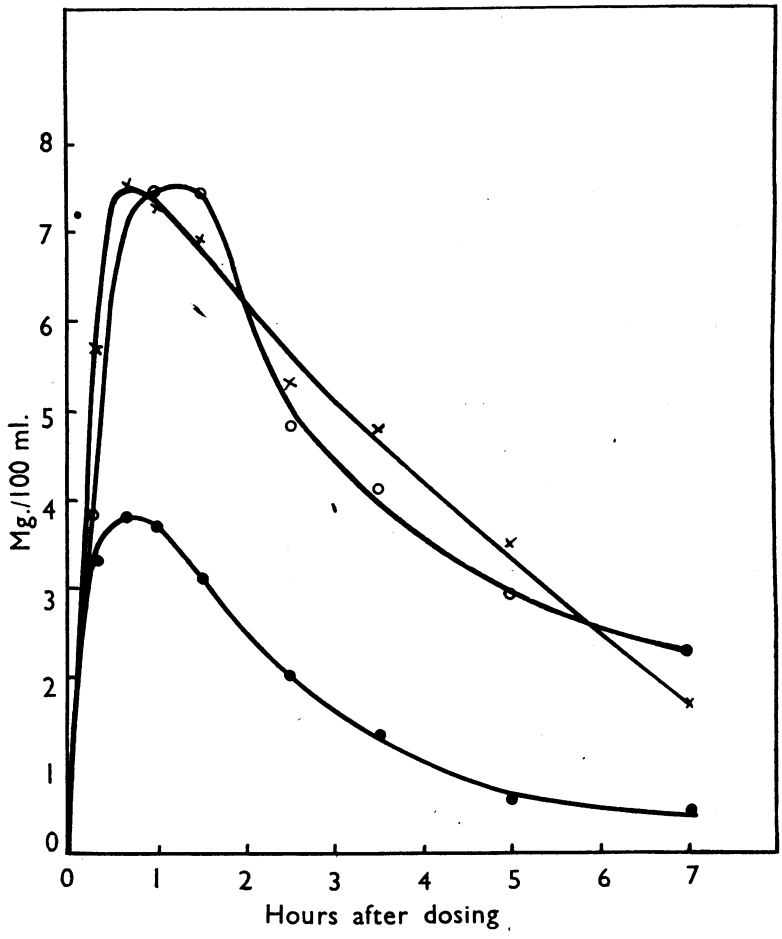


FIG. 1.—Mean blood concentration-time curves in mice of sulphaguanidine (II, ●——●, 30 animals), metanilylguanidine (XII, O——O, 18 animals), and *p*-nitrobenzenesulphonylguanidine (XI, ×——×, 24 animals). Each compound was administered by stomach tube in doses of 5 mg./20 g.

sulphonylguanidine were not very smooth, and it is thought that, owing to residual turbidity, the error of the method may have been as high as 20 per cent. However, the mean curve (Fig. 1) was adequately smooth. The final result, of course, included the *p*-nitrobenzenesulphonylguanidine that had been converted to sulphaguanidine *in vivo*. The extent of such

conversion was separately examined, the blood from mice receiving 5 mg. of *p*-nitrobenzenesulphonylguanidine per 20 g. being analysed for sulphaguanidine itself. No sample contained more than 0.5 mg./100 ml. of the latter. *p*-Acetamidobenzenesulphonylguanidine (XIV) was determined by the method of Rose and Bevan (1944) for total amine, modified so that the protein precipitation was carried out at about 1 in 50 dilution instead of 1 in 20. This involved an increase in the final volume of solution to 5 ml., but satisfactory sensitivity was achieved by reading in 2 cm., 6 ml. cells in the Morris colorimeter.

II. Biological methods

The standard conditions used by us in the examination of sulphonamide blood concentrations in mice have already been described (1946), and the original publication should be consulted for full details. Each compound was administered orally to a group of 3 mice in doses of 5 mg./20 g. and as a 1 per cent solution (of the hydrochloride) or dispersion, pooled tail blood from the 3 animals being analysed at intervals after dosing.

