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RELATIONSHIP BETWEEN SEVERITY OF TETANUS INTOXICATION AND THE LEVEL OF HOST RESISTANCE

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Tetanus still remains high on the list of infections with high mortality. Successful management of the paroxysmal syndrome, which dominates the pathogenesis of the disease [3], has given urgency to the study of secondary infectious complications. Accordingly the need has arisen for a method of determining the level of the natural protective forces of the host, its general resistance, and the state of immunity and of the nervous system in tetanus intoxication.

Nonspecific factors of defense and the specific response were studied in the present investigation at different times after injection of tetanus toxin (TT) in doses causing tetanus intoxication with a slow and nonfatal course (1/3 or 2/3 MLD) or with a more severe course leading rapidly to death (1 MLD).

EXPERIMENTAL METHOD

Experiments were carried out on 110 rats weighing 200-240 g and on 21 rabbits weighing 2.5-3 kg. Experimental tetanus was produced by administration of TT, batch 21 "Leningrad," in doses of 1, 1/3 and 2/3 MLD. The TT was injected intramuscularly into the left leg in a volume of 0.2 ml physiological saline into rats and in a volume of 2.5 ml into rabbits. TT inactivated by heating to 56°C for 2 h was injected into the control animals.

Nonspecific factors of defense were assessed on the basis of a number of indices: phagocytic activity of the leukocytes, plasma-cell response of the lymph nodes and spleen, serum concentrations of complement [1], lysozyme [2], and properdin [5], and the anticomplementarity and cytotoxicity of the serum [4]. The last was judged from the percentage of adrenalectomized mice which died. The specific response was assessed by the passive hemagglutination test with an erythrocytic diagnostic serum for tetanus. The numerical results were subjected to statistical analysis and the significance of differences was estimated by Student's t-test [7].

EXPERIMENTAL RESULTS

Statistically significant activation of the cellular factors – an increase in the phagocytic index, an active plasma-cell response, and general morphological changes in the regional and contralateral lymph nodes and spleen (Fig. 1, 1), and also of humoral factors – complement, lysozymes, and properdin, were clearly observed 24 h after injection of 1 MLD TT (Fig. 1).

Representation of the plasma-cell response in graphic form emphasized the rapid changes in response to injection of the toxin affecting all cell forms tested from this point of view. It will be clear from Fig. 1 that cells of the plasma-cell series were found infrequently in the lymph nodes and spleen. However, one day after injection of TT a sharp increase in their number was noted in the regional lymph node: twofold in the case of

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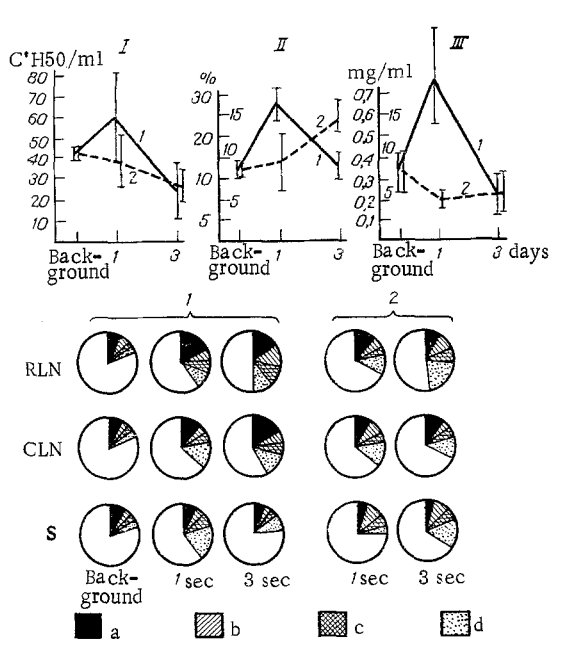

Fig. 1

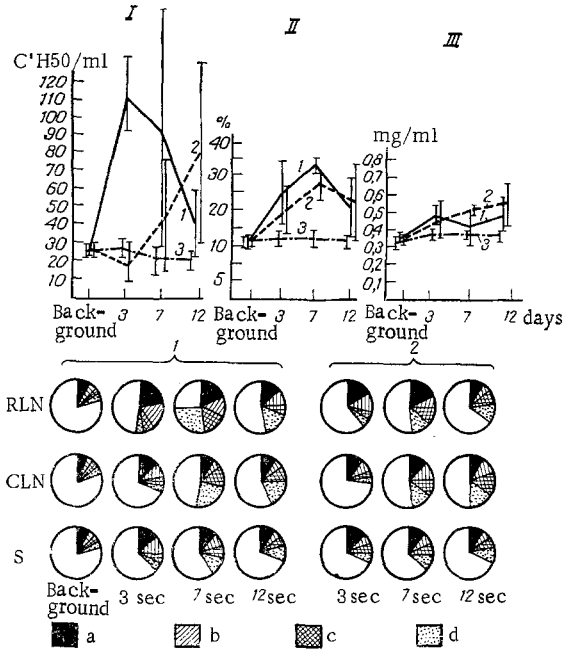

Fig. 2

Fig. 1. Concentrations of complement (I), lysozyme (II), and properdin (III) in blood serum and number (in 100 fields of vision) of immunocompetent cells of regional (RLN) and contralateral (CLN) lymph nodes and spleen (S) after injection of 1 MLD TT (1) and of inactivated TT (2), 1 and 3 days after injection of TT. a) reticular, b) blast, c) immature plasma, and d) mature cells.

