Certainly, the small pore system is important for the exchange of free coumarin and for that bound to the fast and slow α_1 globulins (mol.wt ~45,000) and explains the rapid entry of coumarin into most tissues[10]. The endothelial vesicle and large pore system will allow the entry, albeit slower, of coumarin bound to the larger macromolecules like α_2 globulin.

The mode of action of coumarin and related drugs is very complex[7,11] and while it seems that either a protein-coumarin type complex or just free coumarin could be responsible for macrophage activation[7,12–14], which results in increased protein lysis[15] through its intra and extra cellular digestion, we have yet to elucidate the exact importance of the free and bound coumarin.

It has frequently been reported[7] that in the initial 30 min after benzopyrone administration, there is the release of endogenous amines which result in the opening of additional numbers of endothelial junctions[7,16], and allow some extra protein (and protein bound coumarin) into the tissues. I must mention here that this effect is transient and the small additional protein inflow is more than compensated for by the later action, that of enhancing the lysis of all accumulated protein[7,17,18]. The effect of the drug in causing the opening of additional endothelial junctions does however allow extra protein bound drug into the tissues and into close proximity to the target cells.

Further work is currently in progress to ascertain the importance of drug protein binding in models of mild thermal oedema, acute and chronic lymphoedema and to relate this to the effectiveness of coumarin as an oedema reducing agent.

10 N. B. Piller, Br. J. exp. Path., in press (1977).
11 N. B. Piller, J. vasc. Dis., in press (1977).
12 T. Bolton and J. R. Casley-Smith, Experientia *31*, 271 (1975).
13 N. B. Piller, Br. J. exp. Path. *57*, 170 (1976).
14 N. B. Piller, Res. exp. Med. *168*, 165 (1976).
15 N. B. Piller, Arzneimittel-Forsch., in press (1977).
16 J. R. Casley-Smith and J. Window, Microvasc. Res. *8* (1975).
17 N. B. Piller, Burns *2*, 143 (1976).
18 N. B. Piller, Lymphology *9*, 132 (1976).

The effect of L-Dopa on the spinal monosynaptic mass reflex

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Summary. After i.v. injection of reserpine, the monosynaptic mass reflex (MSMR) is depressed in spinalized cats. However, the complete recovery of MSMR was obtained 30 min after L-Dopa application. Pimozide, a dopamine-receptor blocking agent, blocked this action of L-Dopa. It is presumed that dopaminergic receptors are involved in the action of L-Dopa on spinal MSMR.

Alterations in central catecholamine metabolism have been found to attend a number of neurological disorders. These changes have often been assumed to reflect altered nerve activity in neural systems containing these amines. Dopamine (DA) is a widely distributed, naturally occurring compound[1]. The highest level of DA has been found in the neostriatum in conjunction with the dopaminergic nigro-striatal pathway[2]. However, recent investigations have shown relative high concentrations of DA in the spinal cord[3–7]. Its role in the central nervous system, both as a precursor to noradrenaline (NA) and as a putative neurotransmitter, has been intensively studied[2,8]. The object of this study is to examine further the validity of this assumption by studying the effects of L-Dopa (L-3,4-dihydroxyphenylalanine) on spinal MSMR.

Materials and methods. Experiments were performed on 18 adult cats of both sex. Cats were anaesthetized with thiopental (30 mg/kg i.p.) and the spinal cord was transsected at C_1 segment. The animals were maintained in a slightly hyperventilated condition by respiratory pump. A dorsal laminectomy was performed from L_6 to S_1, and the cord was exposed and covered with warm mineral oil. The medial gastrocnemius plus soleus nerves (GS) were isolated for electrical stimulation. The GS was stimulated (5–10 V/0.1 msec 0.3 Hz) and its monosynaptic reflex recorded monophasically in the L_7 or S_1 ventral root. The resulting electrical activity was amplified and displayed according to conventional methods and recorded before and after i.v. injection of reserpine, L-Dopa and pimozide (diphenylbutyl piperidine).

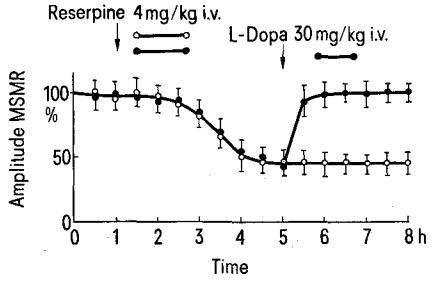

Fig. 1. Effect of reserpine and L-Dopa on monosynaptic mass reflex (MSMR). All values are graphed as percentage of the control value obtained just prior to drug injection. Each point represents the mean of 6 experiments (± SEM).

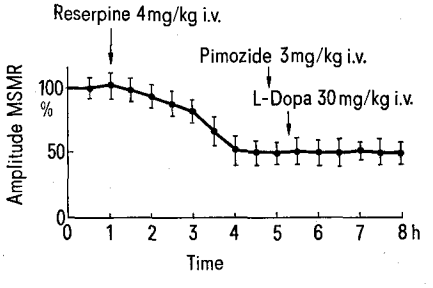

Fig. 2. The time course of pimozide antagonism of the effects of L-Dopa on monosynaptic mass reflex (MSMR). Each point represents the mean of 6 experiments (± SEM).

Results. The effect of reserpine on MSMR evoked from extensor GS nerves was investigated in 6 cats. In all experiments, 5 h after i.v. injection of reserpine (4 mg/kg) marked reduction of MSMR amplitude was observed (figure 1). Thus, in 6 experiments, L-Dopa (30 mg/kg i.v.) completely antagonized the reserpine-induced decrease in the monosynaptic spike height (figure 1). The L-Dopa induced antagonism on reserpine effect appeared within 20–30 min of the injection of L-Dopa. Pimozide (3 mg/kg i.v.) antagonized the L-Dopa induced recovery (increase) in the MSMR spike after reserpine (figure 2). These experiments were performed on 6 cats.

