THE PATHOMORPHOLOGY OF ACUTE EXPERIMENTAL TOXOPLASMOSIS PRODUCED BY INFECTION IN VARIOUS WAYS

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There is reason to suppose that there are as many features of a toxoplasmosis infection as there are many possible natural routes of the infection [1]. We have set out to determine the characteristics of the morbid changes in organs and tissues as related to the means of introducing the infection, and to follow the nature of the tissue changes in acute experimental toxoplasmosis induced by innoculation at various sites.

EXPERIMENTAL METHOD

The experiments were carried out on animals highly sensitive to toxoplasmosis; we used golden hamsters (Cricetulus auratus) and laboratory white mice which were infected by various means, made to resemble as far as possible the natural routes of infection; through the mouth, nose, conjunctiva, mucous membranes of the sex ducts, and by scarification of the skin. For the infection we used the peritoneal exudate of mice infected with the RH strain of toxoplasma. We injected 0.1 ml of a suspension containing 50,000 toxoplasma cells.

The extent of infection of the animals in relation to the means of infection, and the dates of death are shown in the table.

Smear preparations from the abdominal viscera and brain, stained in Romanowsky-Giemsa, were made from all the animals which succumbed and were examined microscopically for the presence of the infective agent. In all the animals which succumbed, in smears from the liver, spleen, and lung a large number of toxoplasma cells were found, but they were less numerous in the kidneys, myocardium, and brain.

The organs of the animals which died were examined histologically (they were fixed in 10% acid formalin, stained in hematoxylineosin).

To observe the rate of development of infection and tissue changes at the sites of innoculation 24 white mice were infected with the same strain and the same dose of toxoplasma which was introduced into the upper respiratory tract through the nose or mouth, or given through the conjunctiva or vagina (6 animals in each group). The mice were killed two at a time on the 2, 4, and 7th day after infection. Histological investigations were made of the liver, spleen, lungs, heart, brain, as well as of the site of innoculation (fixation and staining as for the hamsters).

EXPERIMENTAL RESULTS

Despite the fact that in all cases the reaction consisted of a generalized sepsis, the means of infection did affect the extent of the changes in the organs. These changes are apparently determined not only by the number of parasites penetrating into the organism, but also by the specific properties of the tissues in which they are first located, as well as by the reticulo-endothelial barriers encountered by the toxoplasma as it spreads along the lymphatic and blood vessels.

Results of Infection of Golden Hamsters with Toxoplasma Strain RH

Means of infection	Result of infection									
Through the mouth	10	10	10	11	11	0	0	0	0	0
" nose	7	7	7	8	8	8	8	8	9	9
" conjunctiva	8	9	9	10	10	11	11	12	12	13
" vagina	8	8	8	9	10	11	11	0		
" ureter	10	14	20	27	0	0	0	0		
By scarification of the skin	7	10	10	10	10					

Note: Each square represents one animal; the figures represent the days elapsing between the infection and death; a zero indicates that the animal remained alive, and was not infected.

The death of the golden hamsters after infection by any of the methods resulted from generalized toxoplasmosis with signs of serous hemorrhagic exudative interstitial pneumonia (alveo-septal pneumonia, in the terminology of Ferrara and his co-workers [4]). The survival time of the animals after infection was determined by the severity of the condition. The most severe pathological changes occur in the lungs through direct infection through the respiratory passages (Fig. 1), as well as through rapid penetration by the parasite into the blood stream. This may be explained by the fact that the lungs constitute a reticulo-endothelial barrier able to accumulate a large amount of toxoplasma which can live and multiply in the reticulo-endothelial cells. The walls between the alveoli are greatly thickened and infiltrated by cellular elements which in places form a granuloma consisting of histocytes, macrophages, and lymphocytes surrounding large masses of toxoplasma.

