11375 P

Evidence for the Local Effect of Mercurial Diuretics.*

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Previous attempts to demonstrate "tissue diuresis" by "mercurial diuretics" failed since the investigated changes of blood colloids or salts were unconvincing. This paper describes certain new observations which may throw light upon the problem.

In previous experiments the inhibition of procaine convulsions by calcium salts was demonstrated.[1] Organic calcium salts were found to be particularly efficient.[2] Since magnesium salts were found to prevent the anticonvulsive action of calcium salts it seemed that the well known increase of membrane impermeability produced by calcium salts was the chief factor involved in their action.

This property of calcium salts is probably related to their *diuretic* action. Consequently, we were led to investigate other diuretics, particularly the strong acting mercurial diuretics, such as hydroxy mercuri-methoxy-propyl carbamyl phenoxy acetate, commonly known as "salyrgan". Our expectation was fully justified since salyrgan exhibited an anticonvulsive effect far exceeding that of any calcium salt. The invariably convulsive and oftentimes fatal dose of 200 mg/kg of procaine, intramuscularly in guinea pigs, was rendered entirely harmless by as little as 20 mg/kg of salyrgan simultaneously administered. For comparison, the most effective of all the previously tested calcium salts, calcium benzoate, had to be given in a dose of 50 mg/kg in order to detoxify 200 mg/kg of procaine.

The detoxifying action of salyrgan might be explained as the result of a direct chemical combination with procaine. Various other chemically different convulsant drugs were therefore studied, such as strychnine, picrotoxin, coramin and metrazol. In every instance salyrgan in doses of 10 to 20 mg completely inhibited the action of

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1 Beutner, R., and Miley, G. P., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 279.

2 This work was done in collaboration with H. Wastl and A. Jensen (*Ibid.*, 1939, **42**, 547). See also the extensive publication of H. Wastl (*Arch. int. Pharmacodyn.*, 1939, **43**, fasc. 2) giving quantitative data.

a highly convulsant dose of these drugs. It seems unlikely that salyrgan can combine with any or all of these chemically widely different convulsant drugs. Moreover, various calcium salts such as calcium levulinate, were likewise found to inhibit all of these convulsants. This can hardly be the effect of a direct chemical combination.

The assumption that both salyrgan and calcium salts act primarily on the tissues rendering them more impermeable and *thus* preventing convulsions is further supported by the following findings:

(1) According to our observations no perceptible inhibition of convulsions occurs *in frogs* when salyrgan and strychnine, or another convulsant, are injected simultaneously in any lymph sac. Obviously there is a direct access to the nerve cells in this case, membrane permeability being of less importance in the loose tissue of the frogs. If the convulsions were inhibited by direct chemical interaction the inhibition should occur in the frog just as in the mammal injected intramuscularly.

(2) According to recently published experiments by Spiegel and Spiegel-Adolf[3] convulsions are accompanied by an increase of the electrical conductivity of the brain tissue, pointing to an increased cell permeability brought about by the convulsing agent. Since calcium salts decrease permeability it seems more than likely that this decrease is the *very cause of their anticonvulsive action.* The same seems to be true for salyrgan. Since the decrease of permeability is likely to be associated with a dehydration of the tissue, the diuretic action of salyrgan would be explained on the same ground; in other words salyrgan should dehydrate tissues. The water thus eliminated would be ready for excretion through the kidneys.

In contrast to this theory of "tissue-diuresis" by salyrgan, the well known experiments by Govaerts[4] support the assumption of a renal irritation, favoring glomerular filtration and hindering of tubular reabsorption, as the cause of salyrgan diuresis.

Would it be possible to explain the anticonvulsive action of salyrgan through its renal diuretic effect which possibly leads to an accelerated elimination of the convulsive drug through the kidney? If this were correct salyrgan should also prevent convulsions if injected separately prior to procaine, strychnine, etc. Experiments showed that such an effect does not occur, or, at any rate the inhibition of convulsions is very slight on separate injection.

[3] Spiegel, E., and Spiegel-Adolf, M., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 834.

[4] Govaerts, P., *Compt. rend. Soc. de biol.* 1928, **99**, 647.

The xanthin diuretics were also tested for their possible anticonvulsive action, but were found not to show any such action. Their diuretic effect would, therefore, seem to be of renal origin exclusively. Other heavy metal compounds, however, are likewise anticonvulsive, hence "tissue-diuretic". Detailed data are to be given later.

Conclusion. Mercurial diuretics have a potent anticonvulsive effect. Study of the details of this effect leads to the conclusion that these diuretics increase membrane impermeability, dehydrate tissue and thus work as "tissue diuretics," notwithstanding their well known renal action.

11376 P

Serum Albumin Changes in Hypoproteinemic Dogs Following Administration of Methionine or Phenylalanine.

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The observation by Whipple and his coworkers that single amino acids and pure chemical substances increase the production of hemoglobin[1] and serum protein[2] raises the question of whether observed increases in serum protein after protein feeding are not solely the result of chemical stimulation, or mobilization from body stores of protein, as distinguished from a new synthesis from the ingested protein materials. If so, recorded differences in proteins (when concluded from changes in serum protein levels) would be merely an expression of a difference in amino acid composition and not necessarily express the nutritive value of the proteins for growth or maintenance.

Before such an interpretation can be made, it is essential to have additional data; and especially to determine whether single amino acids under conditions of low dietary protein, as in the procedure of Weech and Goettsch[3] will effect an increase in serum protein.

[1] Robscheit-Robbins, F. S., and Whipple, G. H., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 361.

[2] Madden, S. C., Noehren, W. A., Waraich, G. S., and Whipple, G. H., *J. Exp. Med.*, 1939, **69**, 721.

[3] Weech, A. A., and Goettsch, E., *Bull. Johns Hopkins Hosp.*, 1938, **63**, 154.