the level of the messenger molecules themselves (*11*). Not excluded at this time is an explanation based on the toxic and irritant action of histones on intact, living cells (*12*); many poisons act as stimulants at low concentrations and become inhibitory only at higher dosages. A more plausible interpretation of the results presented, however, is that an inducer acts by inactivating a repressor, and that the primary mechanism of control in cells is always repression. This idea is parallel to the induction-repression hypothesis of genetic regulation (*13*). Our observations can then be explained if it is assumed that the different species of histone molecule present in the total histone extract of chicken liver or calf thymus nuclei have different affinities for different parts of the DNA. The molecular heterogeneity of total histone extracts has been shown by Neelin and Butler (*14*), who obtained up to 18 bands by starch-gel electrophoresis of histones from chicken spleen, liver, erythrocytes, heart, and testis. There is no direct evidence that these fractions have differential affinities for different parts of the DNA, but this specificity seems quite plausible. Even actinomycin D appears to have a differential affinity for different genetic loci in *Escherichia coli*, depending presumably upon the incidence of guanine bases (*15*).

Since the primary effect of histones on DNA is an inhibition of its priming activity, the observed inductive response of LDH to low concentrations of histone may be explained as a secondary result due to the repression of another genetic locus which directs the synthesis of either an aporepressor or a corepressor of the LDH gene, or rather genes, since isozymes of this enzyme occur in chick brain (*16*). This requires that the histones have a higher affinity for this locus than for the LDH genes, so that it is most affected when there is little histone present. As the histone concentration is increased, repression will extend to more loci, with the result that at some concentration the LDH genes will themselves experience a repression. The fact that the amino acid–incorporating activity of the brain tissue can also be increased by relatively low concentrations of exogenous histone indicates that these histones first repress some key loci whose activity tends to control not only LDH synthesis but also the general degree of protein synthesis of the cell. These may be the regulator genes as a group, or they may be some loci directing the synthesis of a set of corepressors with multiple sites of action on the DNA. The added chicken liver or calf thymus histone must then have a relatively high affinity for these key loci so that they are first selected for repression, thereby releasing other loci and raising the amount of general protein synthesis in the cells.

If a step further is taken and histones are identified with aporepressors, then there is the interesting possibility that histones could control their own synthesis in cells. The general picture would thus be that histones are partitioned in their repressive function between histone-producing loci on the DNA (the regulator genes) and other sites directing nonhistone protein synthesis (the operator genes). At different histone concentrations within a cell, structural genes will be differentially influenced, whether derepressed or repressed as in the case of LDH, and at the same time the rate of histone synthesis will be regulated by the amount of histone itself. In this manner the problem of regulating the controls can be resolved by closing the causal sequence of regulation in the cell.

Thus, the synthesis of a particular protein, lactic dehydrogenase, can be almost completely shut off with a concentration of histone (400 $\mu$g/ml) which reduces general protein synthesis to only about 70 percent of the control. This indicates that concentration of histone is an important variable in the selection of cellular states (some genes off, some on at different levels of activity). It is then not necessary to have a large number of distinct histone species in order to generate many stable cellular states, since differing relative concentrations of a few histone species would be effective in producing the different states. This could explain why it is that investigators have often failed to find obvious tissue-specificity of histones (*17*), since the specificity could reside in concentration rather than in type of histone present. These considerations offer another basis for suggesting that histones may be primary regulators of genetic activity, and that they may be identical with the postulated but as yet unidentified aporepressors.

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## Cerebellar Disease in Cats Induced by Inoculation of Rat Virus

Abstract. *Rat virus selectively destroys the external germinal layer of the cerebellar cortex when inoculated intracerebrally into newborn cats. The lesions are marked by numerous intranuclear inclusion bodies and a rise of virus titers. These effects suggest that the spontaneous ataxia of cats which is accompanied by cerebellar hypoplasia, may be of viral origin.*

In a previous report (*1*) we described a lesion of suckling hamsters in which rat virus (*2*) selectively destroys the external germinal layer of the cerebellar cortex and thus induces hypoplasia of the cerebellum and chronic ataxia. Our finding that a similar condition in domestic cats had been described in 1888 (*3*) prompted us to search for a virus as the causative agent of feline ataxia and to study the effects of various strains of rat virus on cerebellar ontogenesis following intracerebral inoculation of neonatal cats.

