role in the local fixation of blood-borne materials in immunological and anaphylactic reactions. They are numerous in sites of chronic inflammation. It is thought that degranulation and liberation of histamine from mast cells under the influence of local stress may help to bring about an inflammatory oedema; after nerve section the histamine content rises[17] and there is a correlation between the increases in serotonin level and the number of mast cells[9].

The reduction in numbers of mast cells in fowl paralsisy of type III may be due to their obliteration by invading lymphoblasts in the same way as these cell masses have been shown to destroy large numbers of the neurites[18]. No increase in mast cells was noted in adjacent tissues although their response as a defence against tumorigenesis in mammals[16] and against the Rous sarcoma of birds[13,14] has been reported.

Zusammenfassung. Bei der spontanen Marekschen Hühnerlähmung, die durch Ödembildung und Ablagerung von Mucopolysacchariden und Collagen zwischen den Nervenfasern gekennzeichnet ist, erhöht sich auch die Anzahl der Mastzellen bedeutend. Es zeigt sich, dass Nerven, die eine neoplastische Infiltration mit primitiven lymphoiden Zellen aufweisen, weniger Mastzellen als gesunde enthalten. Zur Identifizierung der Mastzellen wurde auch das Elektronenmikroskop verwendet.

P. A. L. WIGHT

Agricultural Research Council, Poultry Research Centre, Edinburgh, 9 (Scotland), 17th April 1967.

[17] H. KWIATKOWSKI, J. Physiol., Lond. *102*, 32 (1943).
[18] P. A. L. WIGHT, Res. vet. Sci. *5*, 46 (1964).

Monoamine Pathways to the Cerebellum and Cerebral Cortex

From previous work[1] it is known that the noradrenaline (NA) and 5-hydroxytryptamine (5-HT) nerve terminals of the rat cerebral cortex derive from axons which originate from NA and 5-HT cell bodies in the lower brain stem and ascend mainly in the medial forebrain bundle. After axotomy retrograde changes occur in those cell bodies and monoamines accumulate in the neuron proximal to the lesion[2,3]. Using these principles the effect of removal of the cerebral cortex and cerebellum on the central monoamine neurons has been studied with the help of the histochemical fluorescence method[4,5].

Adult male Sprague-Dawley rats were used both in the histochemical and biochemical experiments. In about half of the animals used for histochemistry the cerebral cortex was removed uni- or bilaterally. In some cases the cortex was transversely cut at the level of anterior commissure. In these operations the scull was opened and the dura removed so that as much as possible of the cerebral cortex was exposed. The lesions were performed by means of suction with a fine glass cannula. In the other animals taken for histochemistry as much as possible of the cerebellum was removed in an analogous way. All operations were performed in ether anaesthesia. At different time-intervals after the operation the animals were killed by decapitation under light chloroform anaesthesia. The various parts of the brain were dissected out, freeze-dried, treated with formaldehyde gas for 1 h, embedded, mounted and examined as described previously[6,7].

In the biochemical experiments the concentration of NA and 5-HT in the cerebellum, the cerebral cortex, the amygdala and the hippocampus were determined spectrophotofluorimetrically after cation exchange chromatography[8-10].

Removal of cerebral cortex. Usually more than $^2/_3$ of the cortex were removed. In most cases the basal layers were preserved. At all time-intervals (1–5 days) studied there was a marked accumulation of NA and 5-HT in axons running fronto-occipitally in the cingulum frontal but not occipital to the place of the lesion (Figure 1). The axons could be traced frontal for several mm and were seen to enter the cingulum just frontal to the septal area.

The axons were very thin and appeared to be unmyelinated. In no case did monoamine-containing cell bodies appear in the remaining parts of the cortex. Sometimes the damage penetrated also into the subcortical structures. In these cases an accumulation of catecholamines (CA) and 5-HT, respectively, was observed in a large number of axons in the striae terminalis, the dorsal fornix, and the fimbriae hippocampi frontal to the lesion. These axons normally innervate the amygdala and the hippocampus, which were found to contain rather high levels of NA and 5-HT (Table) or between 5 and 15% of the total content of these amines in the entire brain. In those cases where the gyrus cinguli remained intact, an increased number of NA nerve terminals with an increased intensity were observed in this area. Retrograde cell body changes with inter alia a swollen appearance and a marked increased fluorescence intensity occurred in CA nerve cells in the ventro-lateral part of the reticular formation of the medulla oblongata (group A1 according to DAHLSTRÖM and FUXE 1964) (Figure 2). However, only part of the cell group (about 20%) was affected. Certain increases in fluorescence intensity were also observed in a small number of CA cell bodies of the pons whereas no certain increases could be seen in the mesencephalic CA

