THE EFFECT OF CHLORTETRACYCLINE ON THE COURSE OF EXPERIMENTAL CANDIDOMYCOSIS OF THE LUNGS IN WHITE RATS*

COMMUNICATION I. EXPERIMENTS IN WHICH CHLORTETRACYCLINE WAS INJECTED SIMULTANEOUSLY WITH INFECTION BY A CLUTURE OF CANDIDA ALBICANS

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In the literature there are many papers dealing with the role of antibiotics in the development of the candidomycoses. Some workers point out the stimulation of growth of candida directly by antibiotics themselves: by multiple [1, 6] or by individual preparations, and in particular, by chlortetracycline [4, 5, 8]. The authors of other papers [7, 9 and others] consider that the action of antibiotics is purely to destroy the symbiotic microorganisms in whose absence the fungi are able to undergo intensive proliferation. Under these circumstances Drouhet denies that antibiotics are,in general,capable of a direct stimulating action on Candida [3], and Strutz andKuntze even note an inhibitory action on Candida by high concentrations of penicillin and xanthocillin [10]. In some research papers [4] the view is expressed that antibiotics act only on the patient, suppressing his defensive reactions, and thereby facilitating the development of candidomycosis

Because of the contradictory reports in the literature on this very important subject, we undertook the study of the effect of chlortetracycline on the course of experimental candidomycocis of the lungs.

EXPERIMENTAL METHOD

In the present paper we give details of the morphological changes in the internal organs of 89 white rats which received intranasal injections of 1.5×10^9 cells of a suspension of a culture of Candida albicans in 0.5 ml of 8% gum arabic; the injections were given in the mycological laboratory of the Institute of Antibiotics. During the histological examinations we used, besides the usual methods, the Shabadash and Gram staining methods.

EXPERIMENTAL RESULTS

The first series of experiments was carried out on 21 control and 25 experimental rats. The latter received 4000 units of chlortetracycline daily from the day of inoculation. Fifteen rats died on the first day (7 experimental and 4 control) or on the second day (3 experimental and one control); the remainder were killed with ether at different times, beginning with 3 hours and ending with 45 days after inoculation.

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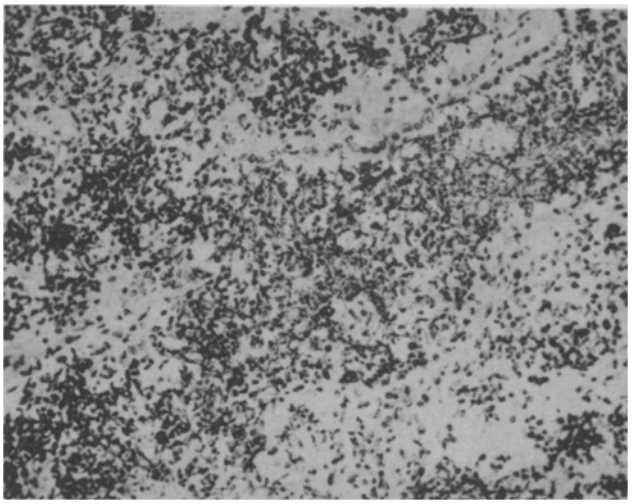


Fig. 1. In a bronchiole, an alveolar passage and the adjoining alveoli is a proliferating mass of Candida albicans, surrounded by granulocytes and macrophages (a rat, not receiving chlortetracycline, which died on the 1st day after inoculation). Shabadash stain. Magnification 240.

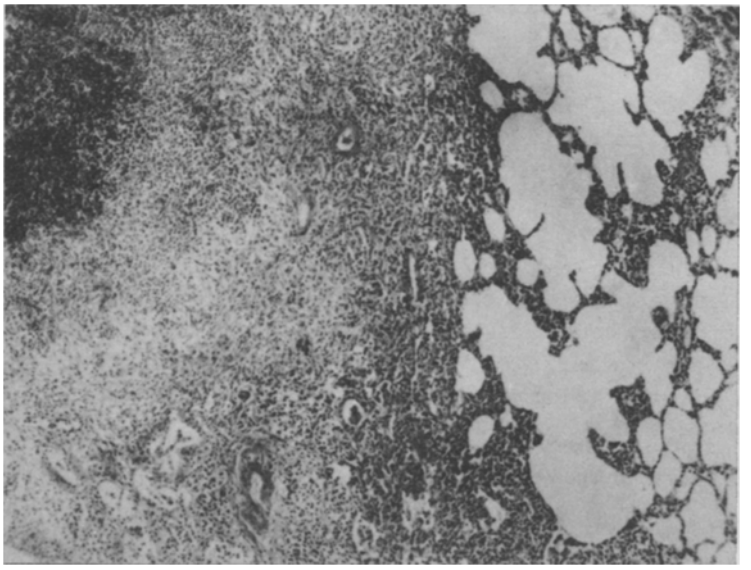
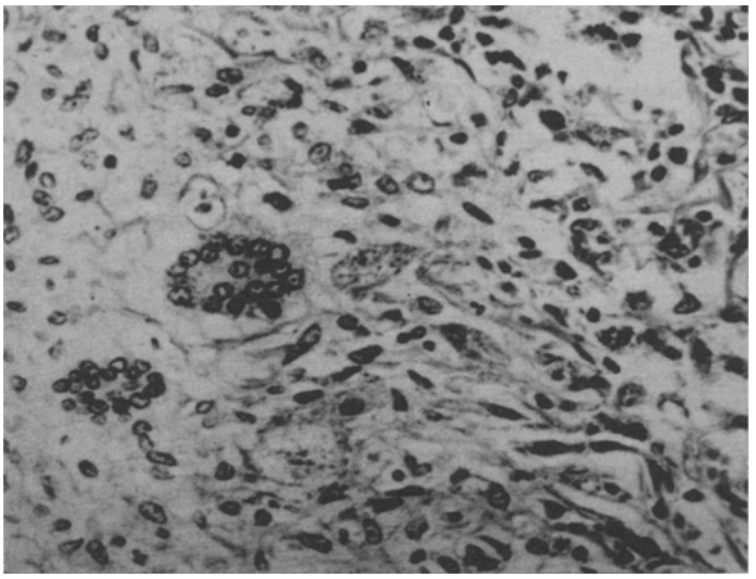


