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A MODEL OF DESTRUCTIVE TUBERCULOSIS IN GUINEA PIGS

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KEY WORDS: experimental destructive tuberculosis of the lungs; vaccination.

The destructive process in the lung tissue of experimental animals has been shown to depend on the method of sensitization. A model of experimental cavernous tuberculosis of the lungs was formed in two series of experiments on 124 guinea pigs. It was shown that in order to undertake long-term experiments with cavernous changes in the lungs of guinea pigs a model with preliminary injection of BCG, followed by a course of treatment with sulfadimethoxine to prevent the nonspecific pneumonia which frequently arises, is the optimal choice. By this method cavernous tuberculosis, with the formation of three-layered cavities and multiplication of the bacterial population which resembles human tuberculosis more closely than other types of experimental model of this disease, can be obtained.

The most convenient model for cavity production was found to be injection of *Mycobacterium tuberculosis* into the substance of the lung by thoracic puncture. The first reports on this method were published in 1954 [3] . Later the method was improved and modified: Killed mycobacteria, their fractions, or even mycobacteria of BCG were injected into the lung [4, 5]. It was also suggested that a strongly depot-forming preparation consisting of a mixture of paraffin and lanolin or rat fat be used in order to reduce the dose of injected agent by 100 times, for a relationship has been found between the dose of a virulent infecting agent and the survival rate of animals sensitive to tuberculosis [1]. Mainly dogs have been used as experimental animals.

Meanwhile tuberculosis obtained in experiments on dogs has little in common with the process found in other experimental animals and is very far removed in pathogenesis and, in particular, in its course from the destructive changes in human lung tissue. For these reasons many workers have used small laboratory animals in their experimental studies.

To investigate problems connected with the study of the dynamics of the bacterial population and of healing processes, especially when antibacterial therapy was used, the creation of an adequate experimental model was necessary.

EXPERIMENTAL METHOD

Altogether 124 animals were used. In the animals of the control group (64 guinea pigs) a model of experimental tuberculosis was produced by the usual method, according to which Freund's adjuvant was injected intradermally 5 times at intervals of 1 week. *M. tuberculosis* cells of human type $H_{37}Rv$ were killed by autoclaving, after which they were suspended in a mixture of petrolatum and lanolin. If skin sensitivity to tuberculin was present (the mean area of hyperemia of the skin was 20 × 30 mm), an injection of *M. tuberculosis* of human type $H_{37}Rv$ was given into the diaphragmatic lobe of the right lung in a dose of 2 mg/kg in 0.2 ml of petrolatum-lanolin suspension. The puncture was carried out by means of a syringe in the 6th intercostal space 1 cm to the right of the spine; the length of the needle was 2 cm and the syringe was perpendicular to the animals' trunk. The needle was inserted throughout its length and the weight of each animal was at least 400 g.

Animals of the experimental group (60 guinea pigs) received a subcutaneous injection of BCG vaccine in a dose of 0.2 mg/kg in 0.5 ml physiological saline instead of Freund's adjuvant. The sensitivity of the skin to tuberculin was determined

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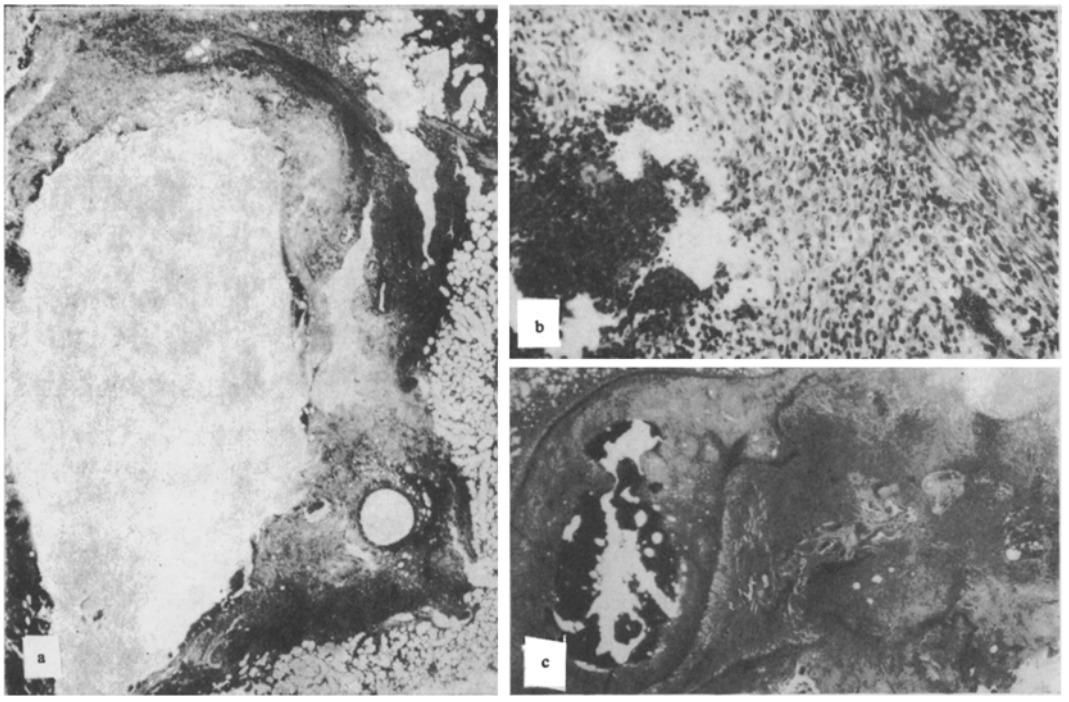

Fig. 1. Cavities in lung of guinea pigs in models produced in different ways. a) General view of cavity obtained after vaccination of animals, 30 X; b) detail of cavity – wall composed of three layers, 125 X; c) caseous lobitis with destruction after preliminary sensitization with Freund's adjuvant, 40 X. Hematoxylin and eosin.

