prime factor in the successful culture medium, the physical condition of the medium also appears to play an important rôle. The consistency of a medium may vary from a very firm jelly to one that is barely solid depending on the amount of water present. In many instances it appears that a particular consistency is favorable to the production of surface growth.

It has become evident that the mitochondria vary in their physiology in different new-born rabbit livers, and that the physiological state is an important factor in determining the character of growth in the culture media. A variation in the response of mitochondria is shown in stained smear preparations of liver from different new-born rabbits. In some cases the mitochondria are well preserved and numerous, in other cases they are few in number. The gross characteristics of the liver also vary in the new-born rabbits. The color varies from a yellowish brown to a deep maroon. So also, the physical nature of the livers vary; some are stringy and tough, while others are friable and easy to cut into pieces.

Mitochondria appear to be extremely delicate in their responses. With variable factors in the culture media on the one hand and variable physiology of the mitochondria on the other, it appears nigh impossible to devise a culture medium that will constantly produce surface growth of mitochondria.

[1] Wallin, Ivan E., *Am. J. Anat.*, xxxiii, 1; xxxv, 3; xxxvi, 1.

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Experimental Typhoid Fever Induced in Guinea Pig With In Vivo Prepared B. Typhosus Toxic Product.*

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Since typhoid fever represents a syndrome manifestly accompanied by toxemia, many and varied attempts have been made to obtain the specific toxic moiety from the typhoid bacillus. While certain of these procedures have yielded toxic materials which when injected into animals produce tissue reactions, they are not, as far as ascertained, analogous to the pathological changes occurring in typhoid fever of man.

* Aided by a grant from the David Trautman Schwartz Research Fund.

The toxic material employed in the experiments herein reported was prepared through an *in vivo* method, *i. e.*, the activities of the living animal body were used to produce in part or set free a toxic