This individual experiment was repeated at least 6 times for each drug, and characteristic values obtained from the individual smooth curves as already described (Rose and Spinks, 1946), including maximum concentration (max.), the time after dosing at which this was attained (t.max.), and the time (C.5) taken for the concentration at 5 hours to fall to two-thirds of the value then observed. The results are given in Table I. The mean results are summarized in Table II, in which the compounds have been arranged in order of falling maximum blood concentration. Limits of error of means are for a probability level of 0.05; that is, there is one chance in twenty of the error exeeding the given limit. A value differing significantly (P=0.05) from that for sulphaguanidine is printed in italics, one differing decisively (P=0.01) in bold type.

Two compounds only (IV and X) differed significantly from sulphaguanidine in rate of disappearance from the blood. It may therefore be concluded that the maximum blood concentration is a fairly satisfactory index of the extent of absorption from the gut.

TABLE I

BLOOD CONCENTRATIONS OF SULPHAGUANIDINE DERIVATIVES AND ALLIED COMPOUNDS

Compound No.	No. of experiments	Mean blood concentrations in mg./100 ml. after									Values from individual curves		
		20 min.	40 min.	1 hr.	1½ hr.	2½ hr.	3½ hr.	5 hr.	7 hr.	24 hr.	Max. (mg./100 ml.)	t max. (min.)	C.5 (hr.)
III	7	7.7	10.3	10.6	10.6	7.2	3.8	1.7	0.9	0.1	11.7	63	1.1
	Standard deviations										3.0	21	0.5
	Limits of error of means										±2.7	±19	±0.5
IIIa	8	6.1	8.0	8.3	7.8	6.5	4.2	3.15	1.2	0	8.9	71	1.2
	Standard deviations										1.6	19	0.6
	Limits of error of means										±1.3	±15	±0.45

TABLE I—*continued.*

Compound No.	No. of experiments	Mean blood concentrations in mg./100 ml. after:—									Values from individual curves		
		20 min.	40 min.	1 hr.	1½ hr.	2½ hr.	3½ hr.	5 hr.	7 hr.	24 hr.	Max. (mg./100 ml.)	t max. (min.)	C.5 (hr.)
IV	9	2.8	3.8	3.9	3.8	2.7	1.8	1.1	0.8	0.2	3.9	67	1.3
	Standard deviations										1.6	8	0.4
	Limits of error of means										±1.2	±6	±0.3
V	6	7.8	8.0	7.3	5.5	3.4	2.25	1.4	1.0	0.2	8.35	42	1.4
	Standard deviations										2.3	24	1.1
	Limits of error of means										±2.3	±24	±1.1
VI	6	5.9	7.05	7.4	7.5	6.3	4.65	3.4	1.9	1.0	7.9	98	2.6
	Standard deviations										1.5	42	1.7
	Limits of error of means										±1.5	±42	±2.0
VII	8	3.2	6.0	5.5	4.6	3.2	2.1	1.2	0.95	0.3	5.7	72	1.6
	Standard deviations										1.45	13	1.0
	Limits of error of means										±1.2	±11	±0.9
VIII	7	4.3	6.0	7.3	7.1	5.6	3.6	2.3	1.2	0.2	7.3	85	1.3
	Standard deviations										2.0	39	0.4
	Limits of error of means										±1.8	±36	±0.4
IX	6	3.35	5.3	5.3	5.2	4.3	2.4	1.2	0.8	0.3	5.6	74	1.3
	Standard deviations										1.3	23	0.6
	Limits of error of means										±1.3	±23	±0.6
X	6	4.6	4.7	3.7	3.2	1.35	0.6	0.15	0.1	0	5.1	37	0.6
	Standard deviations										1.6	4.5	0.2
	Limits of error of means										±1.8	±5.2	±0.2