Fig. 2. Granulation tissue with a small abscess on the 10th day after inoculation (injection of chlortetracycline). Shabadash stain. Magnification 75.

In the animals killed immediately after inoculation, a moderate number of unevenly distributed yeast cells was present in the lumen of the bronchi, in the alveolar passages and sometimes in the alveoli themselves. No changes were present in the lungs. After 3 hours the number of yeast cells in the experimental and control rats increased considerably, as the result of their obvious division. The cells were of various sizes, but formation of threads of pseudomycelium was barely perceptible. In places where yeast cells were situated – the small bronchi, bronchioles, alveolar passages and the adjoining alveoli – a small number of macrophages was present, with which were occasionally intermingled a few granulocytes. The macrophages intensively ingested the yeast cells and some of them, tightly packed with yeast cells, by their appearance were reminiscent of mulberries.



3. Extensive focus, formed of granulation tissue, consisting of epithelioid and giant cells, macrophages and also of lymphocytes. The rat was killed on the 35th day after inoculation (injection of chlortetracycline). Stained with hematoxylin eosin. Magnification 525.

After 5 hours the inflammatory foci in the lungs of all the animals became more widespread. These foci were, as before, connected with the bronchial tree, being arranged in the form of leaves in the region of the alveolar passages. The exudate in these foci consisted of macrophages and granulocytes, sometimes with preponderance of the latter. Often there were fibrin threads among the cells of the exudate. A proportion of the foci were surrounded by a zone, sometimes wide, sometimes narrow, with a serous exudate in the alveoli. In the central areas among the cells of these alveoli and also in the protoplasm of the macrophages a large number of yeast cells were found; threads of pseudomycelium were also fairly numerous. Individual yeast cells could also be found in the serous fluid around the pneumonic foci.

On the first day after inoculation 7 experimental and 4 control rats died. A large part of the lung tissue (and in some animals almost the whole of it) was composed of confluent foci, completely devoid of air. In their central areas were observed abundant felt-like proliferations of yeast cells with the formation of well-marked threads of pseudomycelium. These were situated in the bronchioles (Fig. 1) and along the walls of the alveolar passages, forming irregularly shaped rings. In the lumen of these rings a whitish fluid was present. Around them was usually seen a fairly narrow zone of alveoli, filled with leucocytes, some of them disintegrating, and sometimes with a small admixture of macrophages. In the majority of the animals phagocytosis of yeast cells by macrophages was observed. In some cases yeast cells, in spite of their large size, were evidently also situated within the protoplasm of the leucocytes. The alveoli around these foci were usually under considerable tension and filled with a serous fluid. As a rule they contained no yeast cells.

On the 2nd day after inoculation we investigated 5 experimental and 5 control animals, including 4 which died (3 experimental and one control). The changes in the lungs of the animals which died were identical with those described above. In all the killed animals macrophages began to predominate among the cells in the pneumonic foci, sometimes already showing an elongated appearance. In places small abscesses were formed where, in addition to disintegrating granulocytes, a varying number of yeast cells were observed, and sometimes short threads of pseudomycelium also. Usually no zone of edema was present around the foci.

