These considerations suggest that the increased susceptibility of infants to convulsions is associated with the ease with which various irritants can enter the brain tissue. However, another factor also must be considered. It is probable that not only is it much easier for various substances to enter the central nervous system of the young, but that this organ is much more sensitive to irritants. Thus, Brill and Seidemann[4] have observed that the electroencephalograms of normal children show a considerable tendency to dysrhythmia during hyperventilation and that this tendency diminishes with advancing age. It is probable that in the presence of increased tissue susceptibility, as indicated by cerebral dysrhythmia, and in the absence of a hematoencephalic barrier, as indicated by the passage of bile and dyes into the brain, a toxic agent will produce seizures in young subjects when it would be ineffective in older ones.

Summary. The intraperitoneal injection of bile results in the production of convulsive seizures in rats up to 10 days of age and not thereafter. The intracerebral injection of bile produces convulsions in adult rats. The hypothesis is developed that young animals are more susceptible to convulsive seizures because of an inherent cerebral dysrhythmia and a deficient hematoencephalic barrier.

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Subarachnoid Injection of Thiamine in Cats; Unmasking of Brain Lesions by Induced Thiamine Deficiency.

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This work was undertaken to determine whether the neurological symptoms of thiamine deficiency could be treated more effectively by introduction of the vitamin into the subarachnoid space than by the usual routes of administration. It seemed possible that thiamine might be held up or delayed at the hemato-encephalic barrier when given by the usual routes. Stern[1] has made a rather exuberant report of the effectiveness of subarachnoid injection of thiamine in patients with a variety of diseases.

[4] Brill, N. Q., and Seidemann, H., *Am. J. Psych.*, 1941, **98**, 250.

[1] Stern, E. L., *Am. J. Surg.*, 1938, **39**, 495.

Cats were selected because of their suitability for cisternal puncture. Fifteen adult animals were placed on the diet used by Cowgill[2] for dogs. Amount of food consumed and weight of each animal were recorded daily. Appetite diminished markedly within a few days and tube feeding was adopted to prevent nutritional disturbances other than thiamine deficiency. All the animals developed typical symptoms beginnning with loss of appetite and progressing to weakness, apathy, vomiting, incoördination, and in some cases to convulsions and paralysis. Severe and prostrating symptoms were apt to develop suddenly between the third and fourth weeks, animals becoming almost moribund overnight. One animal was kept on the above diet for 70 days and injected twice weekly with 1.0 mg thiamine chloride. No symptoms of thiamine deficiency appeared.

Several hours to several days after onset of severe symptoms thiamine chloride was administered, 0.5 to 2.0 mg in aqueous solution or in normal saline. Injection was made either intravenously, intramuscularly or into the cisterna magna after removal of an equivalent amount of C.S.F. The animals had reached such a stage of thiamine depletion that no anesthetic was necessary during cisternal puncture. Rate of recovery from symptoms was noted in each instance.

Animals undergoing thiamine depletion for the first time showed rapid and spectacular recovery after a single injection of thiamine. Gait and strength were almost normal within one hour and completely normal by the following day. Recovery was equally good when the vitamin was given intravenously or intramuscularly as when injection was made into the subarachnoid space.

Six recovered animals were kept on the diet and within 14 to 20 days showed symptoms of thiamine deficiency again. The above therapeutic procedures were repeated but improvement occurred much more slowly and some residues of weakness and incoördination usually remained despite repeated daily injections of thiamine. Four animals died despite thiamine administration. In 2 instances thiamine depletion was allowed to occur for a third time. Both animals died after onset of deficiency symptoms despite large amounts of thiamine.

Following subarachnoid injection of thiamine chloride some degree of meningeal irritation occurred as evidenced by increased cell count in the C.S.F. In order to check this point cisternal injection of thiamine chloride was performed 21 times in normal cats. Cell counts were made on the C.S.F. before injection and at 12 and 24 hours after the procedure. Pleocytosis was noted in all instances after

[2] Cowgill, G. R., *Am. J. Physiol.*, 1921, **57**, 420.

injection. The lowest count recorded after 24 hours was 75 lymphocytes per cu mm and the highest was 1500 per cu mm. Four different commercial preparations of thiamine chloride from ampules were used, also a sterile aqueous solution prepared by us from the crystalline substance. Acidity of the various preparations varied somewhat and reactions were more marked with the more acid preparations. Reactions occurred, however, even with neutralized preparations.