[1] N.-E. ANDÉN, A. DAHLSTRÖM, K. FUXE, K. LARSSON, L. OLSON and U. UNGERSTEDT, Acta physiol. scand. *67*, 313 (1966).
[2] A. DAHLSTRÖM and K. FUXE, Acta physiol. scand. *64*, Suppl. *247*, 5 (1965).
[3] N.-E. ANDÉN, A. DAHLSTRÖM, K. FUXE and K. LARSSON, Am. J. Anat. *116*, 329 (1965).
[4] N.-Å. HILLARP, K. FUXE and A. DAHLSTRÖM, in *Mechanisms of Release of Biogenic Amines* (Eds. U. S. v. EULER, S. ROSELL and B. UVNÄS; Pergamon Press 1966), p. 31.
[5] H. CORRODI and G. JONSSON, J. Histochem. Cytochem. *15*, 65 (1967).
[6] A. DAHLSTRÖM and K. FUXE, Acta physiol. scand. *62*, Suppl. 232 (1964).
[7] B. HAMBERGER, T. MALMFORS and CH. SACHS, J. Histochem. Cytochem. *13*, 147 (1965).
[8] Å. BERTLER, A. CARLSSON and E. ROSENGREN, Acta physiol. scand. *44*, 273 (1958).
[9] Å. BERTLER, Acta physiol. scand. *51*, 75 (1961).
[10] N.-E. ANDÉN and T. MAGNUSSON, Acta physiol. scand. *69*, 87 (1967).

cell groups. The number of cells with increased fluorescence intensity were highest after bilateral removal. After unilateral removal cells with increased fluorescence intensity were observed in group A1 mainly on the operated side but also on the unoperated side, indicating a certain degree of crossing. The 5-HT cell bodies and the NA and 5-HT nerve terminals of the lower brain stem all appeared unaffected.

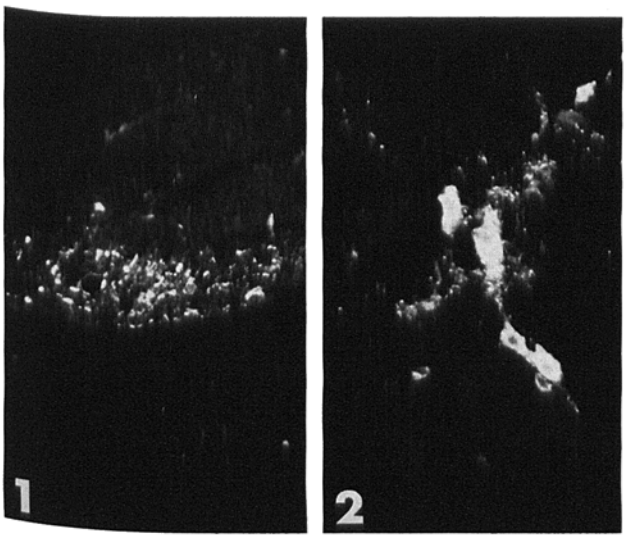
Biochemically the cerebral cortex was found to contain rather high levels of NA and 5-HT (Table). Both the NA and 5-HT in the cortex were found to amount to about 25-30% of the total content of the amines in the entire brain.

Removal of the cerebellum. The cerebellum was usually completely removed with the exception of the lateral parts. The medulla oblongata and pons were usually not damaged. There was a marked increase in intensity in some of the CA cell bodies which appeared swollen and had a displaced nucleus. The changes were mainly limited to group A1 on both sides. The number of cells with retrograde changes was distinctly less than after removal of the cerebral cortex. A small number of CA cell bodies of the pons (mainly in the locus coeruleus area) showed similar changes. Otherwise no certain changes were observed in the fluorescence microscopical picture.

Biochemically, the normal rat cerebellum was found to contain a rather high concentration of NA but only a low one of 5-HT. This NA and 5-HT represented approximately 6–10 and 2–3%, respectively, of the total amount in the brain (Table).