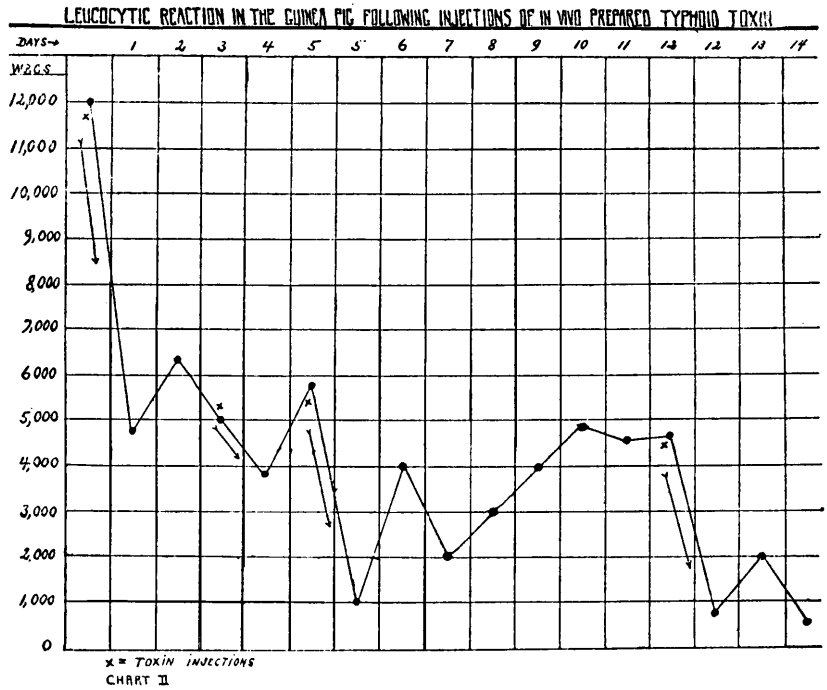

CHART II

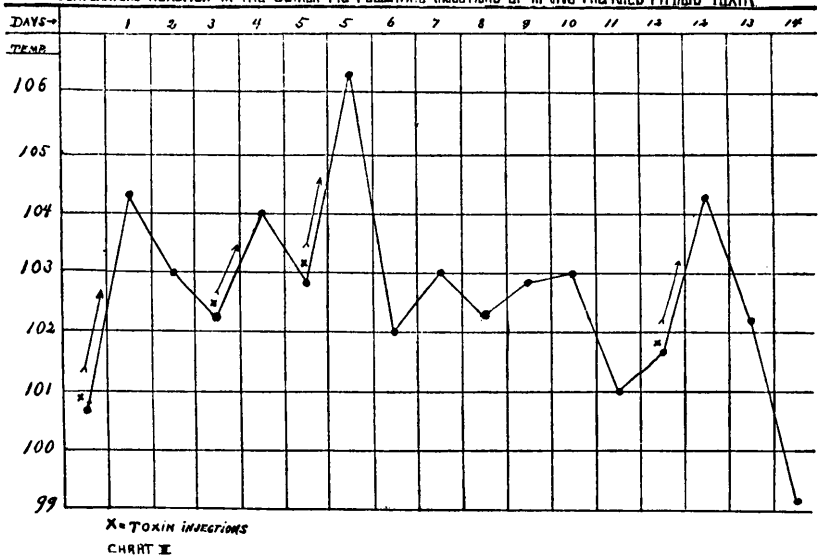

CHART III

portion of the microorganism. By this method peritonitis was first produced in guinea pigs with cultures of *B. typhosus* and the animals were killed after they had become sick, which was usually within 8 to 12 hours. After coarse filtration this exudate was filtered through a Berkefeld letter N filter. A series of guinea pigs were injected with the filtrate thus prepared, by different routes, some subcutaneously, some intracardially and others intraperitoneally. Several injections were given to each animal of a series at intervals of from 2 to 4 days. Subsequent to each injection, irrespective of the route, a febrile rise and marked leucopenia occurred. (See charts.) Death of the animals usually occurred in from 2 to 4 weeks.

At autopsy the chief gross pathological changes were noted in the intestine, lymph nodes, spleen, liver and kidney. The peritoneal lymph nodes were markedly enlarged and at times hemorrhagic. Peyer's patches and the solitary follicles of the intestinal tract were much swollen and elevated; in some instances they were somewhat reddened and revealed early ulceration. The spleen was increased in size, soft and congested. The liver was congested and often showed small scattered yellowish areas of what appeared to be necrosis. The kidneys, adrenals and bone marrow were swollen and congested. The lungs and heart appeared normal and it is noteworthy that in no instance was pneumonia present.

The microscopic study of the lymphoid structures, especially of the peritoneal cavity, including Peyer's patches and the solitary follicles of the intestinal tract, showed the enlargement to be due to an apparent hyperplasia of the lymphoid elements and also to the presence of multiple large, pale and more or less oval cells, many of which were phagocytic and correspond to the type emphasized by Mallory[1] as the principal reactionary cell of human typhoid. These phagocytes had engulfed lymphoid cells and nuclear fragments and at times red blood cells, depending upon the area of their location. In some of the nodes, areas of marked congestion and hemorrhage and small foci of necrosis were present. In the Peyer's patches of certain of the animals, necrosis, loss of the epithelial lining, and rupture of the muscularis mucosa were noted, *i. e.,* early ulceration had occurred. The splenic pulp was markedly congested and in some areas hemorrhagic extravasations were observed. Many of the erythrocytes showed a shadow-cell type due apparently to the loss of hemoglobin. Numbers of "endothelial" phagocytic cells were seen which contained "shadow red-cells" within their cytoplasm. The liver demonstrated focal necrosis of varying extent.

In some areas complete necrosis of the cells had occurred and altered red blood cells were present, many of which were engulfed by the phagocytic cells. In the smaller areas of focal necrosis, the liver cells were replaced by "endothelial" or phagocytic cells. One outstanding feature in the microscopic study of the tissues of all animals, was the absence of reactionary polymorphonuclear neutrophiles.

FIG. 1.

Portion of small intestine of the guinea pig (experimental typhoid fever) showing the type of gross lesion produced in Peyer's patch.

