FEMALE SEX HORMONES IN THE COMPLEX CHEMOTHERAPY OF EXPERIMENTAL TUBERCULOSIS

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One of the main problems in the development of a rational therapy for tuberculosis at the present time is the study of the combined action of specific preparations with nonspecific properties, which intensify the resistance of the organism to tuberculosis infection and thereby increase the effectiveness of antibiotics.

In this respect, the investigation of the female sex hormones was of great interest, since, according to the literature data, they influence the permeability of the connective tissue, the blood vessels, and the function of the reticuloendothelial system [1-5]. Still more important is the fact that in pulmonary tuberculosis, disturbances of the functional state of the ovaries frequently arise.

Our preliminary experiments with the sex steroids showed that the estrogens at a definite stage are capable, on the one hand, of slowing the dissemination of tuberculosis mycobacteria, and, on the other, of intensifying the reparative processes of fibrosis and resorption during its aftereffect.

The purpose of this work was to study the influence of female sex hormones in conjunction with antibacterial preparations on the course of experimental tuberculosis.

EXPERIMENTAL

The experiments were conducted on 60 sexually mature female guinea pigs, infected with a culture of Bovinus 8 tuberculosis mycobacteria in a dose of 0.0001 mg subcutaneously. Some animals received estrone in conjunction with streptomycen or phthivazide; others received the hormone of the corpus luteum (progesterone) in an analogous combination. The observation period was four months. Estrone was injected in a daily dose of 250 Me, progesterone in a dose of 0.5 mg, streptomycin in a dose of 6000 units, phthivazide in a dose of 15 mg. The first three preparations were administered subcutaneously, phthivazide per os.

The injection of the sex steroids and antibacterial preparations was begun a month after infection and was continued for 30 days. Over the following four weeks, the animals continued to receive antituberculosis preparations, but without the hormones. During the last month (fourth after infection), the guinea pigs received no treatment. The control group was made up of animals that received only the antibacterial preparations.

RESULTS

The first period of observations (directly after a month of combined therapy showed that during the period of administration of the estrogenic hormone, there was no noticeable difference between the animals that received it in a combination with antibiotics and the animals treated only with the antibacterial preparations.

At all stages of our experiment, phthivazide gave a better therapeutic effect than streptomycin. This pattern was also preserved in the combination of antibiotics with hormones. Thus, phthivazide with esterone, just like phtivazide alone, exerted a good therapeutic action after a month of administration. Upon autopsy, tuberculosis changes were

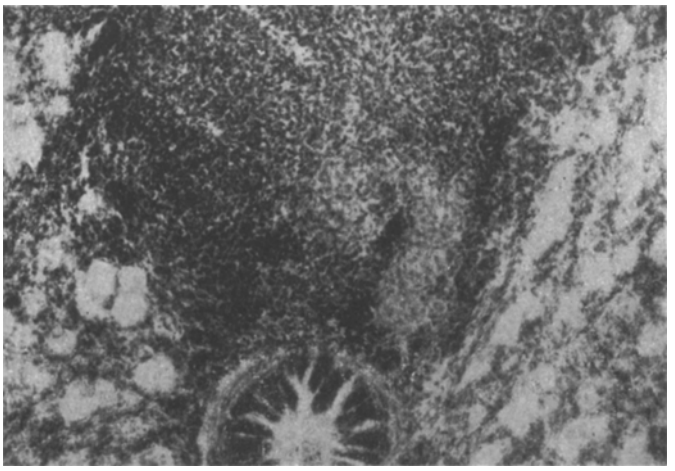

Fig. 1. Peribronchial epithelioid cellular focus in the lungs of a guinea pig in treatment with streptomycin alone. The third month after injection with tuberculosis. Photomicrograph. Magnification x 150.

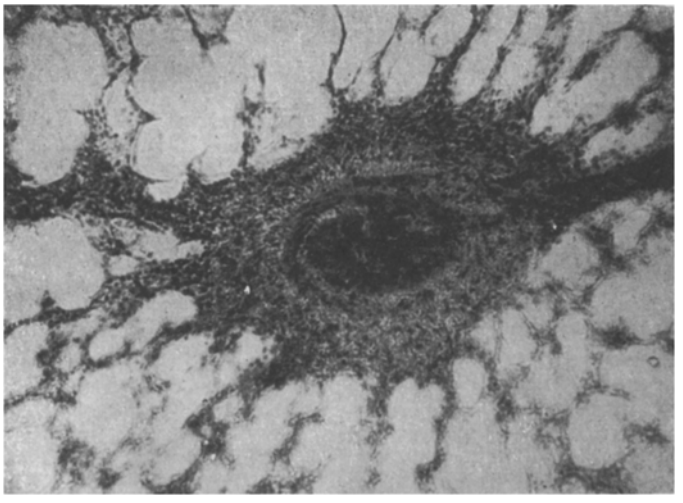

Fig. 2. Residual tuberculous changes in the lungs of a guinea pig around the vessel in combined therapy with streptomycin and progesterone. Third month after infection with tuberculosis. Photomicrograph. Magnification x 210.

detected only in the regional lymph nodes (small foci with areas of caseosis) and lungs (scattered lymphoid nodules). The index of injury in these animals was equal to 5. Individual accumulations of epithelioid cells and a small amount of lymphoid infiltration along the path of the vessels were noted microscopically in the liver. In the spleen, no specific injuries were detected. In the lungs, small accumulations of epithelioid-lymphoid cells, situated along the path of the fine bronchi and vessels or beneath the pleura were encountered against a background of pronounced hyperemia. The therapeutic effect of streptomycin was appreciably lower than that of phthivazide; the conjunction of esterone with streptomycin also proved less effective than the joint administration of estrone with phthivazide.

