Since the addition of cytosine-2-C^{14} to the sediment prior to hydrolysis with perchloric acid did not result in the formation of radioactive uracil, no oxidative deamination occurred under the conditions employed. The failure to find uracil, the only base unique to RNA, is difficult to explain. Perhaps RNA and its component parts are rapidly and selectively removed soon after deposition. In addition to the naturally-occurring purines and pyrimidines, other ultraviolet-absorbing and fluorescent compounds were observed on the paper chromatographs. These compounds have not been identified.

A report (*9*) on the aerobic decomposition of these five bases in the solid phase suggests that, at 25°C, adenine and cytosine have half-lives of approximately 10^6 years, guanine and uracil have half-lives of between 10^4 and 10^5 years, whereas thymine has a half-life of less than 10^3 years. The data in Table 1 are consistent with the relative stability of these bases.

Although the estimation of half-lives from extrapolations of laboratory experiments may be valuable as a measure of relative thermal stability and as first approximations to stabilities under natural conditions, their use should not be restrictive. For example, the half-life of alanine at 25°C (solid phase, aerobic, 1 atm) has been calculated to be 20,000 years (*10*). Although this amino acid should not be detectable beyond 5 or 6 half-lives, if originally existing in quantities similar to those in present-day sediments, nevertheless alanine was found in sample EM 7–7 (2.5 μg/g of dry weight); in fact alanine has been found in samples over 10^8 years old (*11*). Therefore, it would not be unreasonable to find the purine and pyrimidine bases in samples much older than their calculated half-lives.

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Allergic Encephalomyelitis: A Hyperacute Form

Abstract. *The hyperacute form of allergic encephalomyelitis is characterized by its short incubation period, 100 percent incidence, overwhelming severity, and high mortality and by the massive quantities of polymorphonuclear neutrophils, fibrin, and edema fluid which infiltrate the central nervous system. The hyperacute form has been produced with the aid of aqueous pertussis vaccine as an adjuvant. This is the first reproducible laboratory model for human acute necrotizing hemorrhagic encephalopathy.*

Experimental allergic encephalomyelitis (EAE) is an inflammatory, autoimmune disease of the nervous system characterized by perivascular infiltrates of mononuclear cells. Usually, it is produced by injecting an emulsion of myelinated nervous tissue in Freund's complete adjuvant (killed mycobacteria, mineral oil, and emulsifying agent). It has been shown that *Bordetella pertussis* organisms can be substituted for the mycobacteria in the oily adjuvant (*1*). Further, it is known that intraperitoneal vaccination with aqueous suspension of pertussis organisms enhances the encephalitogenic effects of nervous tissue injected later by a different route (*2*). Therefore, it was no surprise to find that aqueous pertussis vaccine mixed with aqueous nervous tissue homogenate had an adjuvant effect. Completely unexpected, however, were the discoveries that this aqueous mixture produced EAE much more rapidly than the usual water-in-oil emulsions, that the disease was much more severe, and that it exhibited a qualitative difference in its histopathology.

The disease was produced in Lewis or Fischer-344 rats by intraperitoneal injection of 200 mg (wet weight) of guinea pig or rat spinal cord homogenate mixed with 0.6 ml of commercial pertussis vaccine and diluted to 3.0 ml with saline. Six to nine days later (usually 7 or 8 days), the rats developed clinical signs of EAE. The incidence was 100 percent. Loss of tail tonus progressed rapidly over a few hours to hind limb weakness, paraplegia, and quadriplegia. Most animals died in 1 or 2 days; only a few survived 3 to 7 days. At necropsy, the spinal cord, medulla, nerve roots, cerebellum, and forebrain contained lesions whose intensity and frequency decreased in the order listed. The spinal cord was peppered with perivascular lesions in all the animals. The inflammatory infiltrate contained enormous numbers of polymorphonuclear neutrophils, many monocytes, and relatively few lymphocytes, an order of frequency quite the opposite of that seen in "ordinary" EAE. The inflammatory cells were present in the lumens and walls of veins and capillaries, in perivascular spaces, in perivascular parenchyma, and in meninges. Confluence of inflammatory lesions led to broad fields, especially in the conus medullaris, where the neutrophil exudate obscured all other tissue elements. Vessel walls and perivascular parenchyma were infiltrated with fibrin. Perivascular tissue was edematous and demyelinated. Hemorrhages, focal necrosis, and myelomalacia were seen often. In advanced cases, many vessels were thrombosed (Fig. 1).

An experimental disease of this histopathologic character has not been produced previously in a reproducible manner, although several investigators have described lesions in occasional animals that had some or all of the features described above (*3*). However, a similar condition occurs in man as "acute hemorrhagic necrotizing encephalopathy" (*4*).