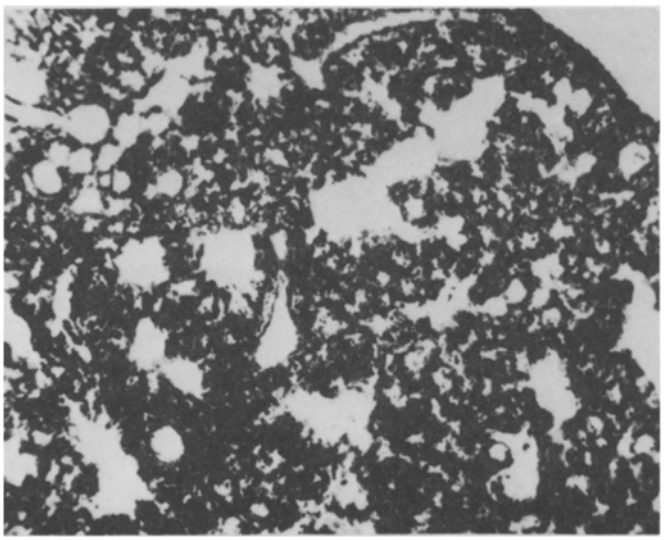

Fig. 1. Well marked alveo-septal pneumonia in the golden hamster after infection through the nose (death on the 7th day). Micrograph. Strain hematoxylin-eosin. Magnification 70 x.

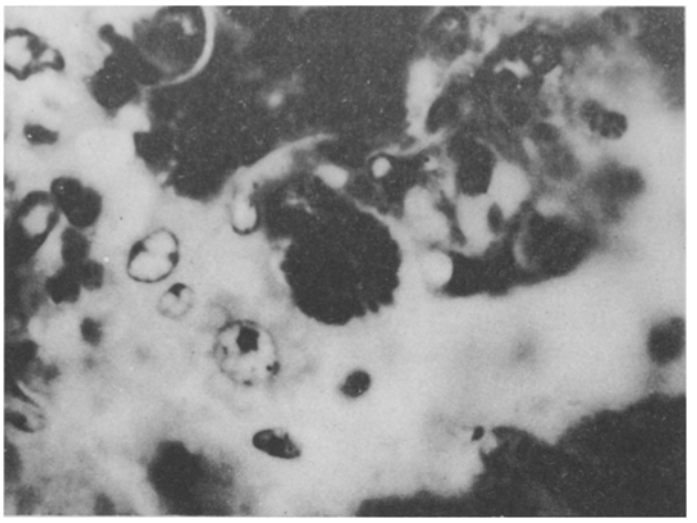

Fig. 2. Rosettes of toxoplasma in a liver cell of a golden hamster infected through the mouth (death on the 10th day). Micrograph. Stain hematoxylin-eosin. Magnification 900 ×.

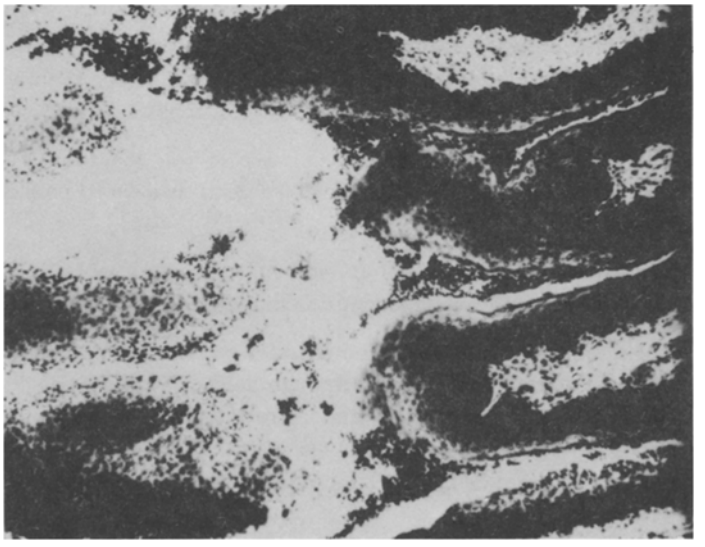

Fig. 3. Inflammatory reaction with exudate in vagina of white mouse on second day after infection through the vagina. Micrograph. Stain hematoxylin-eosin. Magnification 90 ×.

