Parabiosis Intoxication. (18647)

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A condition which is peculiar to the parabiotic state interferes with survival of some pairs longer than about 2 weeks. Its etiology has never been satisfactorily explained. It has been described principally in the German literature and has been called "Parabiose Vergiftung", parabiosis poisoning, parabiosis intoxication, parabiotic disease, parabiotic disharmony, and heterogeneous parabiosis. It was probably originally described by Ranzi and Ehrlich(1), and first mentioned in American literature when Dragstedt and Cooper(2) stated: "It shall be noted that many pairs die suddenly from some cause at present unknown. There are no definite post-mortem abnormalities. In other cases, particularly when there is marked discrepancy in size or strength between animals at operation, the smaller may fail to grow, become weak and anemic and die in the course of 3 to 4 weeks. Stunting in one of a pair of parabiotic twins has been occasionally seen, but is unaccounted for." There are many differences of opinion regarding the incidence, etiology and inevitability of parabiosis intoxication. Some authors believe it is an inevitable consequence of the parabiotic state, others that it is a result of constitutional incompatibility between individual unrelated animals whereas others believe it to be a result of faulty operational technic. Most experimental evidence supports the concept of incompatibility which expresses itself as an anaphylactoid reaction(3). Mayeda(4) attributed "heterogeneous parabiosis" to blood incompatibility between the animals, resulting in hemolysis in one partner. In his experience, 67% of all pairs showed symptoms of intoxication, with a somewhat greater incidence if the partners were not littermates. Herrmansdorfer(5) emphasized cachexia as the primary symptom of parabiosis poisoning, induced by disturbance in appetite of the smaller "parasitic" partner and changes in blood volume. He found 60-70% disharmony, and stated that the condition might be more or less pronounced, so that those animals with greater power of resistance could recover. According to Nissen(6), parabiosis intoxication is essentially a "protein poisoning" and his findings of increased plasma cells and depleted adrenals were attributed to the defensive reaction against protein breakdown products. He compared his finding of hyperplasia of the thymus and lymphoid tissue in the larger partner with Status Thymo-lymphaticus in humans, and suggested that the latter may be the result of derangement in the parabiotic existence of mother and fetus during pregnancy. It now seems probable that Nissen was comparing the essentially normal lymphoid tissue of the larger partner with the extreme atrophy of the smaller intoxicated parabiont. Nevertheless, it may be profitable to consider the possibility that incompatibility between two rats in parabiosis may be an experimental counterpart of incompatibility between mother and fetus. For example, in erythroblastosis fetalis the fetus is the intoxicated partner, and it is conceivable that in the toxemias of pregnancy the mother is the victim. Other interpretations of the etiology of intoxication have been: protein poisoning as a result of humoral exchange of toxins(7,8); chronic progressive anaphylaxis(9,10); nutritional

1. Ranzi, E. and Ehrlich, H., *Z. f. Immunitatsf. u. exp. Ther.*, 1909, v3, 38.

2. Dragstedt, L. R., and Cooper, E. F., *Am. J. Physiol.*, 1923, v67, 48.

3. Møller-Christensen, E., *Acta Path. et Microbiol. Scand.*, 1932, v9, 55.

4. Mayeda, T., *Deutsche Z. f. Chir.*, 1921, v167, 295.

5. Herrmansdorfer, A., *Deutsche Z. f. Chir.*, 1923, v178, 289.

6. Nissen, R., *Z. f. d. ges. exper. Med.*, 1923, v35, 251.

7. Sauerbruch, F., *Munchen med. Wchnschr.*, 1923, v70, 866.

8. Ernst, M., *Deutsche Z. f. Chir.*, 1929, v221, 74.

9. Schmidt, G., *Deutsche Z. f. Chir.*, 1922, v171, 141.

TABLE I. Incidence of Parabiosis Intoxication and Effects of Attempted Therapy in 100 Pairs of Parabiotic Rats.

	No. of pairs	Died (%)	Recovered (%)	Asymptomatic (%)
Non-littermate pairs				
Untreated	40	26 (65)	10 (25)	4 (10)
Antihistaminic-treated	29	18 (62)	9 (31)	2 (7)
Cortisone-treated	9	6 (67)	3 (33)	
Littermate pairs	10	5 (50)		5 (50)
Surgical deaths	12			

differences(11); Bartonella anemia(12); and poor operative technic(13). Since the advent of antihistamine drugs, the possibility of their usefulness in combating parabiosis intoxication has been considered. Simonsen and Christensen(14) reported failure in their attempt to elucidate this problem, but it was probably not a fair test since their experimental approach was so rigorous. They united mice with rats and were unable to prolong the existence of the pair by antihistaminic treatment.

The purpose of the present work is to describe the incidence and symptoms of intoxication in 100 pairs of male rats, and to report the results of attempts to modify the condition by treatment with an antihistaminic and with cortisone.

