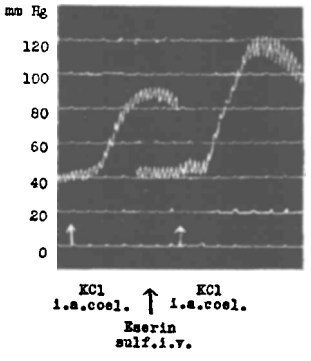

FIG. 3.

Cat. Preparation as in text. Effects on blood pressure of 1.25 mg. KCl injected into the central end of coeliac artery before and after intravenous injection of 0.4 mg. eserin sulfate.

fore, do not yet allow us to conclude that $CaCl_2$ or KCl discharge adrenalin by a cholinergic mechanism. Moreover, we do not believe that in studies of the autonomic nervous system, the effects of eserin and particularly those of atropin by themselves prove whether or not a mechanism is cholinergic. In our experiments, a cholinergic action of $CaCl_2$ or KCl on the adrenals can be definitely proved only by actual demonstration (by bioassay) of the liberation of acetylcholin in the glands following injection of the salts.

9424 P

Neurotoxic Action of Aluminum Salts.

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In the course of experiments involving the fractionation of herpes virus preparations by aluminum salts it was observed that rabbits which had received an intracerebral injection of certain fractions developed a syndrome indicative of a lesion of the central nervous system. The possibility of herpes encephalitis was excluded by the dissimilarity in symptoms and in cellular pathology. Nevertheless, several features of this syndrome, which had a uniformly fatal termination, were suggestive of a neurotropic virus disease, and a further investigation was made of its etiology.

It was found that the characteristic syndrome may be induced in rabbits, mice and monkeys by a single intracerebral injection of a small amount of an aluminum salt. Siem[1] and Döllken[2] reported observing neurologic symptoms in rabbits, cats and dogs which had received subcutaneous injections of aluminum in the form of sodium aluminum tartrate or lactate. They found lesions in the central nervous system of these animals, particularly nerve cell degeneration in the lower cranial nerves. Seibert and Wells[3] reported lesions in the central nervous system of one of a series of rabbits to which large amounts of aluminum or its salts had been administered. Scant attention has been paid to the neurotoxic action of aluminum salts and no instance of intracerebral administration of these salts has come to our attention.

When the proper dose of aluminum salt is given intracerebrally, the animal recovers uneventfully from the injection. The subsequent course is afebrile, except for rare elevations of temperature which appear to be irrelevant. After a lapse of 7 to 10 days in the rabbit, the first characteristic symptom appears. This consists in the disinclination of the animal to resume the normal posture when the hind quarters are twisted through 90 degrees about the longitudinal axis. Normal rabbits resist this procedure vigorously. A distinct diminution in muscle tone accompanies this ataxia, which becomes progressively more severe until the animal is prostrate. Convulsions generally occur in the terminal stage, often accompanied by opisthotonus and spontaneous nystagmus. The animal becomes emaciated and dies 3 to 8 days after the onset of symptoms. The histopathology consists in widespread nerve cell changes of the type known as toxic degeneration, with slight inflammatory reaction. A total of 46 rabbits have received intracerebral injections of aluminum salts in this study. Of these, 5 died within 24 hours, all having received doses of one mg. or more of Al. Three animals remained free of symptoms, all having received 0.17 mg. or less. One rabbit showed symptoms and subsequently recovered. All the remaining animals developed the typical syndrome and either died or were sacrificed. The minimal effective dose for the rabbit was 0.17 mg. Eight mice received intracerebral injections of aluminum lactate, the minimal effective dose being 0.016 mg. of Al. Three monkeys, *Macaca mulatta* (rhesus), received 2.1 to 4.25 mg. of Al intracerebrally. All developed the syndrome in 21 to 24 days.

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[1] Siem, *Inaug. Diss.*, Dorpat, 1886.

[2] Döllken, *Arch. Exp. Path. u. Pharm.*, 1897, **40**, 98.

[3] Seibert, F. B., and Wells, H. G., *Arch. of Path.*, 1929, **8**, 230.

This syndrome has been produced by both the sulfate and the lactate of aluminum. The lactate has been used in most of the experiments because solutions of it may be buffered at pH 6.0 to 7.0 (phenol red indicator) without precipitation of aluminum hydroxide. Intracerebral injection of doses of sodium lactate solution (pH 6.3) chemically equivalent to the amount of aluminum used had no effect upon the experimental animals. Moreover, these same animals succumbed typically to subsequent intracerebral injection of aluminum lactate.

Cultures from the brains of typical cases on blood agar and in Difco brain-heart infusion broth remained sterile. The possibility was considered that the syndrome was caused by a latent virus infection which was activated in the presence of the aluminum. However, negative results were obtained in attempts to transmit the disease in series by intracerebral inoculation of suspensions of brain tissue, from rabbit to rabbit and from rabbit to monkey.

Aluminum determinations have been made on the central nervous system of rabbits sacrificed in the terminal stage. A modification of the aurin method of Eveleth and Myers[4] was used. The results show that 25 to 37% of the injected aluminum is retained in the central nervous system. Of this amount 50 to 70% was in the cerebral hemispheres, 17 to 29% in the pons, medulla and cerebellum, and 13 to 23% in the cord. Normal controls contained an insignificant amount of aluminum in the central nervous system.

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Blood Fats During the Dietary Production of Fatty Livers in Dogs.

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Studies of blood fats were made to determine if any change might be associated with the production of fatty livers in dogs which received a high fat diet. The lipids studied were the neutral fats of the plasma; which were determined by the volumetric method of Allen;[1] and cholesterol, by the Lieberman-Burchard method as used by Bloor.[2] Four dogs were kept on the high fat diet for 35 to 40

4 Eveleth, D. F., and Myers, V. C., *J. Biol. Chem.*, 1936, **113**, 449.

1 Allen, N. N., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 991.

2 Bloor, W. R., *J. Biol. Chem.*, 1914, **19**, 1.