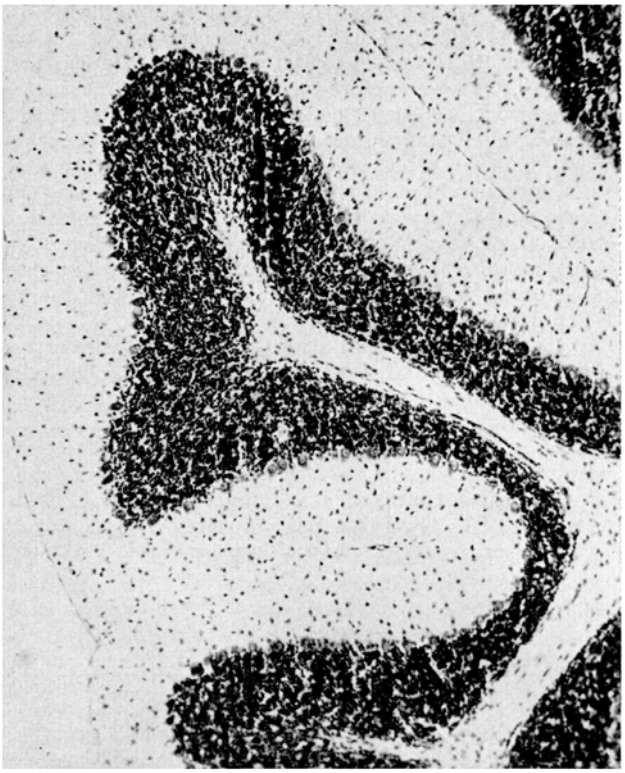


Fig. 2. Comparable sagittal section of cerebellum of normal littermate of the 'reeler' strain. Age 18 days. × 80.

M. Hamburgh

Department of Anatomy, Albert Einstein College of Medicine, New York, July 4, 1960.

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.

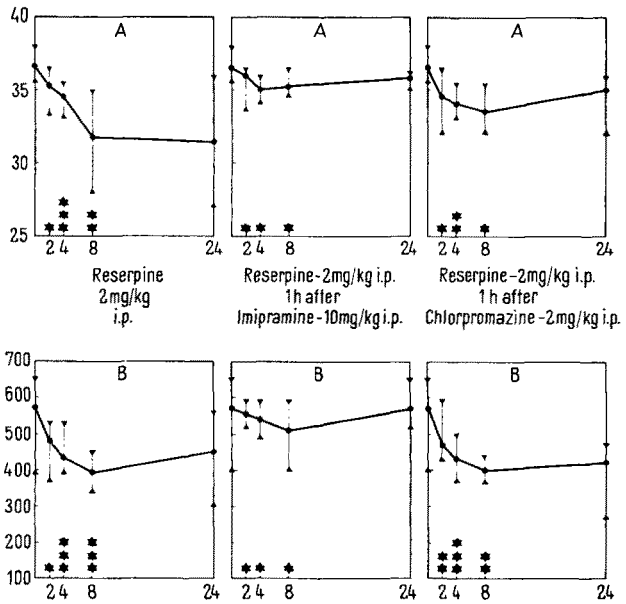
Das Studium der Morphologie des Gehirns der «reeler»-Mäuse ergab, dass die Cytoarchitektonik des Kleinhirns in dieser Mutante verändert und teilweise zerstört ist.

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.

[1] R. Domenjoz, W. Theobald, Arch. int. Pharm. *120*, 150 (1959).

[2] R. Kuhn, Amer. J. Psych. *115*, 459 (1958).

[3] H. E. Lehmann, C. H. Cohn, and R. L. De Verteuil, Canad. Psych. Ass. J. *3*, 155 (1958).

[4] E. B. Sigg, Canad. Psych. Ass. J. *4*, Suppl. 75 (1959).