TABLE I—*continued.*

Compound No.	No. of experiments	Mean blood concentrations in mg./100 ml. after:—									Values from individual curves		
		20 min.	40 min.	1 hr.	1½ hr.	2½ hr.	3½ hr.	5 hr.	7 hr.	24 hr.	Max. (mg./100 ml.)	t max. (min.)	C.5 (hr.)
XI	8	5.7	7.5	7.3	6.9	5.3	4.8	3.5	1.7	0	7.6	53	1.7
	Standard deviations										1.8	18	1.6
	Limits of error of means										±1.5	±15	±1.3
XII	6	3.8	7.1	7.7	7.7	4.8	4.1	2.9	2.25	0.6	7.8	82	2.0
	Standard deviations										3.2	35	1.2
	Limits of error of means										±3.2	±35	±1.2
XIII	6	2.55	2.9	2.75	2.4	1.6	1.6	0.85	0.5	0.2	3.1	48	1.3
	Standard deviations										0.8	18	0.4
	Limits of error of means										±0.8	±18	±0.4
XIIIa	6	10.5	13.1	13.3	12.9	10.6	6.8	5.0	2.9	0.1	13.5	63	1.4
	Standard deviations										3.8	14	0.4
	Limits of error of means										±3.8	±14	±0.4
XIV	6	1.1	1.3	1.4	1.4	1.7	1.55	1.2	0.7	0.4	1.95	127	(3.2*)
	Standard deviations										0.7	51	—
	Limits of error of means										±0.7	±59	—
XV	6	3.6	4.8	4.7	4.2	3.7	2.5	2.0	1.0	0	4.75	67	1.3
	Standard deviations										2.0	16	0.7
	Limits of error of means										±2.0	±16	±0.7
XVI	9	1.4	2.1	2.3	2.0	1.6	1.2	0.8	0.5	0.1	2.7	75	1.3
	Standard deviations										1.1	34	0.95
	Limits of error of means										±0.85	±25	±0.7

*Does not differ significantly from 0; i.e., no mean is justifiable.

TABLE II

SUMMARY OF MEAN DATA ON THE ABSORPTION OF SULPHAGUANIDINE DERIVATIVES AND ALLIED COMPOUNDS

Figures differing significantly (P = 0·05) from those for sulphaguanidine in italics, figures differing decisively (P = 0·01) in bold type.