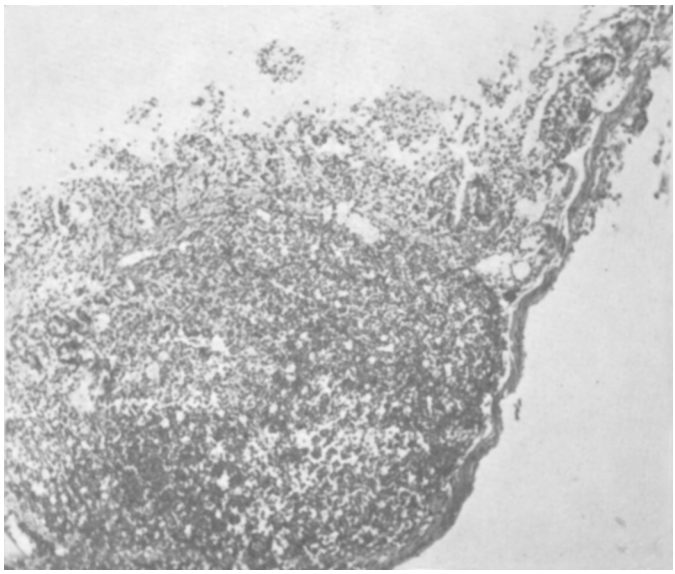

FIG. 2.

Low power photomicrograph of a portion of Peyer's patch of guinea pig, showing marked enlargement. There are many phagocytic "endothelial" cells and a hyperplasia of lymphoid elements. The muscularis mucosa is in part lost, and the overlying mucosa destroyed.

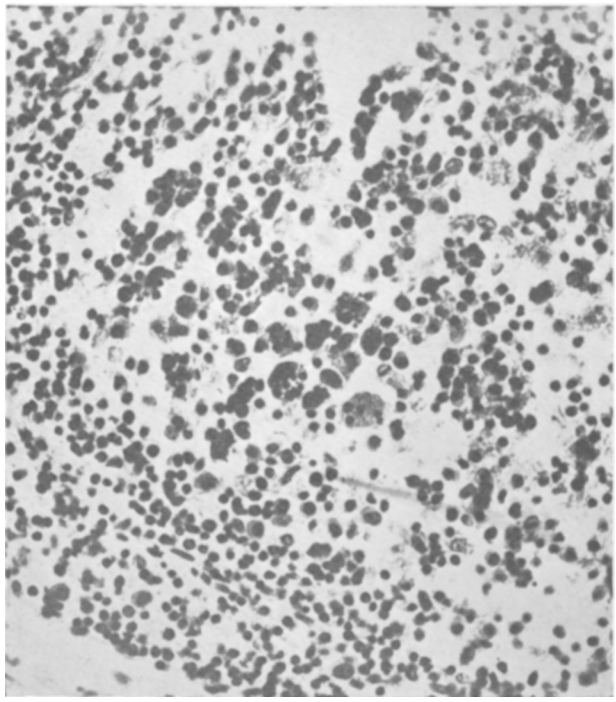

FIG. 3.

High power area of Peyer's patch shown in Figure 2, demonstrating phagocytes containing numbers of lymphoid cells and nuclear fragments.

It would appear from this study that when a peritonitis is produced in the guinea pig by *B. typhosus,* a toxic substance is liberated during the encounter between the invading microorganisms and the host which is very analogous if not identical in its action with that of the toxin present in typhoid infection of man. Whether the toxic moiety is secreted by the microorganism during its invasion of the somatic host structures, or whether it is discharged through the injury of the bacilli by the body tissues and fluids, or is produced through both such activities, has not been determined.

The results obtained in these experiments indicate that through the employment of this *in vivo* method, a bacterial free filterable toxic substance can be produced from the typhoid bacillus which when injected into the guinea pig produces effects and tissue lesions analogous to those occurring in human typhoid infection.

[1] Mallory, F. B., *J. Exp. Med.,* 1898, iii, 611.