The fact that there appear NA cell bodies with retrograde changes mainly in the medulla oblongata but also in the pons after removal of large parts of the cortex cerebri or the cerebellum indicate that most, if not all, of the NA nerve terminals in the cerebral cortex and in the cerebellum arise from axons which originate from NA cell bodies situated probably mainly in the reticular formation of the medulla oblongata (group A1) but also in the pons. In view of the present findings it may even be that the same NA neuron may innervate both the cerebral cortex and cerebellum, since the affected cell bodies lie in the same CA cell-group. A previous study[11] on the effect of large diencephalic-mesencephalic lesions on the monoamine neurons also support such a view, since increases in number and intensity of the NA nerve terminals were observed e.g. in the cerebellum and the medulla oblongata after such lesions. This is probably due to the fact that the amine storage granules which are produced in the cell bodies and transported down to the terminals via the axons[12,13], after such lesions are directed into the collaterals since the axons to the cerebral cortex and other forebrain structures had been damaged. The present findings of increases in the intensity and number of NA nerve terminals in the gyrus cinguli after removal of large parts of the cortex cerebri can be explained in the same way.

The present results also show that the NA and 5-HT axons innervating the cortex cerebri in all probability run in the cingulum, since a large number of nonterminal axons with high amounts of NA and 5-HT were found here after removal of parts of the cortex cerebri. Furthermore, after treatment with nialamide 5-HT axons ascending in the medial forebrain bundle have been seen to by-pass the septal area to enter the cingulum[14]. Studies on the uptake of CA and 5-HT after intraventricular injections have also revealed the presence of fibres able to accumulate NA and 5-HT in this area[15,16]. All these data taken together strongly support the present results. Fibre degeneration has also been observed with the method of Nauta and Gygax in the cingulum after lateral hypothalamic lesions[17,18].



Concentrations ($\mu g/g$; mean ± s.e.m.) of noradrenaline and 5-hydroxytryptamine in the cerebellum, the cerebral cortex, the amygdala and the hippocampus of normal rats. Number of determinations is indicated in parentheses.

	Noradrenaline	5-Hydroxytryptamine
Cerebellum	0.18 ± 0.010 (10)	0.07 ± 0.013 (4)
Cerebral cortex	0.25 ± 0.009 (8)	0.32 ± 0.020 (8)
Amygdala	0.37 ± 0.037 (6)	0.49 ± 0.068 (6)
Hippocampus	0.43 ± 0.041 (6)	0.32 ± 0.032 (6)

Zusammenfassung. In kombinierter histochemischer und biochemischer Untersuchung werden Dopamin-, Noradrenalin- und 5-Hydroxytryptamin-Neurone nach Entfernung von Cortex cerebri und Cerebellum studiert. Es ergibt sich, dass die Noradrenalin-Nerventerminale, welche Cortex cerebri und Cerebellum innervieren, vermutlich von feinen Axonen her stammen, deren Zellkörper mindestens zum Teil in der Formatio reticularis der Medulla oblongata gelegen sind. Die Noradrenalin- und 5-Hydroxytryptamin-Axone, die nach dem Cortex cerebri ziehen, passieren vermutlich zur Hauptsache das Cingulum.

N.-E. Andén, K. Fuxe and U. Ungerstedt

Department of Pharmacology, University of Göteborg and Department of Histology, Karolinska Institutet, Stockholm 60 (Sweden), 6th March 1967.

[11] N.-E. Andén, K. Fuxe and K. Larsson, Experientia *22*, 842 (1966).
[12] A. Dahlström, K. Fuxe and N.-Å. Hillarp, Acta pharmac. tox. *22*, 277 (1965).
[13] A. Dahlström, M. D. Thesis, Stockholm 1966.
[14] K. Fuxe, Acta physiol. scand. *64*, Suppl. 247, 37 (1965).
[15] K. Fuxe and U. Ungerstedt, Life Sci. *5*, 1817 (1966).
[16] K. Fuxe and U. Ungerstedt, Z. Zellforsch. mikrosk. Anat., in press.
[17] G. Wolf and J. Sutin, J. comp. Neurol. *127*, 137 (1966).
[18] Acknowledgments: this work has been supported by grants (No. K67-14x-502-03, 12x-715-02) from the Swedish State Medical Research Council and by grants from Stiftelsen Therese och Johan Anderssons Minne and M. Bergwalls Stiftelse.