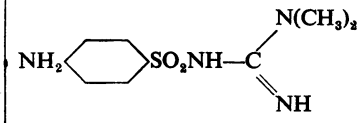
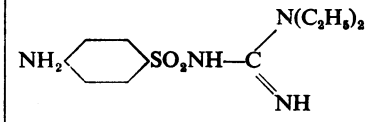
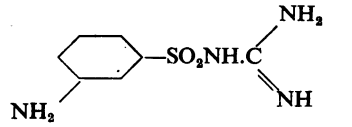
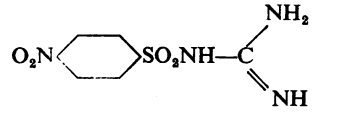
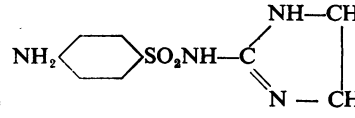
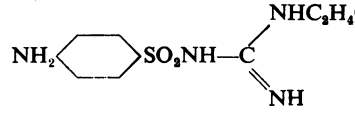
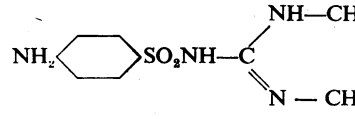
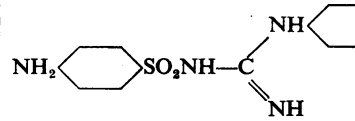
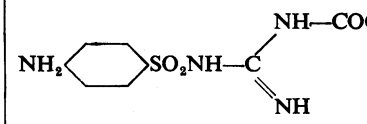
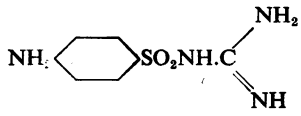
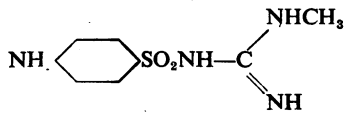
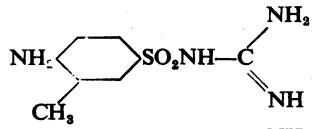
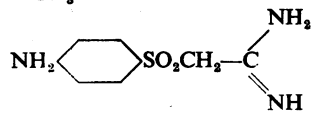
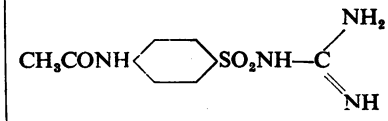
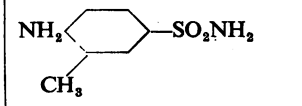
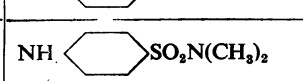
No.	Formula	Max. (mg./100 ml.)	t max. (minutes)	C.5 (hours)
V		**8·35 ± 2·3**	42 ± 24	1·4 ± 1·1
VI		**7·9 ± 1·5**	**98 ± 42**	2·6 ± 2·0
XII		**7·8 ± 3·2**	82 ± 35	2·0 ± 1·2
XI		**7·6 ± 1·5**	53 ± 15	1·7 ± 1·3
VIII		**7·3 ± 1·8**	85 ± 36	1·3 ± 0·4
VII		*5·7 ± 1·2*	**72 ± 11**	1·6 ± 0·9
IX		*5·6 ± 1·3*	*74 ± 23*	1·3 ± 0·6
X		5·1 ± 1·8	37 ± 5·2	**0·6 ± 0·2**
XV		4·75 ± 2·0	67 ± 16	1·3 ± 0·7

TABLE II—*continued.*

No.	Formula	Max. (mg./100 ml.)	t max. (minutes)	C.5 (hours)
II		4·3 ± 0·8	50 ± 12	2·2 ± 0·85
IV		3·9 ± 1·2	*67 ± 6*	*1·3* ± *0·3*
XIII		3·1 ± 0·76	48 ± 18	1·3 ± 0·4
XVI		**2·7 ± 0·85**	*75 ± 25*	1·3 ± 0·6
XVI		*1·95 ± 0·7*	**127 ± 59**	—
XIIIa*		13·5 ± 3·8	63 ± 14	1·4 ± 0·4
III*		11·7 ± 2·7	63 ± 19	1·1 ± 0·5
IIIa†		**8·9 ± 1·3**	*71 ± 15*	1·2 ± 0·45

* Neither III nor XIIIa differs significantly from sulphanilamide in any respect.
† The significant differences indicated are from sulphaguanidine. The maximum blood concentration is decisively lower than that of sulphanilamide. There is no other significant difference from sulphanilamide.

Discussion of Results

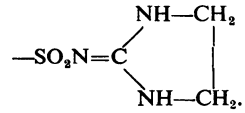
The hypothesis on which this research was based is that sulphaguanidine and related compounds exhibiting poor absorption from the gut owe this property to those features of their molecular structure which permit union with some hypothetical substrate, with the additional possibility of self union to provide a dimeric molecule. It is further supposed that in either event the linking forces are provided by hydrogen bonds associated with the *p*-amino and guanidine groups. The *para* configuration of the sulphaguanidine molecule would be of

special significance in dimer formation, and it is assumed that it might also be of importance in unions of the type postulated with other molecules. These structural features should be reflected in the physical properties of the drug molecules and be capable of measurement. This aspect is receiving the attention of our colleague, Mr. J. C. Gage.

It is convenient to discuss the results obtained under the type headings listed above, noting in each case the extent to which the disturbance of molecular detail has produced the expected effect.

