# FACTORS INFLUENCING PERCUTANEOUS ABSORPTION

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THE percutaneous absorption of drugs from different vehicles or bases through the intact skin of the rabbit seems to be influenced by a number of factors[1,2].

When sulphanilamide in various vehicles and bases is applied to the intact skin of rabbits, it penetrates the skin and is absorbed into the blood stream where it is detected in measurable quantities[1]. After such a test the blood level falls to zero in four to five days. During the six hours of the test the half-hourly blood samples showed a fluctuation in concentration of sulphanilamide (Table I) although the graph of concentration of drug against time remained approximately parallel. The figures in Table I

TABLE I

PERCUTANEOUS ABSORPTION OF SULPHANILAMIDE IN THE RABBIT OVER SIX HOURS
SULPHANILAMIDE OBSERVED, MG./100 ML.

| Time in hours .. | 0·0 | 0·5 | 1·0 | 1·5 | 2·0 | 2·5 | 3·0 | 3·5 | 4·0 | 4·5 | 5·0 | 5·5 | 6·0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Average blood level | 0·00 | 0·56 | 0·75 | 0·54 | 0·85 | 0·46 | 0·45 | 0·41 | 0·77 | 0·66 | 0·75 | 0·36 | 0·51 |
| Total blood level .. | 0·00 | 3·33 | 4·48 | 3·26 | 5·07 | 2·73 | 2·72 | 2·44 | 4·59 | 3·94 | 4·50 | 2·14 | 3·10 |

give the average blood levels and the total blood levels observed for six rabbits (3 male and 3 female litter-mates) over six hours at half hour intervals. A statistical analysis of the blood levels at half hour intervals showed them to be significantly different. These observations suggested that either absorption or excretion of sulphanilamide occurred in cycles. This phenomenon was noticeable with a number of the other bases or vehicles in which sulphanilamide was incorporated. But when other drugs, like salicylic acid, copper sulphate, and copper acetyl-acetonate were used this rhythmic wave pattern was not seen. It is thought that the explanation of the cycle lies in the tubular resorption of sulphanilamide from glomerular filtration; the acetylated form is not reabsorbed. Since absorption by the percutaneous route is probably continuous, a wave pattern occurs in the blood level.

The physico-chemical properties of the incorporated drugs have been shown to play an important part in percutaneous absorption[2]. Statistical analysis of results showed that the difference in the efficiency as "carriers" of the vehicles or bases tested were significant. But an even more significant result was the interaction between drug and base. From an analysis of all components of the variance the theoretical values may be calculated and compared with those observed. This has been done in Table II for three drugs incorporated in three bases; salicylic acid, copper acetyl-acetonate and copper sulphate in lard, Emulsifying Ointment B.P., and water, as a five per cent carboxymethylcellulose gel. Table II also shows

the per cent deviation of the observed from the calculated results, a positive value gives a result greater than the calculated or theoretical result and a negative the reverse. When the observed value is significantly greater or less than the calculated value an interaction between the particular drug and base is concluded to be in operation. Thus it can be seen that the observed value for salicylic acid when incorporated in lard is higher than the theoretical value as is the observed result for copper sulphate from water. Similarly the copper sulphate : lard result was less than the theoretical value. In these instances, the interaction between drug and base can be considered significant. The variation in the amounts of drugs absorbed from different bases may be accounted for by their physico-chemical properties and an explanation may be offered in terms of their local actions and lipid solubilities.

