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].

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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.

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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.

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The number of erythrocytes and leucocytes per mm^3, as well as the percentage ratio of leucocytes in smears stained by Pappenheims' method, were established. In serological investigations, the presence of hemagglutinins in the serum of parabiotic animals was detected by the agglutination test, and incomplete antibodies by Coombs' method.

In the previous experiments, KONIECZNA-MARCZYŃSKA and SKOWRON-CENDRZAK[7] demonstrated that in 60% of cases a hemolytic anemia occurs in homoioparabiosis between unrelated white mice, causing the anemic partner to die within two weeks. In mouse-hamster heteroparabiosis, in 88% of cases severe hemolytic anemia was observed only in mice. The mean survival of mice in heteroparabiosis was 6 days. A few heteroparabiotic pairs whose mice were not affected by anemia lived for 26 days. In the majority of cases with strong hemolytic anemia in mice, hemagglutinins and incomplete antibodies were detected in the serum of hamsters. The detected antibodies had species specificity and produced agglutinations with the erythrocytes of parabiotic and non-parabiotic mice coming from different strains. In parabiotic hamsters, there were no changes in the quantities of erythrocytes in successively examined samples.

SKOWRON-CENDRZAK and KONIECZNA-MARCZYŃSKA[8] stated leucopenia in homoioparabiosis of unrelated mice in both partners. In heteroparabiosis, a fall in the leucocyte count was observed only in hamsters on 4th day of parabiosis. This fall was statistically important and the value t according to the Students' test was 2.306 with the probability of error $p = 0{\cdot}05$. Leucopenia during heteroparabiosis may be explained on a serological basis. Probably hamsters have no great capacity for producing leucoagglutinins against the leucocytes of the mice. Percentage changes of leucocytes were noted only in mice during heteroparabiosis. There was a quantitative increase in neutrophil granulocytes equal to that in homoioparabiosis.

In 32 heteroparabiotic pairs of the hamster-mouse type, full thickness hamster skin grafts[9] measuring 3×3 cm were placed on the backs of the mice at different periods before parabiosis. It was shown that a preliminary immunisation of mice by hamster skin grafts in many cases protects them against hemolytic anemia. Only 18% of mice in heteroparabiosis developed a hemolytic anemia after preimmunisation. The mean survival period for immunised mice in heteroparabiosis was 7 days. A correlation was observed between the length of the period of preliminary immunisation before operation and the appearence of hemolytic anemia conditioning the survival time of mice in heteroparabiosis. The joining of mice in heteroparabiosis 2 or 4 days after transplantation of hamster skin led, in many cases, to hemolytic anemia or the death of the mice within 4 days of parabiosis. These data are in accordance with the results obtained in experiments on heteroparabiosis without preliminary immunisation. In heteroparabiosis carried out 7 days after skin grafting, the mice in many cases died within 3 days after operation. This fact may have been due to the coincidence of the strongest reaction in mice to hamster skin grafts and the parabiotic intoxication. In mice joined in heteroparabiosis 10 and 12 days after grafting the hamster skin, no symptoms of hemolytic anemia were observed; on the contrary, they survived longer in heteroparabiosis, from 10 to 15 days. Acquired transplantation immunity to hamster skin grafts in mice apparently induces a weaker immunological reaction to parabiotic intoxication on the part of the hamster partner.

Serum hemagglutinins in the hamster partner were observed only in one case with strong concurrent hemolytic anemia in the mouse partner.

In conclusion, it would appear that parabiotic intoxication and death of the mouse partners occur in spite of preliminary immunisation which frequently protects mice from hemolytic anemia. However, the protection thus achieved is only transient and the survival of the mouse partner is not much longer than that observed in heteroparabiosis without preliminary immunisation.

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Zusammenfassung

In der Heteroparabiose Maus-Hamster kommt eine parabiotische Intoxikation und hämolytische Anämie bei der Maus in 88% der Fälle zustande. Eine Immunisation der Maus mit Hamsterhauttransplantaten, die 10–12 Tage vor der Parabiose unternommen wird, kann die Erscheinung der Anämie bis auf 18% der Fälle herabsetzen. In Heteroparabiosen, die mit starker hämolytischer Anämie bei der Maus verliefen, wurde stets die Anwesenheit der Hämagglutinine und unvollständiger Antikörper im Serum des parabiotischen Hamsters festgestellt.

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The Influence of Thenalidine[1] on Reserpine- and Serotonin-Induced Gastric Ulcers in Rats

It was shown earlier that large doses of reserpine, administered parenterally, produce gastric hemorrhagic erosions and ulcers in rats[2–4]. The exact mechanism of this effect is not yet clear, although some authors have suggested a certain role of serotonin and/or histamine in it[5,6]. The administration of serotonin(5-hydroxytryptamine) in large doses produces a similar effect on the rat's gastric mucosa[7,8].

It was reported elsewhere that the antihistamine thenalidine(1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine, 'Sandosten') exhibits an antiserotonin action on the isolated rat's uterus[9], the tidal air of spinal cats[10], and on the rat's paws[11].

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