In individual guinea pigs, ulcerations were observed at the site of the infection, along with considerable hyperplasia of the regional lymph nodes (up to 10-15 mm) with caseinification of their centers. In the spleen there were scattered miliary tubercles, and in the pulmonary tissue—individual polymorphic foci. The index of injury was equal to 8.5. A histological investigation of the material confirmed the autopsy data. In the animals of this group, which received streptomycin, alone or in conjunction with estrone, numerous epithelioid cellular foci were detected,

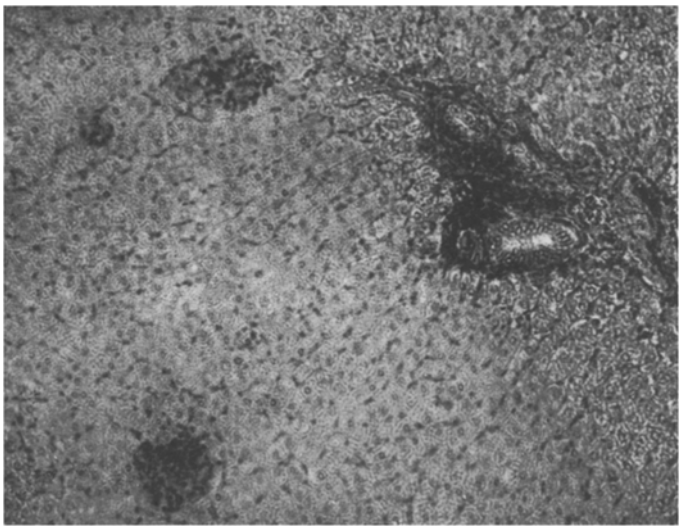

Fig. 3. Appearance of fresh lymphoid nodules in the liver of a guinea pig after cessation of therapy with phthivazide and estrone. Fourth month after infection with tuberculosis. Photomicrograph. Magnification × 200.

frequently confluent, sometimes with caseosis formed. The specific tuberculous changes in the pulmonary tissue represented small infiltrates or circular foci without clear boundaries. The changes in the liver were characterized by the presence of small lymphoid-epithelioid foci and lymphoid infiltrates.

In the animals that received progesterone in conjunction with antituberculosis preparations, the development of reparative processes in this period lagged appreciably in comparison with the development of these processes in the animals treated with antibiotics alone or in conjunction with estrone. However, even here the specific reactions were limited in character (giant cell and fibroblastic structures, absence of perifocal inflammation around the foci).

A study of the dynamics of the specific processes a month after cessation of the administration of hormones against a background of continuing antibacterial therapy showed that the female sex hormones exert an extremely favorable effect a definite period after their introduction into the organism.

During this month, under the influence of continuing antituberculosis therapy, the specific process decreased in all the experimental groups, but the degree of expression of the residual changes in them differed.

In the animals treated with phthivazide, the therapeutic effect, just as at the preceding period of observation, was higher than in the guinea pigs that received streptomycin. A similar advantage was also noted in the combined antibacterial and hormonal therapy.

In a comparison of the morphological changes in the animals of the two groups, it was found that tuberculosis injuries were more pronounced in the pigs treated with antibiotics in conjunction with hormones than in the animals that received only the antibacterial preparations. The most favorable results were noted in the group of animals that received estrone in combination with phthivazide a mouth before. In the lymph nodes of these guinea pigs, the remains of granulation tissue in the process of resorption were detected, while the lungs, liver, and spleen were free of tuberculous injuries. The administration of phthivazide in conjunction with progesterone proved less effective: certain specific changes were retained in the parenchymatous organs and lymph nodes. A more extended character of the process was detected in animals treated with streptomycin in conjunction with estrone or progesterone; however, in this case also the therapeutic effect was higher than in the introduction of streptomycin along (Figs. 1, 2).

The use of hormonal preparations in conjunction with antibiotics produced an intensification of the reparative reactions in the direction of resorption, and even the combination of the hormones with streptomycin, intensifying the proliferative processes in the connective tissue, did not give rise to any pronounced fibrosis. Consequently, the sex hormones against a background of antibiotics stimulated a more perfect type of heating—resorption of the

elements of specific inflammation. It is known that treatment with antibiotics for two months is insufficient to eliminate the specific process. Hence, during the following period of observation—after two month antibacterial therapy and a month of interruption of the therapy—a fresh exacerbation of the tuberculous process in the lymph nodes and parenchymatous organs of the animals of all the groups was ascertained; moreover, the intensity and extent of the process were greater in the animals that received hormonal preparations during the period of antibacterial therapy.

Considering that during the previous period of observation, the best results were obtained in animals treated earlier with hormones, we cannot explain the more pronounced exacerbation of the process in them by the presence of greater residual changes, all the more in that the morphological picture in guinea pigs that received estrone with phthivazide showed the absence of old, unhealed tuberculous foci in different phases of regression. This was a new wave of exacerbation, with the almost total absence of morphological data indicating the presence of the tuberculous process. A fresh outcropping of lymphoid nodules could be observed in the lungs and livers of this group (Fig. 3). In the organs of the animals that received hormones in conjunction with streptomycin, all the phases of the inflammatory reaction were traces (exudative, necrotic, proliferative). Fresh lymphoid cellular nodules and infiltrates, indicating a progression of the process, were encountered against the background of old tuberculous changes.

The material obtained permits us to make some comparison with the clinical observations pertaining to the change in the treatment of tuberculosis during the period of reorganization of the functional activity of the sex glands.

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