[5] E. Costa, Int. Rev. Neurobiol. *2* (1960), in press.

and diarrhea induced by reserpine were not reversed. In rats sedation caused by chlorpromazine injections was synergistic with that of reserpine. Not all the pharmacological actions of reserpine were antagonized by imipramine. In agreement with THEOBALD[6] the blocking induced by reserpine on a previously established avoidance-escape conditioned reflex was unaffected by imipramine. Using imipramine we were unable to shorten the reserpine induced prolongation of pentobarbital hypnosis. However under different experimental conditions DOMENJOZ[1] antagonized the action of the alkaloid to prolong barbiturate narcosis. More recently SULSER[7] *et al.* successfully used imipramine to antagonize the effects of reserpine on the depression induced by alcohol in mice. This antagonism is shown only with selected doses of alcohol. An attempt to elucidate the mechanisms involved in the antagonism of reserpine effects by imipramine was made by determining the concentrations of serotonin in brain of rats given the drugs in discussion. For comparison animals given chlorpromazine either alone or associated with reserpine were also used. The results obtained and the particular experimental conditions are presented in Table I.

Brain serotonin content of rats given imipramine 3 h prior 50 mg/kg i. p. of 5HTP (5-hydroxytryptophan) and killed after 1 h was not greater than that of animals given only 5HTP. It is therefore probable that this increase of brain serotonin was independent from an action of imipramine on synthesis and destruction of the biogenic amine. This idea receives support in the finding that serotonin concentrations of spleen, liver (Table II) lung, intestine, and kidney were unaffected by imipramine.

MARSHALL *et al.*[14] found that imipramine, like reserpine[15], inhibited serotonin uptake by platelets and lowered the serotonin content of platelets. However imipramine does not release tissue serotonin.

The depletion of brain serotonin caused by reserpine was not potentiated by imipramine (Table I). 15 mg/kg of chlorpromazine given 1 h prior reserpine did not prevent the depletion of brain serotonin (Table I).

To complete the study of the interactions between imipramine and serotonin the effect of imipramine on 5HTP induced diarrhea in mice[16] was compared to that of chlorpromazine. *In vivo* (Table III) imipramine was a weaker antagonist of serotonin than chlorpromazine. The latter

Tab. I

Drug injected [a] mg/kg i.p.	Brain Serotonin [b] ng/g	
	Bioassay [c]	Spectrofluorimetric Assay [d]
Saline	241 (285–197) (25)	470 (486–456) (50)
Reserpine 1·0	160 (191–120) (12)	270 (312–288) (8) [e]
Reserpine 2·5	142 (182–102) (12) [e]	170 (190–180) (25) [e]
Imipramine 5·0	259 (288–231) (6)	—
Imipramine 7·5	—	550 (610–490) (8)
Imipramine 10·0	516 (645–404) (16) [e]	—
Imipramine 15·0	422 (476–373) (6) [e]	700 (754–646) (8) [e]
Chlorpromazine 10·0	278 (422–147) (9)	—
Chlorpromazine 15·0	486 (686–286) (6)	530 (574–486) (16)
Imipramine 15·0 + Reserpine 1·0	270 (303–237) (11)	300 (333–267) (8) [e]
Imipramine 15·0 + Reserpine 2·5	—	320 (357–283) (8) [e]
Chlorpromazine 15·0 + Reserpine 1·0	313 (384–242) (6)	—
Chlorpromazine 15 + Reserpine 2·5	—	340 (385–295) (16) [e]

[a] The time interval between injections was 1 h. [b] The animals were killed 4 h after the injections. When reserpine was injected with other drugs the animals were killed 4 h after reserpine. [c] Bioassay was performed in 200 g Wistar rats according to GARVEN[8]. [d] Spectrofluorimetric measurement of serotonin was performed in 200 g. Sprague-Dawley rats according to BOGDANSKY *et al.*[9]. [e] Significant at $P = 0.5$ level versus controls.

In parenthesis are reported the fiducial limits and the number of animals. Fiducial limits = mean + (S. E. × T) calculated at $P = 0.1$ with n-2 degrees of freedom[10].