Discussion. Results obtained clearly demonstrate that reserpine and L-Dopa alter spinal neuronal activity. Because the time sequence of reserpine-induced decrease of the MSMR is correspondent with the time sequence of the reserpine-induced neuronal depletion of catecholamines[9], it seems probable that catecholamines in the spinal cord determine in some way the size of the motoneurons-pool which take part in the MSMR. On the other hand, the recovery (increase) of the monosynaptic spike amplitude following L-Dopa is a reflection of the rise in recruitment of motoneurons which are at monosynaptic input disposal. This effect seems to be due to a neuronally restored content of catecholamines (DA and/or NA) synthesized centrally from L-Dopa[10]. Pimozide was reported to be a DA-receptor blocking agent without any apparent NA-receptor blocking ability in the central nervous system[11]. In fact, antagonizing action of pimozide on the L-Dopa-induced recovery (increase) of monosynaptic spike after reserpine, strongly indicates that dopaminergic receptors could be involved in the action L-Dopa on spinal MSMR. Further study will be done to prove or disprove definitely this assumption.

1 M. Holzbauer and D. F. Sharman, Handbk. of expl. Pharmac. *33*, 110 (1972).
2 O. Hornykiewicz, Pharmac. Rev. *18*, 925 (1966).
3 T. Magnussen, Naunyn-Schmiedebergs Arch. Pharmak. *278*, 13 (1973).
4 C. V. Atack, Br. J. Pharmac *48*, 699 (1973).
5 J. L. Reid, J. A. Zivin, F. Foppen and I. J. Kopin, Life Sci. *16*, 975 (1975).
6 J. A. Zivin, J. L. Reid, J. M. Saavedra and I. J. Kopin, Brain Res. *99*, 293 (1975).
7 W. G. Birgham, R. Ruffolo, J. H. Goodman, J. Knofel and S. Friedman, Life Sci. *16*, 1521 (1975).
8 A. Carlsson, in: Recent Advances in Parkinsons Disease. McDowell and Markham, Philadelphia 1971.
9 A. Dahlström, K. Fuxe and N.-A. Hillarp, Acta pharmac. toxic. *22*, 277 (1965).
10 N.-E. Anden, M. G. M. Jukes and A. Lundberg, Nature *202*, 1222 (1964).
11 N.-E. Anden, S. G. Butcher, H. Corrodi, K. Fuxe and U. Ungerstedt, Eur. J. Pharmac. *11*, 303 (1970).

Changes in gentamicin pharmacokinetics after reduction of renal parenchyma

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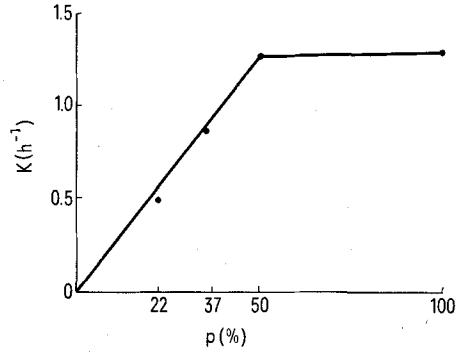
Summary. The relationship between the elimination constant of gentamicin and the percentage of functioning nephrons in rats cannot be characterized by a simple linear relation. The results support the assumption that gentamicin elimination per residual nephron increased.

The decrease of renal function caused by various pathological processes is associated with a decrease of the elimination constant (and an increase of biological half-life) of drugs, which are eliminated from the body predominantly by the kidneys. The elimination constant of many drugs decreases in linear relation to the decrease of glomerular filtration rate[1]. However this renal function does not decrease in a simple linear relation to the number of functioning nephrons[2]. We have attempted to study the relationship between changes in the elimination constant (K) of gentimicin and the percentage of functioning nephrons.



Elimination constant of gentamicin in rats with different amount of renal parenchyma. K = elimination constant (total); p = % of remaining renal parenchyma.

Methods. In our experiments we used female SPF rats of the Wistar strain. Before the experiment, their weight was about 200 g. The renal parenchyma was reduced to 50, 37, 22 and 0% of the normal amount (for details see table). After the operation, the rats were fed a high protein diet. On postoperative day 11, gentamicin was administrated i.m. in doses 6 mg/kg. Gentamicin concentrations in serum were measured by the technique described earlier[3].

The amount of remaining renal parenchyma expressed as percentage of the initial value (p) was calculated according to the formula:

$$p = \frac{KW - E}{KW} \times 100 \qquad (1)$$

Where KW = weight of both kidneys, E = weight of the extirpated tissue. The values of K and biological half-life were calculated in the usual way[4]. As the K of gentamicin in rats is given practically only by its renal excretion (see the K value after bilateral nephrectomy), this value may be regarded as the renal elimination con-

1 L. C. Dettli, Clin. Pharmac. Ther. *16*, 274 (1973).
2 E. A. Arrizurieta de Muchnik, E. M. Lipham and C. W. Gottschalk, in: Compensatory Renal Hypertrophy. Ed. W. Nowinski and R. Y. Goss. Academic Press, New York and London 1969.
3 M. Hatala, J. Morávek and O. Schück, Int. J. clin. Pharmac. *11*, 1 (1975).
4 F. H. Dost, Grundlagen der Pharmakokinetik. G. Thieme, Stuttgart 1968.