A similar state of preferential localization of toxoplasma in the lungs associated with a rapid entry first into the greater and then into the lesser circulation has been described for intravenous infection of mice [3].

Damage to the liver showed up in every case as acute toxic hepatitis with the formation of perivascular infiltration and lymphoid plasmocytic microgranulomas around accumulations of the parasite. There was also a well-marked hisiotcytic reaction.

When the infection was into the gut of golden hamsters these changes in the liver were more marked; however no severe necrotic changes were observed such as were found after intra peritoneal infection, where the disease took an acute course.

Typically the parasites are distributed within the hepatic cells so as to form a fan-shaped or stellate colony (rosettes) similar to those which are found in the development of toxoplasma in a tissue culture (Fig. 2).

Changes in the spleen, myocardium, and brain were the same whatever the method of infection, and resulted in a morphological condition characteristic of acute toxoplasmosis in other animals [2].

In studies of the various sites of innoculation in white mice it was found that the most marked changes developed when infection was through the vagina or nasal cavity. As early as the second day after infection and inflammatory exudative reaction with a comparateively small amount of exudate occurred in the sex ducts (Fig. 3). In the lumen of the vagina, in the exudate consisting of mucous, fibrin, and neutrophils, the toxoplasma parasite was regularly found. Large numbers were present in the surface layers of the stratified squamous epithelium, and usually they were disposed intracellularly in the form of isolated organisms or pseudocysts. Next they penetrated into the submucosa and then to the muscle layer, as well as into the regional lymph nodes. By the fourth day toxoplasma were found in the cavity of the uterus, and in the epithelial cells of its mucuous membrane. In the sex organs there was an enhanced proliferative reaction affecting the surrounding fat, where at first there was a nodular periphlebitis, and then a diffuse paracolpitis and parametritis with a well-developed microphagic and histocytic reaction.

Ulcers of the vaginal mucosa developed. A large number of toxoplasma in the form of a pure culture were found in the lumen of the vagina and uterus. Extensive necrotic areas developed on the seventh day in the submucosa and muscular layers of the vagina and uterus. In the necrotic regions the toxoplasma parasites quite frequently assumed an atypical bean-shaped or rounded form.

Occasional structures resembling toxoplasma were found in the ovary among the loose epithelium of a developing follicle.

The rapidity with which the parasite multiplied at the site of injection caused them to spread rapidly within the body. This was confirmed by the marked tissue changes and by the presence of toxoplasma in many of the viscera.

When infection was through the nose the local changes appeared on the fourth day after infection. Damaging the ciliated epithelium of the nasal mucosa and accessory sinuses and multiplying rapidly the toxoplasma penetrated into the underlying tissue as far as the periostium of the skull, bringing about destructive and necrotic non-gangrenous processes.

Following the results of similar work [5] carried out on other animals we will now consider the problem of the existence of a toxoplasma sinusitis.

Despite the presence of parasites in the viscera (liver, spleen, and lungs), when toxoplasma is introduced through the mouth (in cases when an infection was produced) no changes were found in the gastro-intestinal tract.

Thus with all the means of infection which we used and which were as near as possible to the natural routes, the infectious process developed most acutely in infection through the respiratory passage and mucous membrane of the sex ducts. The degree to which the local destructive and necrotic changes are manifest, and the rate at which the parasite enters the blood stream to cause first a generalized infection and then an alveoseptal pneumonia determines the acute course of the disease in animals highly susceptible to toxoplasma.

SUMMARY

An examination was carried out to investigate the pathology of changes induced in the golden hamster and albino mice infected with toxoplasma of the RH strain; the infection was made to resemble the natural routes as far as possible, and was made through the mouth, nose, conjunctiva, scarified skin, and mucosa of the genital tract; the material was fixed in 10% formalin, and stained in hematoxylin-eosin. The most acute infection followed transmission of the pathogens through the respiratory passages or through the mucosa of the genital tract. The acute course of the disease is determined by the degree of necrotic changes to the site of infection, and by the speed with it gains entrance into the blood causing a generalized infection, and death from alveoseptal pneumonia.

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