1.5 months after vaccination, and if a papule measuring on average 15 X 17 mm was present, intrapulmonary infection was carried out by the same method as that used on the group of control animals.

To prevent nonspecific lung infections an additional course of chemotherapy was given in accordance with the following scheme: On the day after intrapulmonary infection sulfadimethoxine was given perorally in a dose of 80 mg/kg initially, followed by 40 mg/kg daily for the next 9 days. The total duration of the course of treatment was 10 days.

The number of *M. tuberculosis* cells was determined by counting colonies and calculating the seeding index [2], and pathological changes were analyzed by calculating the index of lung involvement. The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Morphological study of animals of the experimental group, conducted in the Laboratory of Pathomorphology (Director, Professor O. A. Uvarova), Central Research Institute of Tuberculosis, Ministry of Health of the USSR, showed that destructive tuberculous changes developing in the vaccinated animals were relatively localized, although multiple small destructive cavities were found in the zone of infiltration surrounding the lobe. The wall of the tuberculous cavity in this group of animals was formed toward the end of 1 month after infection, and it had the typical three-layered structure with caseous-necrotic, specific-granulation, and developing fibrous layers, bounding the cavity (Fig. 1a). Specific changes around the cavities were productive in character. The lung tissue surrounding the zone of infiltration was relatively aerated, and the interlobar septa were thickened and infiltrated by lymphoid cells (Fig. 1b). No tuberculous changes were found in the liver and spleen. When this technique was used the survival rate of the animals was 92%. Cavities were formed in 87% of animals.

A more acute and progressive process, accompanied by the development of pneumonia and affecting the whole lung or large portions of it, was observed in the control animals. In 40 of 60 animals infection was disseminated over the lungs with the formation of tuberculous foci also in other parenchymatous organs. Multiple progressive cavities were formed as early as 2 weeks after infection; the specific layer was not present in the cavities, but the cavity wall consisted of lung tissue undergoing pneumonic changes (Fig. 1c), with multiple microabscesses and with inflammatory changes of an allergic character. The acutely progressive destructive process was complicated by the development of nonspecific, hemorrhagic pneumonia and suppuration. The reproducibility of cavity formation was limited as a result of the rapid death of the animals from the concomitant nonspecific pneumonia. The number of animals which died as a result of the extensive lung lesions was 63%; 16% of the animals died in the first week after infection. In the experimental group only five of the 60 animals (8%) died before treatment with sulfadimethoxine, and after treatment with this agent there were no deaths.

A comparative study of the dynamics of the bacterial population in the pathological focus, in different parts of the cavity wall, the lung tissue surrounding the cavity, and the parenchymatous organs of the animals gave the following results: During the month after infection the number of *M. tuberculosis* cells in the vaccinated animals fell in all organs and tissues. The period of decline of viability of the pathogenic agent last up to 3 months from the beginning of vaccination and from 1.5 to 4 weeks correspondingly after infection. For instance, by 2 weeks after infection the seeding index for the animals of this group was 1.2 ± 0.03. The bacteriological indices fell considerably, depending on changes in the technique used ($P < 0.001$). In the period of decline of hypersensitivity of tuberculin, which was observed toward 3 months after vaccination, the number of *M. tuberculosis* cells in the pathological material again increased. The seeding index by this time rose to 2.8 ± 0.14. The difference is statistically significant ($P < 0.01$). The largest number of *M. tuberculosis* cells was observed in the cavity wall and in the lung tissue surrounding the cavity. Parallel with the increase in the number of bacterial cells, reactivation of the pathological process was observed. The number of *M. tuberculosis* cells in the pathological material increased directly proportionally to the time after infection. Between 1 and 2 weeks after infection accumulation of the bacterial population took place in the focus of infection only. The seeding index of the animals of this group was 2.8 ± 0.14, after 3-4 weeks it reached 4.0 ± 0.23 ($P < 0.01$), and after 3-5 months it was 70 times higher ($P < 0.001$).

The suggested model of experimental destructive tuberculosis of the lungs thus resembles human tuberculosis much more closely than other types of model which have hitherto been used.

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CHANGES IN THE TACTILE PAPILLAE OF THE HUMAN TONGUE IN ONTOGENY (DATA OF SCANNING ELECTRON MICROSCOPY)

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The formation of the mechanoreceptor structures of the mammalian and human tongue has hardly been studied. Yet the tactile papillae of the tongue at different periods of human life play an important role in the formation and development of such complex acts as sucking, swallowing, chewing, determination of the solid component of the food, and the articulation of speech [5]. The approximate times of formation of keratinization of the filiform papillae of the human and animal tongue are given in a number of publications [1-4, 6, 7].

This paper gives the results of an investigation of the tactile receptor structures of the human tongue at different ages.

EXPERIMENTAL METHOD

Autopsy material was used. The tongues of 3-week fetuses, newborn and 5-month-old infants, adults (40 years), and older people (age 60-80 years) were investigated. The tongues were washed to remove saliva, for 30 min initially in tapwater, then in distilled water, after which they were fixed in 4% formalin solution or 2.5% glutaraldehyde solution. The surface of the tongue was then washed again to remove the fixing solution, quickly frozen, and dried. Different parts

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