We have observed signs of meningeal irritation in 4 patients to whom thiamine chloride was administered by the lumbar route. Increasing doses of from 1.0 to 12.0 mg were injected at intervals of several days. The preparations were so faintly acid that they were neutralized by only 2 to 6 cc of C.S.F. When doses of 6.0 to 8.0 mg were reached the patients complained of some stiffness in the back and pain down the legs, whilst protein and cells in the C.S.F. were found to be elevated (Fig. 1). No serious or persisting results of subarachnoid injection of thiamine were noted either in animals or humans.

Four cats with surgical brain scars were placed on the thiamine deficient diet. They had been operated upon several months previously by our colleague, Dr. T. C. Erickson. They showed no clinical evidence of neurological defect. The first symptoms of deficiency were referable to the area of brain damage and appeared to be unmasked by the vitamin deficiency. The most striking result was seen in a cat from which the left frontal pole had been removed.

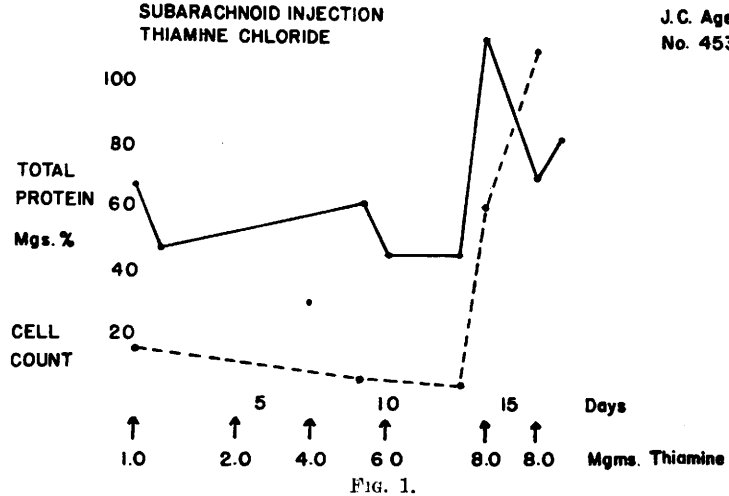

FIG. 1.

After 28 days on the diet the limbs on right side of the body became spastic and extended. Later a right sided convulsive seizure occurred with head turned to right and right limbs rigid. One hour after intracisternal injection of thiamine all symptoms had disappeared. The diet was continued and 15 days later the right limbs were again spastic and frequent tonic convulsions involved the right side. Convulsions ceased after administration of 0.5 mg thiamine but a residue of spastic paralysis remained in the right hind limb. The animal died 17 days later whilst in thiamine deficiency for the third time.

The above findings may explain partial improvement with thiamine therapy of some neurological diseases which are not the direct result of vitamin deficiency.

Summary. 1. Subarachnoid injection of thiamine causes rapid recovery of thiamine-deficient cats. Recovery is equally rapid when the vitamin is given intravenously or intramuscularly. 2. Moderate signs of meningeal irritation follow introduction of thiamine chloride into the subarachnoid space. 3. Thiamine deficiency may unmask symptoms due to an organic defect in the brain.

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Effects of Cozymase upon Growth of Staphylococci and Antistaphylococcal Action of Sulfonamide Compounds.*

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Following the report of Knight[1] that thiamin chloride and nicotinic acid are essential growth factors for *S. aureus*, Gladstone[2] demonstrated that a medium of known chemical composition may be used for growth experiments with staphylococci. A chemically-defined medium has certain advantages for the study of the bacteriostatic effect of the sulfonamide compounds upon staphylococci.[3] West and Coburn[4] utilized Knight's "synthetic" medium for an investigation

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1 Knight, B. C. J. G., *Brit. J. Exp. Path.*, 1935, **16**, 315.

2 Gladstone, G. P., *Brit. J. Exp. Path.*, 1937, **18**, 322.

3 Spink, W. W., and Jermsta, J., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 395.

4 West, R., and Coburn, A. F., *J. Exp. Med.*, 1940, **72**, 91.