lesion, there was inhibition (▲), which changed into excitation after a low spinal section (×). In addition the pontine lesion gave a release of inhibition to contralateral flexor motor nuclei, which sometimes remained, sometimes changed to excitation after a lesion at obex. Thus the effect of a low pontine lesion is a generalized release of inhibitory group II and III pathways to ipsilateral and contralateral extensor and flexor motoneurones with no sign of a reciprocal or a double reciprocal organization.

There are similarities in the supraspinal control of ipsi- and contralateral effects by high threshold muscle afferents which suggest a functional linkage. However, the experiments with supraspinal control have also given further evidence of the existence of two sets of pathways mediating actions of opposite modality from these afferents to contralateral extensor as well as flexor motoneurones. It is possible (as has been suggested for the ipsilateral effect[4] that the opposite actions on a given contralateral motor nucleus are evoked by one and the same afferent system and that supraspinal centres can select either channel or close both.

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Résumé

Chez le chat spinal des impulsions provoquées dans les fibres afférentes à seuil élevé d'origine musculaire chez le chat spinal facilitent ou inhibent des motoneurones contra-latéraux fléchisseurs et extenseurs. Chez l'animal décérébré, ces actions croisées sont supprimées, tandis qu'après une lésion pontine, les actions inhibitrices se manifestent.

Fig. 1. Sagittal section of cerebellum of a mouse homozygous for 'reeler' gene. Age 18 days. Note: Invasion of molecular layer by various cells, reduction of granular layer and disturbance of the arrangement of Purkinje cells. × 80.

Observations on the Neuropathology of 'Reeler', a Neurological Mutation in Mice[1]

The 'reeler' syndrome is caused by a single recessive gene mutation. The main features of the derangement caused by the 'reeler' gene are: lack of muscular coordination, balancing difficulties and tremors. Mice homozygous for the 'reeler' gene show the disturbance after the 12th day of postnatal age. They rarely survive beyond the 21st day, and we have never been able to raise any of them to breeding age. Mice heterozygous for the 'reeler' gene behave normally.

In a previous communication[2] we reported a 100% increase of cerebellar cholinesterase in mice homozygous for the 'reeler' gene over the values obtained for cerebellar enzyme concentration of normal littermates, who carry the 'reeler' gene either in heterozygous condition or not at all.

A study of the neuropathology of this mutation was begun with a histological analysis of brains of 'reeler' animals.

'Reeler' mice and their normally behaving littermates were sacrificed between the ages 18–21 days postnatally. Their brains were fixed in 10% formalin. The material was embedded in paraffin, cut 15 μ thick in sagittal or parasagittal plane. The sections were stained with cresyl violet.

The histological analysis revealed that the organization of the cerebellum is markedly altered in afflicted 'reeler' animals. The typical appearance of the folia is missing. The arrangement of Purkinje cells which normally surround the granular layer is severely disturbed. The granular layer is much reduced and the area of white matter contains large numbers of cells, which resemble Purkinje cells (Fig. 1 and 2).

The meaning of our findings in terms of neurophysiology is still obscure. The nature of the 'reeler' syndrome, the most dramatic symptoms of which consist of fine intentional tremors, and failure to maintain locomotor balance in homozygous animals certainly suggests cerebellar involvement.

In considering these findings it is of interest that the histological analysis of brains of the 'reeler' mutants revealed a severe disturbance of the cytoarchitectonics of the cerebellum. In a number of neurological mutants in mice, which have been investigated, no gross histological changes within the central nervous system have been detected[3–5]. There are a few exceptions. In the 'agitans' mutation, which resembles the 'reeler' syndrome in some respects, degenerative changes limited to Purkinje cells and to a lesser degree to mossy fibers of the cerebellum of afflicted animals have been reported by MARTINEZ and SIRLIN[6].

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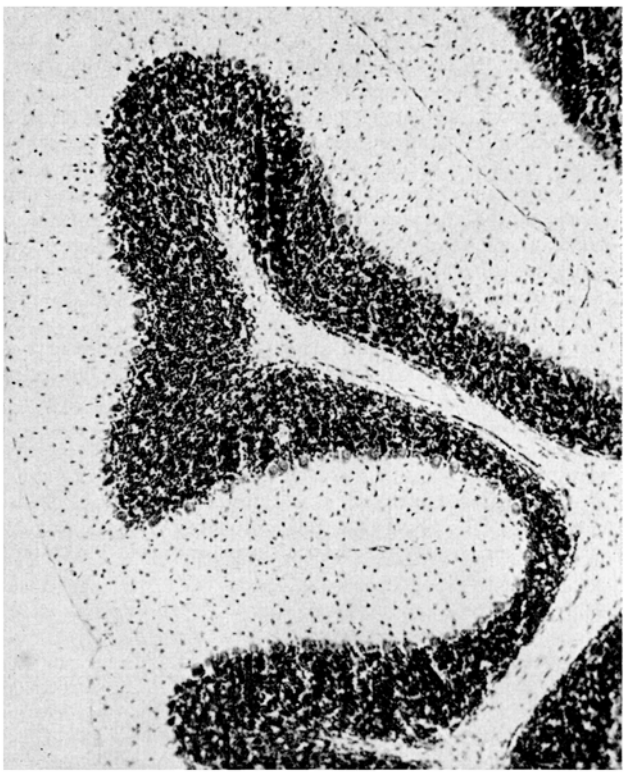

Fig. 2. Comparable sagittal section of cerebellum of normal littermate of the 'reeler' strain. Age 18 days. × 80.

