FURTHER OBSERVATIONS ON SODIUM AMYTAL EXPERIMENTS

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(Received October 8, 1941.)

DERIVATIVES of barbituric acid are in general sedatives, hypnotics and analgesics, but sodium amytal (S.A.) occupies a special position, because of its effect on certain mental and nervous conditions. It produces transient amelioration in catatonic schizophrenia and hypnosis-like conditions in neuroses. The latter is important through the fact that one is able to study hypnosis from a different pharmacological point of view.

Pharmacological studies into the effect of S.A. are numerous, and the present report deals only with those regarding the blood-sugar changes. While Zerfas and Mulinos, Chambers, Edwards and many others could not find any changes in the "carbohydrate metabolism," Hines and collaborators showed that S.A. lessens the ability to utilize glucose; hyperglycaemia and glycosuria occurred. Underhill, too, found hyperglycaemia in his S.A. experiments, as did Hollinger and Maddox. On the other hand, according to Brill, and also to Campbell and Morgan, S.A. prevents hyperglycaemia following injections of morphine in animals, in other words, S.A. lowers the blood-sugar level. In accordance with these findings are Tod's results, namely, that hypnotics (including barbituric derivatives), influence the glucose tolerance test: "lowered maxima and shortened hyperglycaemia with decreased hyperglycaemic index occurred." The various contradictory statements indicated further investigations into S.A. and blood-sugar reactions—investigations which I summarized in a preliminary report (2), and which I have completed since.

METHOD AND RESULTS.

It is not within the province of the present paper to deal with the detailed technique of S.A. administration or to describe the clinical phenomena observed during the experiments; as mentioned before, only the blood-sugar changes are dealt with. In all the experiments S.A. was administered intravenously and all blood-sugar estimations were obtained by the Folin-Wu method. The cases chosen were of different diagnosis (psychoses and neuroses—the latter in

https://doi.org/10.1192/bjp.88.370.122 Published online by Cambridge University Press

a majority), different sex, though females prevailed, and of different constitutional make-up, so that the reactions obtained could, if consistent, be attributed to the effect of the drug and not to the individual under treatment. In each case a glucose tolerance test was carried out first. The second series of investigations included blood-sugar estimations under S.A. influence. The third series were control experiments with Ringer solution (not containing glucose) given with a technique which simulated entirely the S.A. treatment. Finally glucose tolerance tests were performed, the patient consuming 50 gm. of glucose in solution and afterwards receiving S.A. (This experiment was only performed on 15 cases.) Between each series of investigations three to four days elapsed, and each experiment was carried out under similar conditions.

The preliminary glucose tolerance tests were of selective significance, and all cases with an abnormal sugar curve were excluded from further experiments. The second set of experiments ascertained that in 25 out of 30 cases the blood sugar had risen roughly about 25–30 mgm. per cent., and fallen slowly to normal level within 25 minutes of the S.A. injection being given. The control experiments with Ringer solution helped to exclude emotional reactions found in only two cases. The glucose tolerance tests under S.A. showed in six cases out of 15 a slight hypoglycaemic " lag " in the first 25 seconds of the experiment ; in one additional case the hypoglycaemic lag occurred about the end of the 25 seconds ; the rest did not show any alteration in the sugar tolerance curve. The average altitude of the hypoglycaemic " lag " was 20–25 mgm. per cent.

Before commenting on the results, the exceptional reactions should be summarized. Eight out of 30 cases did not respond to the S.A. psychologically, i.e., no S.A. hypnosis could be obtained. These cases were : hysteria, anxiety, obsessional and traumatic neuroses, psychopathy, depressive state (one of each group), and two schizophrenias. Five cases (as mentioned before) did not produce hyperglycaemia under S.A.; two of them (a schizophrenia and an anxiety neurosis) failed to give a psychological response. The unaltered sugar tolerance was irregularly distributed amongst the case material. Four cases gave psychologically negative results, and two corresponded with cases where no hyperglycaemic but good psychological responses were observed. The irregularity of the exceptional cases makes the value of their occurrence impossible to estimate.

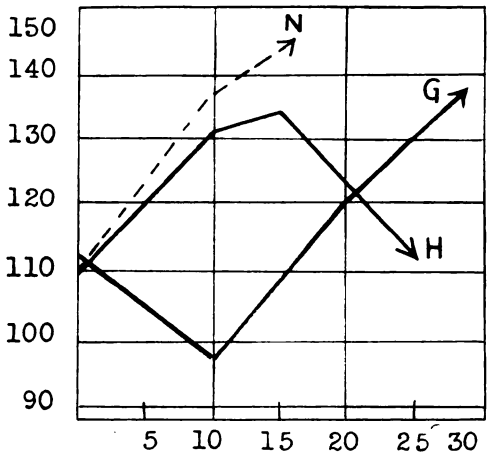
Comment.