Imipramine and to a lesser extent chlorpromazine significantly increased brain serotonin concentrations. After single intraperitoneal injections of imipramine (15 mg/kg) the increase of brain serotonin reached its peak within 4–5 h and disappeared in approximately 8 h. Maximal effects were obtained with 10–15 mg/kg of imipramine, while greater doses were eventually less effective. The necessity to select dose and time could explain the negative results obtained by PLETSCHER[11]. The increase of brain serotonin after imipramine was smaller than that found[12] in brain of rats given monoamineoxidase inhibitors but comparable with that found after electroshock[13]. Unlike slow acting MAOI[11] the rise of brain serotonin caused by imipramine was not greater in chronic (Table II) than in acute experiments.

[6] W. THEOBALD, Med. exper. *1*, 102 (1959).
[7] F. SULSER, J. WATMS, B. B. BRODIE, Fed. Proc. *19*, 268 (1960).
[8] J. D. GARVEN, Brit. J. Pharmacol *11*, 66 (1956).
[9] D. F. BOGDANSKI, A. PLETSCHER, B. B. BRODIE, and S. J. UDENFRIEND, J. Pharmacol. *117*, 82 (1956).
[10] W. J. DIXON and F. J. MASSEY, *Introduction to Statistical Analysis* (McGraw-Hill 1951), p. 157.
[11] A. PLETSCHER and K. F. GEY, Helv. physiol. pharm. Acta *17*, C 35 (1959).
[12] S. SPECTOR, P. A. SHORE, and B. B. BRODIE, J. Pharmacol. *128*, 15 (1960).
[13] S. GARATTINI, Sonderd. Schweiz. Arch. Neurol. Neurochem. Psych. *84*, 269 (1959).
[14] E. F. MARSHALL, G. S. STIRLING, A. C. TAIT, and A. TODRICK, Brit. J. Pharmacol. (1960), in press.
[15] B. F. HUGHES and B. B. BRODIE, J. Pharmacol. *127*, 96 (1959).
[16] D.W.WOOLLEY, Proc. Soc. exp. Biol. Med., N.Y. *98*, 367 (1958).

also antagonized more efficiently than imipramine the actions of histamine[4] and catecholamines[1].

Conclusions. The results reported in this paper demonstrate that imipramine curtails selected pharmacological actions of reserpine including brain serotonin depletion. *Imipramine* antagonizes reserpine more extensively than chlorpromazine does. Yet the latter inhibits the effects of the biogenic amines released by reserpine more promptly than imipramine[1,4]. In cats the effects of blood-borne norepinephrine are inhibited by chlorpromazine[17] but potentiated by 2 to 5 mg/kg of imipramine[4]. Greater doses of imipramine inhibited epinephrine and norepinephrine effects[18]. However imipramine differently from classic cocaine-like sensitizers[19] fails to potentiate the response of nictitating membrane to the stimulation of cervical sympathetic postganglionic nerves[17]. The sedative activity of chlorpromazine and imipramine seems to be roughly correlated to their respective capacity to inhibit norepinephrire effects.

The inhibition of serotonin uptake by platelets caused by reserpine[14] and imipramine[13] suggests that these drugs impare active transport of the amine. Imipramine and reserpine also alter brain serotonin concentrations but these changes are in opposite direction. Thus a competition for identical sites of action although possible does not readily explain the interactions between reserpine and imipramine. However the possibility that the effects of imipramine on active transport of serotonin play a role in the interrelations between this drug and reserpine cannot be excluded.

In conclusion the mechanisms involved in the antagonism between reserpine and imipramine and by and large in the therapeutic action of imipramine remain practically unknown. The difference between the pharmacological effects of chlorpromazine and imipramine are at present only quantitative, but not qualitative. Chlorpromazine and imipramine are both sedative and antagonist of reserpine. In the case of chlorpromazine both activities have a comparable low threshold and the two actions almost overlap. In the case of imipramine the sedation is caused by doses greater than those antagonizing reserpine.

