

# PATHOGENESIS OF PARABIOTIC POISONING

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Experiments on parabiont mice showed that line CBA mice have an immunologic advantage over line C57BL/6 mice. If CBA mice were sutured to (CBA  $\times$  C57BL/6) hybrids, the F<sub>1</sub> hybrids developed anemia and parabolic poisoning, whereas this did not occur in C57BL/6 and (CBA  $\times$  C57BL/6) F<sub>1</sub> parabionts. If CBA mice were sutured to C57BL/6 mice, the C57BL/6 mice died first. Similar results were obtained in experiments in which hybrids were sutured simultaneously to individuals of both parent strains.

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In parabiosis experiments, i.e., experiments in which two genetically different partners are sutured together, the condition known as parabolic poisoning (PP) develops. This is manifested, in particular, in the development of anemia by one partner and of polycythemia by the other, leading to death of the parabionts.

The study of the pathogenesis of PP is a matter of considerable interest because it can be regarded as a variant of transplantation disease. Most investigators now consider that the pathogenesis of PP is based on immunologic conflict between the parabionts. Important evidence in support of this view is given by experiments in which parabiosis took place between individuals of parent strains and hybrids, i.e., under conditions in which the immunologic reaction of parents versus hybrids can take place in only one direction. In these experiments the hybrids usually developed anemia and the individuals of parent strains developed polycythemia [1, 2, 4, 6, 7].

Previous investigations (unpublished data) showed that intraperitoneal injection of large doses of spleen cells from C57BL/6 mice led to a higher incidence and greater severity of serum sickness in (CBA  $\times$  C57BL/6) F<sub>1</sub> hybrids irradiated in sublethal doses than injection of similar doses of CBA cells.

The object of this investigation was to compare the development of PP after suturing hybrids to partners of both parent lines.

## EXPERIMENTAL METHOD

CBA and C57BL/6 mice and (CBA  $\times$  C57BL/6) F<sub>1</sub> hybrids weighing 18-20 g, obtained from the nursery of pure-line animals of the AMN, SSSR (Stolbovaya) were used in the experiments.

In all parabiosis experiments, the mice were anesthetized with sodium amytal, placed side by side on special frames, and a lateral incision made in the skin and muscles from the axillary region to the proximal end of the thigh. To form a common peritoneal cavity, the peritoneum was separated from the abdominal muscles from the costal margin as far as the iliac crest. The peritoneum and muscles were sutured together with cat gut and the skin wound closed with a continuous silk suture.

The parabionts were weighed before the operation and at various times thereafter. Their weight before operation did not differ by more than 0.5-1 g. In every case the parabionts were of the same sex. After the operation they were placed in individual cells. Before the operation and at various times thereafter the erythrocyte count was determined in the blood of each partner, and in some experiments the total number of leukocytes and lymphocytes in the blood was also determined.

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## EXPERIMENTAL RESULTS

In the first three series of experiments parabiosis was studied between CBA mice and (CBA × C57BL/6) F<sub>1</sub> hybrids (26 pairs of parabionts). This study showed that after suture of intact CBA mice to hybrids, the latter developed anemia on the 5th-7th day, while the CBA partners developed polycythemia. Symptoms of PP developed in the hybrids after the 5th-7th day: cachexia, matting and falling of the hair, and bowing of the spine. The hybrids died first (on the 8th-16th day after operation). Preliminary whole-body x-ray irradiation of the CBA mice before operation in a sublethal dose (500 R) led to the development of severe leukopenia, but did not prevent the development of anemia or signs of PP in the hybrids and of polycythemia in the CBA partners. Differences observed in all series of experiments were statistically significant ( $P < 0.01$ ).

After suturing of intact C57BL/6 mice with hybrids (19 pairs), the parabionts did not develop the anemia-polycythemia syndrome. If, on the other hand, before the experiment the C57BL/6 mice were sensitized 4 times with spleen cells of the hybrids and sutured to hybrids 7 days after the last injection of cells (10 pairs), the hybrids developed a statistically significant anemia and the C57BL/6 parabionts developed polycythemia. Death of the parabionts occurred more rapidly than when unsensitized C57BL/6 mice were sutured to hybrids.

The immunologic advantage of the CBA mice was manifested in cases not only of unilateral (parent-F<sub>1</sub> hybrid), but also of bilateral differences at the H-2 locus, i.e., after suturing to C57BL/6 mice (19 pairs). In these experiments anemia and signs of PP developed after the 5th day in the C57BL/6 mice, whereas the CBA partners developed polycythemia.

When intact mice of both parent strains were sutured simultaneously to hybrids (7 trios), the use of hybrids as buffer between the two parents did not prevent the development of anemia and signs of PP in the C57BL/6 mice. Preliminary triple immunization of C57BL/6 mice with CBA antigens (6 trios) prevented the development of anemia among the hybrids but not among the C57BL/6 mice; the CBA tribionts, as in the first series of experiments, developed polycythemia.

The results generally confirm the view that PP develops as the result of an immunologic reaction between the partners, seen most distinctly when CBA mice are sutured to hybrids: signs of PP and anemia developed only in the hybrid and not in the parent; in the case of parabiosis between C57BL/6 mice and hybrids, the latter developed PP and anemia only if the C57BL/6 partners had been preliminarily sensitized with cells from the hybrids.

Altogether 76 pairs of parabionts and 13 trios of tribionts were used in these experiments (a total of 191 mice).

The results described above demonstrate the higher immunologic potency of CBA mice compared with C57BL/6 mice, which was observed not only when they were sutured together, as Nakic and co-workers [5] showed, but also in the case of parabiosis with hybrids and in tribiosis experiments.

It is not yet clear, however, why in experiments in which parent spleen cells were transplanted into (CBA × C57BL/6) F<sub>1</sub> hybrids, more severe serum sickness was produced by the cells of C57BL mice than of CBA mice. These results were obtained in the authors' laboratory (unpublished data) and also by other investigators [3]. Further experiments must be carried out to explain this contradiction.

## LITERATURE CITED

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