cerebral hemisphere. On the blood pressure of the cat or rabbit, smooth-muscle-stimulating substance exerts a depressor response both before and after atropine and mepyramine, yet it is pressor on the blood pressure of the rat. On cardiac and skeletal muscle, it is relatively inactive.

The active material is extracted from cerebral hemispheres with different concentrations of acetone (1–20 vol.) and with trichloracetic acid (2 vol. of 10 per cent) but not with saline containing 0·1 *N* hydrochloric acid. Extracts prepared in this way retain activity for more than 1 month if maintained at 0° C. at neutral or acid *p*H values; but the activity slowly disappears when the extract is kept at *p*H 11. Smooth-muscle-stimulating substance is not inactivated by incubation with trypsin or chymotrypsin. On paper chromatograms, the active material has an R_F value of 0·60 in a sodium chloride solvent (8 per cent w/v), but it does not move from the origin in solvents of butanol–acetic acid, *iso*propanol–ammonia, or aqueous methanol (60 per cent v/v). With potassium iodate, ninhydrin reagent, Pauly's reagent, Folin–Ciocalteau's phenol reagent, or Ehrlich's reagent, the active material gives no colour reactions characteristic of catechols, amines, amino-acids, compounds containing hydroxyl groups, or indoles.

Thus, smooth-muscle-stimulating substance differs from histamine (which is inactive on the rat uterus), 5-hydroxytryptamine (actions blocked by *BOL*–148), acetylcholine (blocked by atropine), bradykinin (insoluble in acetone)[1], substance *P* (inactivated by chymotrypsin)[2], irin (inactive on rat uterus)[3], γ-aminobutyric acid (inactive on rabbit duodenum)[4], γ-aminobutyryl choline (blocked by atropine)[5], nasal mucosa factor (unstable in acid)[6], and cerebellar factor (which is insoluble in acetone)[7]. It is unlikely to be a polypeptide.

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Production of Muscular Weakness in Rats by a Creatine Analogue

In an effort to clarify the role of abnormal creatine metabolism in producing muscular dystrophy a search for an antimetabolite to creatine has been made. If a specific defect in either the synthesis or utilization of creatine could be produced by an antimetabolite, it would then be possible to assess the change in muscle structure and metabolism which results from impaired creatine metabolism.

One analogue of creatine which has been tested is D,L α-guanidinopropionic acid (alacreatine)[1]. A group of 10 weanling Sprague–Dawley rats of both sexes was fed a purified diet containing 18 per cent casein, 74·4 per cent sucrose, 3 per cent hydrogenated vegetable fat, 2 per cent cod liver oil, and the usual salts and vitamins and supplemented with 2 per cent alacreatine. While receiving this diet during a 6-week period the rats gradually became quite weak in comparison with control animals receiving only the purified diet. The type of weakness seen in the rats receiving alacreatine resembled that seen in rabbits suffering from nutritional muscular dystrophy resulting from vitamin E deficiency. When placed on their side they had difficulty in righting themselves, particularly after exercise.

The finding of severe muscular weakness in animals fed an analogue of creatine strongly suggests that the analogue is a metabolic antagonist to creatine and that the weakness of muscular dystrophy is the result of the abnormal creatine metabolism of that disease. Study of the enzymes of creatine synthesis (transamidinase and guanidoacetate methylpherase) and utilization (creatine kinase) in animals given alacreatine should readily demonstrate a specific defect in creatine metabolism if one is present. This work and experiments to determine the influence of creatine feeding on the syndrome are now in progress.

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Damage to Liver induced by DL-Methionine-Ethylester

Perri *et al.* have observed that tryptophan-methylester inhibits the growth of several bacteria[1]. Horváth *et al.* found that the adaptive enzyme product of *Penicillium chrysogenum* inhibits glycine-, *iso*leucine- and phenylalanine-methylester and supposed that the amino-acid-ester takes part in protein synthesis after the acyl-activation and with its bound carboxyl group stops peptide production[2]. According to this hypothesis the amino-group of the esterified amino-acid is more reactive than the natural one, therefore the activated amino-acid reacts mainly with the ester. Although in the above-mentioned work no completion experiments were performed, the results suggest that the amino-acid-esters behave like antimetabolites on lower organisms.

On the basis of the above we supposed that DL-methionine-ethylester is a methionine antagonist causing liver injury, which then could be inhibited by methionine administration.

Dimethionine-ethylester was synthesized by esterification of DL-methionine and of absolute ethanol in dry hydrochloric acid. The salt of the compound was isolated and recrystallized from absolute ethanol. The dimethionine-ethylester thus produced was chromatographically uniform.

Albino rats of both sexes weighing 80–90 gm. were used in the experiments. They were fed a normal diet during the experimental period and were divided in three groups. 7 rats (Group I) were given 0·34 m.mole methionine; 16 rats (Group II) 0·24 m.mole dimethionine-ethylester and 7 rats (Group III) 0·34 m.mole methionine + 0·24 m.mole dimethionine-