On the 3rd-7th day after inoculation, the lungs of all the rats showed a fairly widespread distribution of foci devoid of air, in which the alveoli were filled mainly with macrophages, some of which were elongated in shape. The protoplasm of many macrophages, especially those situated in the center of the foci, took on a red color when stained by Shabadash's method. Solitary, palely staining yeast cells were sometimes found here. On the 3rd day a small number of leucocytes was found in these foci, and in one animal these cells were actually predominant in the exudate. Often formation of granulation tissue took place in the central areas of these foci,

consisting of epithelioid and solitary giant cells with lymphocytes at the periphery. In half the animals small abscesses could be found among this tissue. A few dying yeast cells were usually to be seen among the disintegrating granulocytes. The tissue surrounding such areas was usually observed to contain a considerable admixture of fibrin. In individual animals the alveoli around certain foci were partially filled with a serous fluid.

On the 10th-15th day in all the experimental animals, widespread foci were observed from which air was absent, where the lung tissue was occupied by granulation tissue of the structure described above. In the majority of thses animals abscesses with a varying number of yeast cells were also found (Fig. 2). In almost all the control animals (not receiving chlortetracycline) the foci in the lungs were comparatively few in number. The alveoli in these foci were full or partially filled with macrophages, often with red cytoplasm when stained by Shabadash's method. Sometimes areas containing granulation tissue were also present, and small abscesses with disintegrating granulocytes, but no yeast cells were present here.

At the subsequent times (22-45 days) the changes in the lungs of the experimental and control animals took the form of more or less widespread foci devoid of air. The alveoli in these areas were filled with macrophages, less commonly macrophages and epithelioid cells; no yeast cells were found (Fig. 3).

In order to obtain a more accurate picture of the dynamics of the process, we carried out a second series of experiments on 20 control and 23 experimental white rats. In order to prevent the possibility of development of inflammatory changes unconnected with the inoculation (associated with the low external temperature), all the experimental animals and 15 of the controls were given chlortetracycline for two days before inoculation. After the inoculation only the experimental rats continued to receive the drug. For the investigation the animals were killed with ether at different times, starting from the moment of inoculation and ending with 22 days. Only one experimental rat died. The changes in the lungs of the animals in this series of experiments were mainly in accordance with those described above.

The exception in this series of experiments was the specific changes found in one experimental and one control rat in the first series, killed on the 26th day after inoculation. In these animals there were very extensive foci devoid of air, filled mainly with epithelioid cells. In the foci were found numerous abscesses with well-preserved leucocytes, only those in the center of the abscess being in a state of disintegration. The abscesses contained many yeast cells. In the control rat a large number of staphylococci was found, and in the experimental rat, many small Gram-positive particles, probably from disintegration of microorganisms. It may be thought that these foci developed as a result of the superimposition of fungi of the Candida genus on a staphylococcal lesion which preceded it, or developed simultaneously with it, in consequence of migration of microorganisms from the upper respiratory tract after intranasal inoculation of the Candida suspension.

We were unable to find any instance of the presence of inflammatory foci containing Candida in other internal organs (brain, heart, spleen, kidneys, liver, intestine and thymus gland).

The results of a mycological investigation of all the internal organs, made concurrently by N. P. Elinov, were in agreement with the pathological anatomical findings.

Thus the administration of chlortetracycline to white rats with experimental candidomycosis of the lungs aggravated the course of the infectious process. This could be judged first, by the larger number of animals in the experimental group which died (11 of 48, i.e., 23%) by comparison with the control group)5 of 41, i.e., 12%), and secondly, by the longer period of preservation of Candida in the foci of inflammation which, as a rule, were more widespread in the animals of the experimental group.

SUMMARY

This paper deals with the pathologicoanatomical study of internal organs in 89 white rats infected intranasally with Candida albicans culture. In 50% of the animals tetracycline per os administration was commenced at the day of infection or 2 days prior to it.

This preparation aggravated the course of infection: a) more animals perished in the experimental group than in the control; b) in experimental animals Candida remained in the foci of infection (which, as a rule, were more widespread in this group of animals) for longer periods of time.

LITERATURE CITED

[1] N. P. Elinov, Experimental and Clinical Research, vol. 11, pp. 143-148, Moscow, 1956 [In Russian].

[2] N. P. Elinov, Experimental and Clinical Research, vol. 11, pp. 148-150, Moscow, 1956 [In Russian].

[3] E. Drouhet, Presse méd., 1955, v. 63, p. 620-623.

[4] G. W. Fischer, Zbl. Bakt., 1953, Bd. 160, S. 275-278.

[5] M. Huppert, Cazin J., H. Smith, J. Bact., 1955, v. 70, p. 440-447.

[6] R. G. Janke, Zbl. Bakt., 1954, Bd. 160, S. 628-636.

[7] F. Klose, Schürmann R., Ztschr. Hyg., 1952, Bd. 134, S. 63-77.

[8] R. B. Pappenfort, E. S. Schnall, Arch. Intern. Med., 1951, v. 88, pg. 729-735.

[9] H. M. Robinson, Arch. Dermat. a. Syph., 1954, v. 70, p. 640-652.

[10] I. Strutz, C. Kuntze, Naturwissenchaften, 1955, Bd. 42, S. 464.