We used the procedures described in detail previously (*2*, *4*). Rat virus was prepared in rat embryo tissue cultures which thus served as stock pools of virus. The rat embryo cells were first cultured in Eagle's basal medium containing 10 percent calf serum from which the γ-globulin had been removed; the amount of serum was reduced to 2 percent for maintenance of the tissue cultures.

Four strains of rat virus were used for inoculations of kittens. Of these four strains, strain 171 was originally isolated from rats infected with the Moloney leukemia virus (*5*) and another, the original rat 12 strain (*2*), had been carried through 44 passages in hamsters. The origin of the third strain, HHP, has remained uncertain. It was recovered on two occasions from hamsters inoculated at birth with a suspension of a human placenta, obtained from a case of spontaneous abortion at 5½ months. Four other attempts to isolate the virus were unsuccessful, as were attempts to demonstrate antibodies in the patient's serum. Strain HHP differed from other strains of rat virus in its pathogenic effects on hamsters and kittens. These three strains of rat virus were similar antigenically; the fourth strain, H-1 (*6*), originally described by Toolan (*7*), was serologically distinct.

Brain and cerebellar tissues from inoculated cats were made up as suspensions of tissue culture fluid (that is, containing Eagle's basal medium, 10 percent, and calf serum, 10 percent). The methods (*4*) employed for titrating the virus in these preparations were (i) intracerebral inoculation of newborn hamsters, and (ii) inoculation of rat embryo tissue cultures, the appearance of hemagglutinins in the tissue culture fluid being used as endpoints. The results obtained from both types of tests were comparable.

The presence or absence of circulating antibodies to rat virus in cats was determined by inhibition of hemagglutination tests with heat-inactivated serums. Results obtained were verified, in some instances, by neutralization tests performed in the brains of suckling hamsters.

Evidence for proliferation of the HHP strain in cat brain was obtained by titrating the infectivity of the virus in brains of kittens killed on successive days after an intracerebral inoculation of a preparation having a titer of $10^{-6}$. Results obtained were approximately the same for both first and second passages. In each instance there was a rise of virus titer by the 10th day with little or no virus being demonstrable in tissues taken during the 1st week.

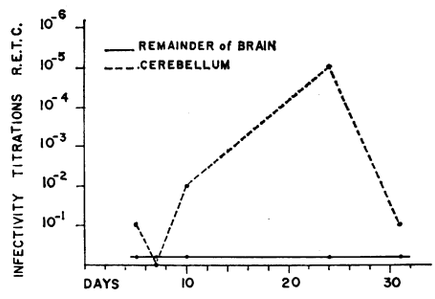


Fig. 1. Growth curve of strain HHP of rat virus in the cerebellum and the remainder of the brain of kittens injected intracerebrally at 1 to 2 days of age with virus obtained after two passages in hamsters. Infectivity was titrated in rat embryo tissue cultures.

Figure 1 shows the results of titrating virus obtained after two passages in kittens. The titer of $10^{-2}$ observed at the 10th day rose to $10^{-5}$ on the 24th day, but fell to $10^{-1}$ in the cerebellum of a kitten of the same litter killed 31 days after inoculation. Little or no virus was recovered from the main portions of brain even though virus was injected into the cerebral hemispheres. Increasing titers were obtained only from the cerebellum, a finding consistent with the histologic evidence for a concentration of virus in this location.