Experimental procedure. Male rats obtained from the Holtzman-Rolfsmeyer Co. were put in parabiosis at the age of 31 days, according to the method of Bunster and Meyer (15) except that metal skin clips were used instead of sutures. Each pair was examined carefully twice daily for the succeeding 7 weeks. The distribution of these pairs into experimental groups is shown in Table I. The pairs which were treated with antihistaminic therapy were injected twice daily intraperitoneally with 1.0 mg chlorocyclizine hydrochloride (Perazil, Burroughs Wellcome and Co.) from the 3rd to the 21st day following operation. Those which were treated with cortisone received 0.75 mg cortisone acetate (Cortone acetate, Merck and Co.) from the 3rd to the 21st day.

Results and discussion. The first appearance of parabiosis intoxication was hyperemia (redness and dilation of blood vessels of ears, feet, tail and external genitalia) of one partner, and/or slight size difference. During the next few days a progressive increase in size difference occurred with the hyperemic partner remaining larger and the smaller partner becoming increasingly pale and anemic in appearance. About a day before death the smaller, anemic partner usually became sluggish, moribund, and in our experience always died first. Rarely pairs were observed in which both rats were hyperemic, or both anemic, a condition which persisted for several days followed by recovery or by alteration of one partner so that the usual symptoms obtained. If the larger rat is separated soon after the death of its partner, it usually survives in good health.

In this series, initial signs of intoxication appeared between the 8th and 14th days after pairing, followed by death within 2 to 8 days or by recovery. Onset of signs was never observed after the 21st post-operative day, and few deaths occurred thereafter.

Autopsy of pairs in which one partner had died revealed that the larger surviving partner was essentially normal, except for slightly enlarged adrenal glands. The smaller, intoxicated animal exhibited extreme hypertrophy of adrenals, extreme atrophy of the thymus and a completely empty gastro-intestinal tract. Adhesions or infections were found in some pairs which were intoxicated, but not

10. Niekau, B. and Duschl, L., *Deutsche Z. f. Chir.*, 1925, v191, 221.

11. Kojima, K., *Deutsche Z. f. Chir.*, 1931, v232, 578.

12. Sauerbruch, F. and Knake, E., *Klin. Wchnschr.*, 1936, v15, 884.

13. Pearlman, L. R. and Kolpakow, I. V., *Vrach. Delo.*, 1938, v20, 871.

14. Simonsen, M. and Christensen, R., *Acta Path. et Microbiol. Scand.*, 1950, v27, 323.

15. Bunster, E. and Meyer, R. K., *Anat. Rec.*, 1933, v57, 339.

in the majority. Hemoglobin determinations indicated that homogeneous pairs had comparable hemoglobin concentrations in their blood, but in pairs with a marked "hyperemia-anemia" difference the anemic parabiont had only one-third to one-half as much hemoglobin. Hyperhemoglobinemia and polycythemia have been observed in the "hyperemic" partner of intoxicated pairs by Diepenhorst and de Vaal(16). They also have been unable to correlate hematological phenomena induced by parabiosis with any known blood group differences. The color difference has been attributed to differences in blood pressure between the partners which results in one rat "bleeding into the other", but blood pressure determinations in heterogeneous pairs show no constant pattern which would support such a contention(17).

The incidence and results of attempts at treatment of parabiosis intoxication are shown in Table I. Of the 100 pairs, 12 died during the operation or within a few days from the effects of surgery (death from anesthesia, hernia and fighting between partners). It can be seen that no significant difference exists in the incidence of intoxication between those pairs which were untreated, antihistamine-treated or cortisone-treated. Also no change was noted in the duration or severity of the condition as a result of therapy. Littermate pairs showed only slight difference in percentage of death from intoxication, but marked difference in this group is shown by the fact that half of them showed no signs of intoxication at all.

Changes in the adrenals and thymus as a result of parabiosis intoxication simulate the responses of an animal to severe stress and probably are comparable to Selye's "adaptation" phenomena. It may be of importance to consider this factor in evaluating results of endocrine studies in which the parabiosis technic is used(16).

From our data and from a survey of the literature, we conclude that parabiosis intoxication is a result of constitutional incompatibility between the partners, complicated by infection, inanition and other factors which either accentuate or mask the primary signs. In spite of the belief of Pearlman and Kolpakow(13) that it can be explained on the basis of poor operative technic, the facts that littermates show less intoxication and that use of highly inbred strains practically eliminates the condition, as shown in the work of Braun-Menendez(18), and Huff, Trautman and Van Dyke(19), are cogent arguments for a genetic basis. Antihistaminic and cortisone treatment are ineffective in altering the course or incidence of the intoxication.

Summary. Mortality of rats from parabiosis intoxication in non-littermate pairs was 64%, signs of intoxication followed by recovery were shown by 28% and 8% remained asymptomatic. Treatment of non-littermate pairs with an antihistaminic or cortisone had no effect on the incidence or severity of the intoxication. Littermate pairs showed less tendency toward intoxication, but those which were affected died as readily as non-littermates.

16. Diepenhorst, M. J., and de Vaal, O. M., *Acta Physiol. et Pharmacol. Neerl.*, 1950, v1, 342.

17. Hall, C. E., and Hall, O., personal communication.

18. Braun-Menendez, E., personal communication.

19. Huff, R. L., Trautman, R. and Van Dyke, D. C., *Am. J. Physiol.*, 1950, v161, 56.

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