Fig. 2. Concentrations of complement (I), lysozyme (II), and properdin (III) in blood serum 3, 7, and 12 days after injection of 1/3 MLD TT (1), inactivated TT (2), and in intact animals (3), and also number (per 100 fields of vision) of immunocompetent cells of regional (RLN) and contralateral (CLN) lymph nodes and spleen (S) 3, 7, and 12 days after injection of 1/3 MLD TT (1) and of inactivated TT (2). Legend as in Fig. 1.

reticular and mature cells, threefold for immature, and fivefold for blast cells. Characteristically the contralateral lymph node and spleen participated actively in the general immunologic response, and the intensity of plasmatization was only a little less than that of the regional lymph node. Anticomplement activity and cytotoxicity were absent at this period.

After 3 days the humoral factors of defense were sharply depressed compared with the previous time of investigation. The rats' sera exhibited cytotoxic properties but, as before, no anticomplement activity. Meanwhile the number of cells of the plasmacyte series in the regional lymph node had reached maximal values, in the contralateral lymph node it remained at its former levels, and in the spleen it had reverted to its initial level.

To differentiate between the antigenic and toxigenic effects of TT, inactivated TT was injected into animals of another group. Marked morphological changes and an active plasma-cell response were observed under these circumstances in the lymph nodes and spleen, whereas the humoral factors were very slightly reduced or remained within normal limits. The exception was the serum lysozyme activity, which increased until the 3rd day. By contrast with animals receiving TT, the sera exhibited anticomplement and cytotoxic properties. The latter were recorded as early as 24 h after injection of inactivated TT.

Nonspecific factors of defense were thus modified after injection of 1 lethal dose of TT, and the humoral factors of defense were more labile. In order to test the acute, subacute, and chronic stages of experimental tetanus, the dose of TT was reduced to 1/3 MLD. Under these circumstances the nonspecific factors of defense were considerably activated (Fig. 2), especially the serum complement and lysozyme activity.

During analysis of the plasma-cell response (Fig. 2, 1) it must be noted that marked morphological changes and active plasmatization in the lymph nodes and spleen, observed in the severe, rapidly progressive form of experimental tetanus, also took place in tetanus intoxication following a slow course. In this case the most marked plasmatization was observed in the late stages of the disease (7th-12th days). A similar tendency, only a little less marked, also remained after injection of inactivated TT (Fig. 2, 2).

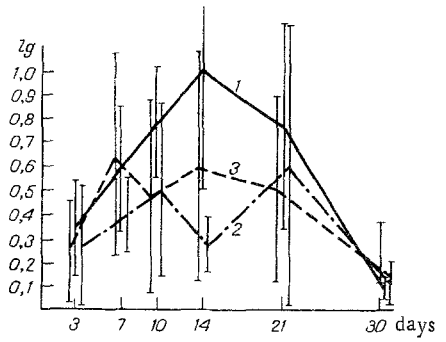

Fig. 3. Dynamics of serum antibody titers (in log units) in rabbits after injection of TT (1), TT and butyroxan (2), and inactivated TT (3).

In previous investigations [6] the course of experimental tetanus in rats was found to depend to a definite degree on the functional state of the hypothalamic region. The use of different techniques (injection of TT directly into the hypothalamus, production of experimental tetanus against the background of injured hypothalamic nuclei) enabled clinical forms of the disease to be differentiated, the duration of survival to be lengthened, and the mortality from experimental tetanus to be reduced.

These results served as the basis for the study of differences between the course of experimental tetanus following intramuscular or intravenous injection of pharmacological agents mainly with essential action. For this purpose the neuroleptic butyroxan, which has a well-marked central adrenoblocking action in a dose of 10 mg/kg body weight, was used. Simultaneous injection of butyroxan and 2/3 MLD TT into rats was found to give no change in the clinical picture of the experimental tetanus compared with the control, but the overall survival period of the rats was increased statistically significantly by 1.8 days (from 4.8 ± 0.2 to 6.6 ± 0.43 days). The day by day mortality of the control rats was distributed as follows: 5th day 30%, 6th day 60%, 7th day 10%; in the rats receiving butyroxan: 6th day 30%, 7th day 20%, 8th day 10%, 9th day 40%. Investigation of nonspecific humoral factors showed that they were completely identical in the groups compared.

Similar results were obtained in rabbits also when local tetanus was produced and butyroxan injected in a dose of 10 mg/kg daily for 14 days. The dynamics of the changes in the nonspecific factors of defense in this case was indistinguishable from that following administration of TT without butyroxan, but meanwhile the indices reflecting the state of specific immunity showed significant changes. The titer of hemagglutinating antibodies (Fig. 3) was depressed statistically significantly by the action of butyroxan by 1.5 times compared with that of animals receiving TT alone.

The results of the experiments in which butyroxan was used thus showed that the overall survival rate of the animals with experimental tetanus was increased by blockade of adrenergic brain structures. This is probably evidence that adrenergic brain structures play an essential role in the central mechanisms of responses of the body to TT, and the change in their functional state induced by the action of adrenoblockers may evidently be one way of influencing the course of tetanus intoxication by pharmacological means.

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