Histologic manifestations of active stages of rat virus infections of the cerebellum were: (i) a phase of extensive infection of the outer germinal layer of the cerebellum indicated by the presence of type A intranuclear inclusion bodies (see Fig. 2) in almost all cells of this rapidly dividing cell population, followed by (ii), a cytopathic phase in which karryorhexsis, lysis, and disappearance of cells became the dominant feature of the tissue reaction.

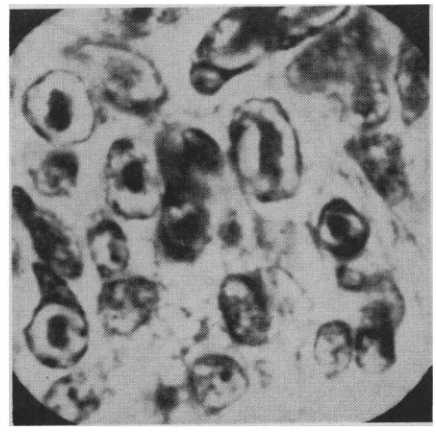

Fig. 2. External germinal layer of cerebellum from a 2-week-old kitten, showing the inclusion-body phase of the rat virus lesion. Virtually every neuroblast shows a type A intranuclear inclusion body. (× 1500)

The cerebellums of five kittens injected intracerebrally with strain HHP at 2 days of age were examined 8, 14, and 21 days later. Intranuclear eosinophilic inclusions were prominent in the germinal zone at 8 and 14 days, and still persisted in the somatic organs at 21 days. Cytopathic effects, present as early as 8 days, were more advanced at 14 days. At both 14 and 21 days, a moderate depletion of outer germinal cells, a mild depletion of the definitive granular zone, and foci of necrosis, involving particularly the Purkinje cells, were noted.

An animal inoculated intracerebrally with strain 171 at 1 day of age and killed on the 11th day, showed the inclusion-body phase of the disease in the outer germinal zone of the cerebellum, but none of the cytopathic effects, which might have developed later, were apparent. The cerebellums of twelve kittens injected with strain H-1, and of two kittens injected with rat 12 strain of rat virus obtained after 44 passages in hamsters, showed no histopathologic changes.

At present it appears unlikely that the rat virus can be the agent of cerebellar hypoplasia and ataxia in cats, since hemagglutination inhibition tests performed with the serums of four kittens (6 to 8 weeks old) and one 1-year-old cat, all with spontaneous cerebellar hypoplasia, and the serums of two normal female cats which bore kittens later developing ataxia, were all negative for antibody against both the rat 12 and the H-1 strains of rat virus. Serums from 30 adult cats in New Hampshire and Vermont were also negative.

None of the kittens given rat virus intracerebrally developed antibodies to the virus within the 31-day period in which they were tested. However, the serum of a single kitten injected intraperitoneally with the HHP strain showed a hemagglutination titer of 1 : 20 when tested 15 days later.

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## Scarp Woodlands, Transported Grassland Soils, and Concept of Grassland Climate in the Great Plains Region


Abstract. *Nonriparian woodlands occur on escarpments and other topographic breaks throughout the grassland province of central North America. Grassland vegetation is mainly correlated with gently sloping or flat terrain mantled by deep, transported soils of Pleistocene or younger age. Paleobotanical evidence suggests that extensive treeless grasslands may be a relatively recent development on the plains. Interaction of topography, wind, and fire may partly account for the observed distribution of vegetation.*


The extensive grasslands of central North America have long been regarded as corresponding to a grassland or steppe climate (*1*). The treeless condition of the flat or gently rolling plains was supposed to be determined primarily by a range of seasonal precipitation too scanty and irregular to support tree growth. The general restriction of trees to riparian habitats is a well-known feature of the Great Plains, and long stringers of gallery forest are shown extending westward along the streams on most vegetation maps. However, one of the more striking vegetational features of the plains region is the widespread but local occurrence of woodlands along escarpments or abrupt breaks in topography, remote from fluvial irrigation (Figs. 1 and 2). A number of nonriparian woodlands of the grassland province, such as the extensive stands of *Pinus ponderosa* along the Pine Ridge escarpment in Nebraska, have received incidental notice in the literature (*2*), but numerous other examples of scarp woodlands in the plains region have apparently escaped much attention. The significance of the prevalence of scarp woodlands throughout the grassland province has therefore not been understood.