We have designated this syndrome "hyperacute" because of the unprecedented severity of the lesion and because of the short incubation period. A few rats developed mild clinical and histologic signs as early as 6 days after inoculation, and some asymptomatic rats also had lesions at this time. The latent period was shortened further by bilateral adrenalectomy on the day the injection was given. All of these rats died or developed clinical signs of EAE 5 or 6 days after injection. However, the pathogenic agent

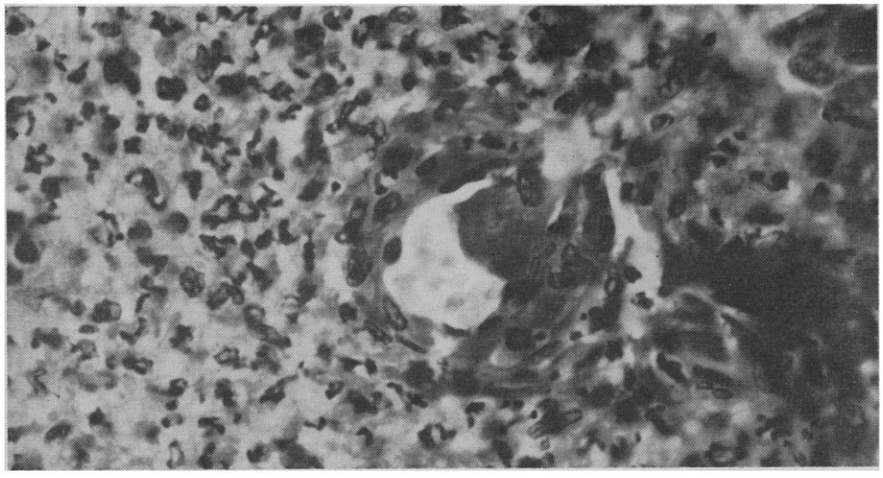

Fig. 1. Section of spinal cord. The upper right portion of the venule is partially occluded by a thrombus. A capillary coming in from the right is also thrombosed. The venule wall and contiguous parenchyma are infiltrated with fibrin and inflammatory cells. There are many polymorphonuclear neutrophils and some monocytes wandering far out into the edematous parenchyma. Lesions of this type were present in enormous numbers in the hyperacute form of allergic encephalomyelitis. Hematoxylin-eosin (× 500).

of the disease was circulating at even earlier times. Its presence was detected by creating focal brain lesions with implants of sterile graphite at intervals after the injection was given, and killing the animals 24 hours later. The EAE lesions were localized around the implant, probably because the blood-brain barrier was disrupted and there was a consequent enhancement of permeability (*5*). With this technique, EAE lesions were found as early as 4 days after the injection of homogenate and pertussis vaccine.

In view of the exceptionally short incubation period and the predominance of polymorphonuclear leukocytes in the lesions, it is necessary to defend our identification of this hyperacute syndrome with ordinary EAE. Both forms of EAE were produced by injection of nervous tissue with an adjuvant. In both forms, the lesions were perivascular, with particular involvement of venules, predilection for the spinal cord, and a tendency to localize around areas in which the blood-brain barrier was artificially attenuated. In both syndromes, the intradermal route of injection (particularly via foot pad) was more effective than the subcutaneous route; mammalian nervous tissue was more effective than nonmammalian; and central nervous tissue was more effective than peripheral nervous tissue. Both syndromes were enhanced by adrenalectomy. Hyperacute EAE was produced with regularity only in those strains of rats that have manifested exceptional susceptibility to ordinary EAE. In most cases of hyperacute EAE, a few lesions could be found that had only mononuclear inflammatory cells and therefore resembled ordinary EAE. Also, the very early presymptomatic lesions were of mononuclear nature. Hyperacute EAE was produced by a mixture of nervous tissue and pertussis vaccine only when the strain of rats, type of nervous tissue antigen, dose of antigen, and route of inoculation were optimum; when any of these conditions was not optimum, then the mixture produced ordinary EAE. Finally, and most conclusively, the passive transfer of mediastinal lymph node cells from rats with hyperacute EAE produced EAE in isogenic recipients, but it was ordinary rather than hyperacute in histologic character. Transfer of serum from the same donors was ineffectual.

Cultures of hindbrain from rats with hyperacute EAE did not grow any bacteria. When 0.4 ml of pooled, homogenized hindbrain tissue collected from rats with hyperacute EAE was injected subcutaneously, no evidence of hyperacute EAE was produced in either of two recipients.

The discovery of the hyperacute form of EAE has raised many questions, and may eventually contribute to the understanding of mechanisms of adjuvant action and pathogenesis of EAE and other delayed hypersensitivities. The histologic character of the lesions is reminiscent of the Arthus reaction and unlike delayed allergies. The predominance of polymorphonuclear neutrophils and the prominence of edema and fibrinous exudate cannot be written off as merely an expression of severity of tissue damage, since there were many very mild lesions (especially in rats with induced localization) that had exactly these features. Despite failures with serum transfers, the possibility that humoral antibody participates in the pathogenesis of hyperacute EAE cannot be excluded. Apart from these conjectures, the most significant feature of this work concerns the nosological identification of acute disseminated encephalomyelitis and acute hemorrhagic necrotizing encephalopathy. It has been suspected that these two human diseases are closely related. Ordinary EAE is widely accepted as the experimental counterpart of the former. The hyperacute form of EAE is clearly a laboratory model for the latter. The relationship between ordinary EAE and hyperacute EAE provides an experimental basis for linking the two human diseases under one pathogenetic mechanism. A complete report on this work will be published elsewhere.

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