Tab. II

Tissue	ng/g of Serotonin	
	Controls	Imipramine [a]
Brain	(30) 309 (359–269)	(18) 445 (499–391)
Spleen	(30) 1520 (1780–1260)	(18) 1692 (2050–1334)
Liver	(30) 146 (170–122)	(18) 113 (133–93)

[a] 20 mg/kg of imipramine were injected 7 times during 96 h, last injection 70 min before killing the animal. Serotonin assayed according to the biological method of GARVEN[7].

Tab. III. Antagonism on 5-HTP Induced Diarrhea in Mice

Drug injected mg/kg i. p. 20 min before 5-HTP (mg/kg i. p.)	ED_{50} [a] mg/kg i. p.	ID_{50} mg/kg i. v.	LD_{50}/ED_{50}
Chlorpromazine	3·64	50	13·73
Imipramine	20·00	38	1·94

[a] According to LITCHFIELD and WILCONXON[20].

E. COSTA, S. GARATTINI, and L. VALZELLI

Galesburg State Research Hospital, Galesburg (Ill.) and Istituto di Farmacologia, Università degli Studi, Milano (Italy), February 18, 1960.

Riassunto

Sia la cloropromazina che l'imipramina antagonizzano determinati effetti farmacologici della reserpina. L'effetto antagonista dell'imipramina, che come quello della cloropromazina richiede condizioni sperimentali appropriate ha un più ampio spettro. L'effetto sedativo della cloropromazina è più marcato di quello della imipramina ed è sinergico con la depressione indotta dalla reserpina.

[17] S. CURVOISIER, J. FOURNEL, R. DUCROT, M. KOLSKY, and P. KOETSCHET, Arch. int. Pharmacodyn. *92*, 305 (1953).
[18] U. TRENDELENBURG, J. Pharmacol. *125*, 55 (1959).
[19] C. MORPURGO and E. COSTA, unpublished observations
[20] J. J. LITCHFIELD, JR., and F. WILCOXON, J. Pharmacol. *96*, 99 (1949).

Hematological and Serological Investigations in Heteroparabiosis

Many investigations on experimental homoioparabiosis of adult animals have shown that parabiotic intoxication occurs between unrelated specimens[1]. This intoxication in one of the partners appears in the form of strong hemolytic anemia, loss of weight, and involution of lymphoid tissues, resulting in death within two weeks[2]. In the other parabiont, these manifestations are frequently accompanied by polycythemia and hyperplasia of lymphoid tissues. Parabiotic intoxication is due to genetic and serological differences between the partners, since the symptoms of intoxication have never been observed in parabiosis of inbred-strain mice or in mice of closely-related strains[3–5]. CHUTE and SOMMERS[6] confirmed the immunological basis of parabiotic intoxication by their discovery of hemagglutinins against erythrocytes of the anemic parabiont during rat parabiosis with severe hemolytic anemia in one of the partners.

This report refers to hematological and serological investigations on experimental mouse-hamster heteroparabiosis where an intensification of symptoms of parabiotic intoxication were to be expected in consequence of greater genetic and serological differences between the parabionts.

In our experiments, unrelated white mice and inbred C57 BL and CBA mice, and golden hamsters (*Mesocricetus auratus*) were used. In all, 100 heteroparabiotic pairs were carried out by uniting mice with hamsters under ether anesthesia by coelioanastomosis. Blood for investigations was taken in mice from the tail and heart, and in hamsters from the heart immediately before parabiosis and on the 4th, 7th, 10th, and 14th days during parabiosis.

[1] J. C. FINERTY, Physiol. Rev. *32*, 277 (1952).
[2] R. E. BILLINGHAM, Science *130*, 947 (1959).
[3] A. SKOWRON-CENDRZAK, B. KONIECZNA-MARCZYŃSKA, and A. GROMCZAKIEWICZ, Folia Biol. *5*, 117 (1957).
[4] B. KONIECZNA-MARCZYŃSKA and A. SKOWRON-CENDRZAK, Folia biol. *7*, 9 (1959).
[5] P. KOLDOVSKY and A. SKOWRON-CENDRZAK, Folia biol., Prague *5*, 322 (1959).
[6] R. N. CHUTE and S. C. SOMMERS, Blood *7*, 1005 (1952).