The presence of grassland on deep soils with mature profiles contributes to an appearance of great antiquity. There has been a notion that the black or dark-colored grassland soils (chernozems, for example) of the plains region are residual on a variety of underlying bedrocks, which are continually weathering downward under the influence of grassland climate and vegetation to produce a mantle of soil in equilibrium with the denuding agencies of erosion (*3*). However, most of the grassland soils are derived from transported parent materials, chiefly silt and sand, because most of the plains region is mantled by unconsolidated sediments of eolian, alluvial, lacustrine, or glacial origin (*4*). Since the surficial deposits are late Pleistocene or more recent in age, the grassland soils derived from them cannot be of greater antiquity. Eolian silt (loess) or sand (*5*) has spread out in great sheets from alluvial sources, such as periodically dry floodplains of rivers carrying heavy loads of sediment through the plains from glaciated headwaters (*6*). The presence of a constructional mantle of silt or sand has often subdued irregularities on the old erosion surfaces of underlying deposits. The vast sheets of loess have been particularly effective in augmenting the flatness of an already essentially horizontal topography.

There is, then, in the plains region a pattern of very large areas of grassland on deep, transported soils, corresponding to gently sloping or flat topography, and relatively small but widely distributed areas of woodland on escarpments or breaks in topography, characterized by steep slopes and thin, residual soils with bedrock at or near the surface. The type of bedrock on which the scarps are cut is not usually a limiting factor for the occurrence of woodland. Sandstone, shale, limestone, basalt, and other rock types exhibit wooded scarps in various parts of the plains (*7*). Nor is the orientation of the scarp with reference to the sun consistently limiting; woodland often occurs on slopes facing southward as well as northward. The principal features common to the wooded scarps of the plains are their great abruptness, height, and length. Low or gently sloping scarps, or abrupt scarps of small extent, usually lack woodland. The dominant woodland trees are not only reproducing on the thin, rocky soils of the scarps, but in many instances certain species are spreading to the deeper soils of the adjacent grasslands (*8*). Nevertheless, the rule of restriction of nonriparian woodlands to the vicinity of scarps and other rough or broken topography has wide application throughout the vast region of grassy plains; and this is true despite the great diversity in floristic composition of both woodland and grassland, corresponding to the great diversity of climatic conditions (Fig. 1). It may be noted that, on the average, the 50-cm isohyet traverses sectors of the central plains where nonriparian woodlands are few, but it happens that these sectors are particularly lacking in bold escarpments. On the other hand, the average position of the 40-cm isohyet intersects numerous scarp woodlands on the more dissected plains to the west. This suggests that physiography outweighs climate as a factor in the distribution of extensive treeless grasslands.

It is, therefore, misleading to describe the range of climate in the Great Plains as a grassland or steppe climate, with the implication that precipitation, or a combination of precipitation and potential evapotranspiration, is limiting for tree growth. A number of woodland species, notably the junipers, *Juniperus monosperma* and *J. pinchotii*, are remarkably drought resistant. Their present range extends into the Chihuahuan Desert region as extensive woodlands, which intergrade with desert scrub. The junipers often grow in association with one of the most xerophytic shrubs of the American deserts, the creosote bush (*Larrea divaricata* Cav.), under a mean annual precipitation of less than 35 cm, which is highly erratic and interspersed with extremely prolonged and severe droughts. On the other hand, the ranges of the same ecospecies, and other species of *Juniperus*, are continuous with less xerophytic woodlands of ponderosa pine or various oaks, growing in areas with a mean annual precipitation of more than 50 cm; and these wood-