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Zusammenfassung

Eine genetisch bedingte Bewegungsstörung in der Hausmaus «reeler» wurde untersucht. Der Erbgang der «reeler»-Mutation ist einfach rezessiv. In homozygotem Zustand führt das Gen zu Gleichgewichtsstörungen und leichtem Zittern.

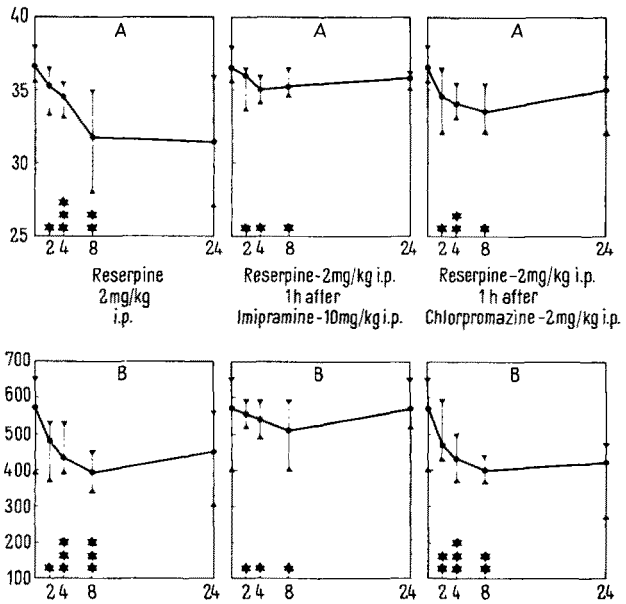
Das Studium der Morphologie des Gehirns der «reeler»-Mäuse ergab, dass die Cytoarchitektonik des Kleinhirns in dieser Mutante verändert und teilweise zerstört ist.

Interactions between Reserpine, Chlorpromazine, and Imipramine

The similarity between the chemical structures of imipramine [N-(γ-dimethyl-aminopropyl/iminodibenzylhydrochloride] and chlorpromazine [10-(-3-dimethylamino propyl)-2-chloro phenothiazine hydrochloride] may account for some analogies in their respective pharmacological properties[1]. Occasionally the therapeutic action of both drugs is comparable[2] but, as a rule, overactive schizophrenics are sedated by chlorpromazine while endogenous depressions are relieved by imipramine[2-3]. Experimental models for the study of the antidepressant effects of imipramine are not at present available. On the other hand differences between the action of this drug and that of other C. N. S. stimulants or antidepressants have been described: (1) Therapeutic doses of imipramine do not attenuate the drive for food nor produces insomnie[2]. (2) Imipramine elates depressed patients but induces neither psychomotor hyperactivity nor manic excitement in normal controls[2]. (3) Motor activity of animals is not increased by imipramine even in doses several times greater than the therapeutic ones[4]. (4) Monoamineoxidase activity of tissue of animal given imipramine remains unaltered[4,5]. This report deals with the effects of imipramine in rats sedated by reserpine.

Results. 10 to 15 mg/kg i. p. of imipramine given to rats before or after reserpine (up to 2·5 mg/kg i. p.) weakened certain effects of that alkaloid. Among others palpebral ptosis was less enduring and its onset was delayed. This antagonism was even greater when three doses of imipramine were given 20, 10, and 1 h before reserpine.

As presented in the Figure palpebral ptosis, hypothermia, bradycardia, and diarrhea all induced by 2 mg/kg i. p. of reserpine were antagonized by the subsequent administration of 10 mg/kg of imipramine. Other experiments revealed that the degree of this antagonism may vary in intensity. The selection of proper doses and time was critical in this respect. Chlorpromazine, 2 mg/kg i. p., given 1 h after reserpine also curtailed hypothermia and diarrhea caused by reserpine (Figure). This antagonistic effect was consistently weaker than that evinced by imipramine, and was observed only with low doses for when the dose of chlorpromazine was increased hypothermia



Interactions between reserpine, Imipramine and chlorpromazine

Abscissas = ←→ Time in h after reserpine injection. Ordinates = ←→ C^0-[*A*], or pulses per minute-[*B*]. * = Degree of diarrhea and ptosis evaluated by an artbitrary score. Number of stars directly proportional to intensity of symptomatology. *A* = Rectal temperature and diarrhea. *B* = Heart rate and ptosis. Vertical bars = Range. Each point is the mean of at least 10 rats.

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