Type I

Of the alkyl derivatives of sulphaguanidine only the monomethyl homologue gives a maximum blood concentration lower than that of the parent compound, and the difference is not significant. The remaining alkyl derivatives all achieve higher maxima, in particular the dimethyl and diethyl homologues. The contrast between the former and the monomethyl derivative is marked, and, in so far as hydrogen bond formation is concerned, would indicate that the steric rather than the inductive effect of the alkyl groups is the governing factor, the greater hindrance to the necessary close approach to a substrate or a second molecule being provided, as would be anticipated, by the presence of two alkyl groups. The two ring alkylene compounds (VIII) and (IX) provide a further contrast, the former being absorbed the more completely, although somewhat more slowly. Compound (IX), incidentally, is the tetrahydropyrimidine corresponding to sulphadiazine, a drug which under similar conditions achieves an average maximum blood concentration of 17.5 mg./100 ml. (Rose and Spinks, 1946). A theoretical explanation of the difference between (VIII) and (IX) can at this stage be no more than speculation. It is unlikely that the small increase in molecular weight corresponding to the additional methylene group in (IX) is the responsible factor. The main chemical feature of the latter substance would be a tendency for the double bond of the guanidine residue to be stabilized in the heterocyclic ring as formulated, while in (VIII) the disposition of the double bond giving the minimum strain in the ring system might be expected to be that provided in



These differences would almost certainly influence the relative hydrogen-bonding propensities of the ring nitrogen atoms, and be reflected in different degrees of absorption.

Type II

The *meta* isomer of sulphaguanidine (XII) attains a maximum blood concentration which is approximately double that of the parent compound. Some slight change in physical properties (base dissociation constant, solubility, etc.)

would be expected in passing from the one isomer to the other, but it is unlikely that these differences would be solely responsible for the marked increase in absorption of the *meta* compound. At the same time the maximum concentration attained is below the known value for sulphanilamide (13.2 mg./100 ml.). It would appear, therefore, that the sulphonylguanidine grouping is *per se* less favourable to absorption from the gut than the sulphonamide group and that this inhibiting effect is markedly increased in association with a *para* amino group. The close identity of the absorption data of (XII) and the nitro compound (XI) (see Fig. 1) adds further support to these views. In the latter substance a *para* substituent is present, but it is of a chemical type unable to provide hydrogen atoms for bond formation.

The presence of a methyl group *ortho* to the amino group of sulphaguanidine (XIII) suppresses rather than enhances absorption. Reference to formula (IIa) shows that for the methyl group to inhibit hydrogen bonding to any marked extent, the molecules must be oriented with the alkyl groups adjacent to, and on the same side as, each of the two hydrogen bonds. No inhibition would be expected with the methyl groups in the alternative *ortho* positions. The actual experimental results are inconclusive, therefore, as regards substantiation of the hypothesis. It should be noted that compound (XIIIa), which was included as a control substance in this aspect of the investigation, does not differ significantly in its absorption characteristics from sulphanilamide (Rose and Spinks, 1946).

Among the miscellaneous substances included in this research, the results obtained with the sulphonylacetamidine (XVI) are of some significance. This compound differs structurally from sulphaguanidine only in that the imido group of the latter is replaced by a methylene linkage. The terminal amidine residue $-C(=NH)-NH_2$ is common to both. Since both compounds are poorly absorbed, it would appear that the amidine moiety is the controlling feature. This is in accord with expectations. On the other hand, the experimental findings with the acetyl derivative of sulphaguanidine (XV) were not anticipated. The combined influence of the sulphonyl and acetyl groups on the guanidine residue is such that this substance regains the weak acidic properties characteristic of the simple sulphonamide group. The guanidine group in (XV) would, therefore, be expected to function less readily as a hydrogen acceptor and the compound should then resemble sulphanilamide rather than sulphaguanidine. Against this, it has been observed that the acetyl group of (XV) is removed with unusual ease, for example, on standing for a short period of time in cold dilute sodium hydroxide solution, to regenerate sulphaguanidine, and it may be that such deacetylation occurs in the gastro-intestinal tract resulting in an observed absorption characteristic of the latter drug.