The summarized experimental results suggest, in the first place, that S.A. induces a slight hyperglycaemia. As the coincidence of favourable psychological responses and hyperglycaemia has been frequently established, one feels justified in stating that there is a definite parallelism between psychological response and hyperglycaemia under S.A. influence. This parallelism concerns not only the occurrence, but also the onset and duration. The comparison

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with the depressed sugar tolerance reaction shows that there was a hypoglycaemic "lag" or a "depression of the curve" present in 40 per cent. of 15 cases tested, roughly corresponding in time with the S.A. hyperglycaemia.

The interpretation of the experimental results could only be made in relationship to other observations. The interpretation from an endocrine point of view seems unlikely; it is known that the basal metabolism rate is only slightly altered during S.A. experiments, and previously reported laboratory controls (series of blood chlorides and blood urea estimations), together with clinical observations, enables us to exclude adrenal influences. Although the results of Drabkin (S.A. applied to obstetrical material) are suggestive of direct pituitary influences, there are no further reports available regarding functional endocrine changes under S.A. effect.



Case No. 12, illustrating the different blood-sugar reactions under S.A. influence. H = S.A. hyperglycaemia. G = S.A. glucose tolerance. N = Normal glucose tolerance.

The appearance of cerebellar symptoms under S.A. are known toxic consequences of the barbiturates, and it is also frequently found that cerebellar dysfunctions involve disturbances of the blood-sugar regulation. Yet cerebellar symptoms, e.g. nystagmus, were noted in my own experiments only in about 50 per cent. of the cases, and only in the second half of the 30 minutes, at a time when the blood-sugar changes were reverting to normal levels. These facts seem to rule out a cerebellar origin of the blood-sugar changes.

Herman, Layman, Lindeman and Berrington agree on the cerebral action of S.A. in the sense of a cortical depressant, but this explanation could hardly satisfy all the symptoms observed. The transient ameliorating and hypnosis-like effects of the drug remain unique in comparison with general cortical depressants. Zerfas, commenting on adverse effects of the drug (e.g. hypersensitive states), doubts whether these are to be attributed to an individually

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different reaction of the central nervous system, or to a different localization of the action. Indeed several authors, such as Himwich and Fazekas, Harris and collaborators, etc., point out the functional influences on the brain-stem, thus making, from a localizing viewpoint, a vague statement as they are pointing to an area extending from the region of the corpora quadrigemina to the medulla inclusive. Hoff et al., Van der Horst and others advocate that the barbiturates act on the medulla; although the medulla could be responsible for blood-sugar changes similar to those described, it leaves unexplained the various other clinical effects. E.g. my experiments with evipan did not produce lucid intervals in catatonic schizophrenia, yet evipan acts on the medulla as other barbiturates are supposed to do. Summarized, the cerebellar, the cortical and the medullary localizations do not offer a satisfactory explanation for the various symptoms observed.

The likely localization of S.A. action seems to be the hypothalamus. This region not only subserves the described blood-sugar changes, but also the other phenomena, noted during S.A. treatment (hypnosis, emotional personality and mental effects, etc.). Masserman's experiments with picrotoxin and S.A. (the latter injected directly into the hypothalamus) confirmed the action of the drug on the hypothalamus. Functional changes in the posterior hypothalamus (Barbour) and in the paraventricular nuclei (Barris and Ingram) involve blood-sugar alterations similar to S.A. Campbell and Morgan (as mentioned before) found an antagonism between S.A. and morphine effect. On the other hand, Creutzfeldt described acute degenerative changes notably in the nucleus paraventricularis in acute morphine poisoning. Campbell's and Creutzfeldt's results seem to point again to the hypothalamus as the seat of origin of the S.A.-morphine antagonism. It would, however, be unwise to enumerate all the parallelisms between pathological phenomena of the hypothalamus and the consequences of the S.A. effect, as the present paper deals only with the blood-sugar changes. It should only be emphasized that the quoted hypothalamic syndromes are the results of direct influence in the sense of stimulation or depression, thus supporting again the view that the S.A. effects (notably the blood-sugar changes) are not merely release symptoms after cortical depressions, but results of direct influences on the hypothalamus.

Summary.

(1) Slight hyperglycaemia accompanies the psychological effects of sodium amytal.

(2) Sodium amytal seems occasionally and temporarily to depress the glucose tolerance curve.

(3) These facts, together with other findings, support the view that sodium amytal acts *inter alia* on the hypothalamus.

I wish to express my thanks to Dr. Helen Boyle and the Honorary Staff

https://doi.org/10.1192/bjp.88.370.122 Published online by Cambridge University Press

of The Lady Chichester Hospital for permission to use their material for my experiments.

The laboratory examinations were partly completed at the Royal Sussex County Hospital's laboratory, and I am indebted to Dr. L. R. Janes for his kind help.

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