TABLE II

THE DEVIATION BETWEEN CALCULATED AND OBSERVED RESULTS
DRUGS EXPRESSED IN MG. PER TWO SIX-HOUR TESTS

| | Lard | | | Emulsifying ointment | | | Water | | |
|---|---|---|---|---|---|---|---|---|---|
| | Calculated | Observed | Per cent deviation | Calculated | Observed | Per cent deviation | Calculated | Observed | Per cent deviation |
| Salicylic acid | 206·41 | 223·43 | +8·2 | 191·84 | 187·61 | −2·2 | 180·95 | 168·17 | −7·1 |
| Copper acetylacetonate | 56·17 | 49·55 | −11·8 | 41·60 | 43·58 | +4·8 | 30·71 | 35·37 | +15·2 |
| Copper sulphate .. | 52·41 | 42·03 | −19·8 | 37·84 | 40·01 | +6·2 | 26·96 | 35·07 | +30·0 |

Sufficient results have been obtained from the series of experiments to analyse for the components of variance. It is a valuable property of variance that if a process has a number of factors, each making a contribution to the variance of the final phenomenon, then this total variance is equal to the sum of the component variances and this makes possible the analysis of the total variance into its component factors[3]. The following sources of variance are found to be significant; between drugs, between vehicles or bases, and the drug x vehicle or base interaction. Certain factors were found to be insignificant and could therefore be ignored in the test devised for the measurement of percutaneous absorption. No difference was observed in rabbits of different sex. All rabbits chosen for test weighed between 2·5 and 3·5 kg. and no significant difference was observed for rabbits of different weights. The variation noted between individual rabbits was also found to be insignificant and in addition the difference between replicate tests was never significant.

We are indebted to Mr. J. C. Eaton, M.A., for his assistance with the statistical analysis.

## REFERENCES

1. Gemmell and Morrison, *J. Pharm. Pharmacol.*, 1957, **9**, 641.
2. Gemmell and Morrison, *ibid.*, 1958, **10**, 553.
3. Brownlee, Industrial Experimentation, H.M.S.O. 1946.

## DISCUSSION

The short communication was presented by MR. J. C. MORRISON.

THE CHAIRMAN. How did the Authors arrive at the 'calculated' figure in Table II? Was the rate of absorption of the drug faster than its diffusion through the layer of ointment base on the skin?

MR. T. D. WHITTET (London). It was not justifiable to describe the absorption of materials from a 5 per cent sodium carboxymethylcellulose solution as absorption from water. Swallow and he had shown in 1942 that copper sulphate was incompatible with sodium carboxymethyl cellulose and the Authors had obtained better absorption with an incompatible material. Why was copper acetyl-acetonate chosen and was it soluble in water?

MR. S. G. E. STEVENS (London). Had any compound been used which had relatively similar solubilities in the oil and water phase? Was there any significance in the possibility of a sodium bridge carrying through the copper salts?

MR. G. R. WILKINSON (London). What was the area of skin to which the preparation was applied? How was the preparation maintained in position? Had the Authors considered that by rubbing every 15 minutes the surface layer and the subcutaneous tissue were disturbed by agitation?

DR. G. F. SOMERS (Liverpool). How was the sulphanilamide applied and what was the vehicle? Hadgraft and he had also found that in general the absorption of an oil-soluble substance was retarded if applied as an emulsion. Absorption was not always wanted.

MR. B. B. NEWBOLD (Sheffield). The differences found in the blood concentrations of sulphanilamide might not be due to biological effects, but to the insensitivity of the method used to determine the drug.

MR. MORRISON replied. The calculated figures were found by subtracting the deviation from the grand mean of all results from the average value. If there were no interaction between drug and base, the calculated and observed values should be the same. There was a possibility that the rate of absorption was faster than the rate of diffusion. A colloidal preparation of carboxymethylcellulose had been used, since water was difficult to apply to rabbits in practice, but the point was still valid. Copper acetyl-acetonate which is insoluble in water, was chosen since it could be estimated, and copper sulphate because it was astringent. They had tried a drug with approximately the same solubility in water as in oil, but they were limited by suitable assay methods. He did not support the existence of a sodium bridge. The area of application was 24 square inches: the rabbits were in boxes with their heads protruding and a barrier put down. The ointment was only rubbed on sufficiently to keep it in close contact with the skin.