In conclusion, it is apparent that the results of the experiments *in vivo* recorded above can at best provide only indirect substantiation of the hypothesis proposed. Further, with compounds such as the alkylguanidine derivatives, two

effects were expected to result from the introduction of the alkyl groups, the one tending to decrease, the other to increase the stability of hydrogen bond formation, but in the absence of the necessary physical data relating to these substances it was not possible to forecast with certainty which feature would predominate. However, the marked contrast between the absorption of sulphaguanidine and, for example, its diethylhomologue (VI), in which the molecular weight is increased by nearly sixty units, would be contrary to expectations were it not postulated that the action of the alkyl groups is one of steric hindrance to the approach to the guanidine residue of some other chemical structure which by its presence would inhibit passage of the drug through the gut wall. The increased absorption noted by Winnek *et al.* (1942), in particular of the monopropyl derivative of sulphaguanidine, can also be accounted for on the same basis. The conclusions to be drawn from the data for the *p*-nitro (XI) and *m*-amino (XII) compounds are more precise. Clearly the capacity of these compounds to be involved in association with a second structure in which the potential hydrogen bonding is oriented to accommodate the *p*-aminobenzenesulphonyl guanidine molecule will be markedly influenced in these two instances in favour of more ready absorption from the gut.

SUMMARY

The blood concentrations, following oral administration to mice, of a number of derivatives of sulphaguanidine have been determined, and the results analysed in the light of the hypothesis that the poor absorption from the gut of the parent compound is associated with structural features which may permit this substance to exhibit hydrogen bond phenomena. While much of the experimental evidence circumstantially supports this view, some of the results are inconclusive.

REFERENCES

Ambrose, A. M., and Haag, H. B. (1942). *Surgery*, **12**, 919.
Anderson, O. E. W., and Cruickshank, R. (1941). *Brit. med. J.*, **2**, 497.
Beling, C. A., and Abel, A. R. (1941). *J. med. Sci., New Jersey*, **38**, 629.
Cameron, H. S., and McOnie, W. A. (1941). *Cornell Vet.*, **31**, 321.
Eckert, H. W. (1943). *J. biol. Chem.*, **148**, 197.
Fisher, S. H., Troast, L., Waterhouse, A., and Shannon, J. A. (1943). *J. Pharmacol.*, **79**, 373.
Frisk, A. R. (1941). *Acta med. scand.*, **109**, 355.
Hunter, L. (1941). *J. chem. Soc.*, 777.
Krebs, H. A., and Speakman, J. C. (1946). *Brit. med. J.*, **1**, 47.
Marshall, E. K., Bratton, C., Edwards, L. B., and Walker, E. (1941). *Johns Hopk. Hosp. Bull.*, **68**, 94.
Marshall, E. K., Bratton, C., White, H. J., and Litchfield, J. T. (1940). *Johns Hopk. Hosp. Bull.*, **67**, 163.
Roblin, R. O., Williams, J. H., Winnek, P. S., and English, J. P. (1940). *J. Amer. chem. Soc.*, **62**, 2002.
Rose, F. L., and Bevan, H. G. L. (1944). *Biochem. J.*, **38**, 116.
Rose, F. L., and Spinks, A. (1946). *J. Pharmacol.*, **86**, 264.
Spinks, A., and Tottey, M. M. (1946). *Ann. trop. Med. Parasit.*, **40**, 101.
Winnek, P. S., Anderson, G. W., Marson, H. W., Faith, H. E., and Roblin, R. O. (1942). *J. Amer. chem. Soc.*, **64**, 1682.
Zozaya, J. (1941). *Ciencia (Mex.)*, **2**, 255.